Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, January 30th, 2014 1:00-5:00 PM
Clackamas Community Training Center
29353 SW Town Center Loop East
Wilsonville, OR 97070

MEETING AGENDA

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to utilization control recommendations to the OHA. Timing, sequence and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee and staff. The DUR/P&T Committee functions as the Rules Advisory Committee to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9).

I. CALL TO ORDER
- a. Roll Call & Introductions — R. Citron (OSU)
- b. Conflict of Interest Declaration — R. Citron (OSU)
- c. Election of Chair & Vice Chair — R. Citron (OSU)
- d. Approval of Agenda and Minutes — Chair
- e. Department Update — T. Douglass (OHA)

II. DUR ACTIVITIES
- a. Quarterly Utilization Reports — R. Citron (OSU)
- b. ProDUR Report — R. Holsapple (HP)
- c. RetroDUR Report — T. Williams (OSU)
- d. Oregon State Drug Reviews — K. Sentena (OSU)
  1. Update on the New Oral Anticoagulants with a Focus on Apixaban

III. PREFERRED DRUG LIST
- a. Fish Oil — B. Liang (OSU)
  1. Class Review
  2. Public Comment
  3. Discussion of Clinical Recommendations to OHA

IV. DUR NEW BUSINESS
- a. Fish Oil Drug Use Evaluation (DUE) — K. Ketchum (OSU)
  1. DUE
  2. Public Comment
  3. Discussion of Clinical Recommendations to OHA

V. PREFERRED DRUG LIST CONTINUED
- a. Sirturo (bedaquiline) New Drug Evaluation — S. Argyres (OSU)
  1. New Drug Evaluation (NDE)
  2. Public Comment
  3. Discussion of Clinical Recommendations to OHA

b. Hepatitis C Abbreviated New Drug Evaluations — M. Herink (OSU)

1. Olysio (simeprevir) NDE
2. Sovaldi (sofosbuvir) NDE
3. Public Comment
4. Discussion of Clinical Recommendations to OHA

c. Second Generation Antipsychotics — A. Meeker (OSU)

1. Class Update
2. Public Comment
3. Discussion of Clinical recommendations to OHA

d. Gout Medications — M. Herink (OSU)

1. Class Update
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

e. Drug Class Scans — M. Herink (OSU)

1. Oral HSV
2. Hormone Replacement Therapy
3. Calcium Channel Blockers
4. Beta-Blockers
5. ACEI/ARBs/DRIs
6. Public Comment
7. Discussion of Clinical Recommendations to OHA

VI. EXECUTIVE SESSION

VII. RECONVENE for PUBLIC RECOMMENDATIONS

VIII. ADJOURN

Drug Use Research & Management Program
OHA Division of Medical Assistance Programs 500 Summer Street NE, E35; Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

OREGON PHARMACY & THERAPEUTICS COMMITTEE MEMBERSHIP REPORT

First Name	Last Name	Title	Position	Date Began	Term Ends	Specialty/Practice Setting	Geography
Joshua	Bishop	PharmD	Pharmacist	Nov-11	Dec-14	Pharmacy Director	Bend
Zahia	Esber	MD	Physician	Nov-11	Dec-16	Internal Medicine	Eugene
Tracy	Klein	PhD, FNP	Public	Nov-11	Dec-14	Nurse Practitioner	Portland
Phillip	Levine	PhD	Public	Nov-11	Dec-15	Retired	Lake Oswego
Meena	Mital	MD	Physician	Nov-11	Dec-14	Deputy Medical Director	Portland
William	Nunley	MD	Physician	Jan-13	Dec-15	Associate Medical Director	Portland
William	Origer	MD	Physician	Nov-11	Dec-14	Medical Director	Corvallis
David	Pass	MD	Physician	Nov-11	Dec-16	Medical Director	West Linn
Stacy	Ramirez	PharmD	Pharmacist	Nov-11	Dec-16	Ambulatory Care/Community Pharmacist	Albany
James	Slater	PharmD	Pharmacist	Nov-11	Dec-14	Associate Pharmacy Director	Beaverton
Cathy	Zehrung	RPh	Pharmacist	Nov-11	Dec-15	Pharmacy Manager	Silverton

Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, November 21, 2013 1:00-5:00 PM
Wilsonville Training Center
29353 SW Town Center
Wilsonville, OR 97070

MEETING MINUTES

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to utilization control recommendations to the OHA. Timing, sequence and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee and staff. The DUR/P&T Committee functions as the Rules Advisory Committee to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9).

Members Present: Cathy Zehrung, RPh; Phillip Levine, PhD; William Origer, MD, Tracy Klein, PhD, FNP;

Members Present by Phone: Stacy Ramirez, PharmD; William Nunley, MD; James Slater, PharmD

Staff Present: Kathy Ketchum, RPh, MPA:HA; Megan Herink PharmD, BCPS; Richard Holsapple, RPh; Roger Citron, RPh; Ted Williams, PharmD; Trevor Douglass, DC, MPH; Shannon Jasper; Amanda Meeker, PharmD;

Staff Present by Phone: Kathy Sentena, PharmD, Bing-Bing Liang, PharmD

Audience: Kimberly Blood, (WVP Health Authority); Venus Holder, (Lilly); Paul Barham (NovoNordisk); Jeana Colabianchi, (Sunovion); Kathleen Rogers, FNP, MSN, (Sunovion); Anne Marie Licos, PharmD (MedImmune); Bruce Smith (GSK); Barry Benson, (Merck); Barbara Felt (GSK)*; Kyle Linhard (Upsher-Smith); Theresa Lane (Trillium Community Health Plan); Jo Crawford (Serenity Lane); Tammy Grasty (Serenity Lane); Amy Burns (AllCare CCO); Gina Guinasso (Acorda); Bruce Howard (Acorda); Phillip Kenner (Accorda)*; Joe Chan (Otsuka America); Patrick Moty (Supernus); Dean Haxly (OSU); John McIlveen, PhD, LMHC (OHA – Addictions & Mental Health)*

(*) Provided verbal testimony

I. CALL TO ORDER

a. The meeting was called to order at approximately 1:10 pm. Introductions of Committee members and staff.

b. Mr. Citron reported there are no new conflicts of interest to declare.

c. The July 25th meeting minutes were reviewed. (pages 3 - 8)

ACTION: Motion, Approved as is.

d. Department updates by Dr. Trevor Douglass.
Dr. Douglass announced OHA is currently seeking and will be hiring a new Policy Manager for the Pharmacy Division. This will occur by the end of December. Mr. Citron explained the state is looking at the implementation of the policy regarding sanctioned providers and how that would affect the Point of Sale system for Pharmacy.

II. DUR ACTIVITIES

a. Quarterly Utilization Reports (page 9) Third quarter 2013
Drug Utilization Review, Federally required, for state Medicaid that provide coverage. (Hand out given) Changes on report include (1) encounter data from CCO's; (2) Quarterly rebates invoiced CMS and supplemental rebates; (3) Physician administered drugs.

b. ProDUR Report (page 13) also 2 page hand out
Mr. Holsapple gave the highest volume of ProDUR alerts. Reports generated provide early refill, therapy changes, and or loss of medication. Pharmacies do have ability to override with clarification code.

c. RetroDUR report (page 14-16)
Dr. Williams stated there will be a new format effective in January.

d. Oregon State Drug Reviews
   1. Managing Metabolic Side Effects in Children Receiving Antipsychotics. (Page 17 - 18) Ms. Sentena presented the newsletter.
   2. Updates and Comparisons of Type 2 Diabetes Guidelines. (Page 19-20)
   Ms. Sentena presented the second part of the newsletter.

III. PREFERRED DRUG LIST NEW BUSINESS

a. Vivitrol® (naltrexone) New Drug evaluation (Page 21-34)
Dr. Liang presented the following information: Naltrexone injection is indicated for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with naltrexone. It is also indicated for the prevention of relapse to opioid dependence following opioid detoxification. It should be part of a comprehensive management program that includes psychosocial support.

Conclusion was:
   1. Evaluate comparative costs of injectable extended release naltrexone in executive session and require prior authorization for the use in opioid dependence requiring:
   2. The failure of other oral agents for the treatment of opioid dependency OR the patient requires injectable therapy
   3. The member is part of a comprehensive treatment program for substance abuse that includes a psychosocial support system.
   4. Patients be opioid free for 7 days prior to administration.

b. Allow for use in alcohol dependence until a subsequent full evidence review is done.

Public Comment: Dr. McIlveen offered to help with any information and or studies regarding the pharmaceuticals for Alcohol and drug dependence. He is also going to help with the language for the Prior Authorization.

Jo Crawford from Serenity Lane (Alcohol and Drug Treatment Program) testified regarding the success they have had at their clinic using Vivitrol® with certain clients.

c. *(After Executive Session) Make Vivitrol non-preferred. Will bring back full alcohol dependence review when literature is fully published. Committee and staff will work with Dr. John McIlveen to clarify and tighten PA criteria.

IV. HCMB Submcommittee Follow-Up

a. SubCommittee Report (Page 35-36)
Dr. Douglass stated that if medication is not on a list, there will be a pathway for Coverage for that drug that has appropriate criteria.

b. Ampyra® (dalfampridine)

c. Kuvan® (saproterin)

Public Comment: Phillip Kenner testified the studies showed improvement in walking for clients. An MSW S12 study validated the outcome with improvement in all 12 areas tested, they updated safety data, and there were no new safety signals. There is value if patients are able to try the product.

1. Add Kuvan® (saproterin) to the HCMB list.
2. Add Ampyra® (dalfampridine) to the HCMB lsit.
3. Change the language in the Kuvan® PA criteria to criteria #4 to: *Is the patient "compliant" with a Phe-restricted diet.*

ACTION: Motion, 2nd, All in Favor. Approved.

V. DUR OLD BUSINESS

a. Juxtapid® (lomitapide) and Kynamro® (mipomersen) (Page 37-38)
Ms. Ketchum presented the following updates:
1. Approve modified PA criteria to remove language approving treatment if LDL-C apheresis is not available to them and changing the length of approval from 6 months to 1 year.

ACTION: Motion, 2nd, All in Favor. Approved.

VI. DUR NEW BUSINESS

a. Benzodiazepine Drug Use Evaluation (Page 39-51)
Ms. Ketchum to presented the following updates:
1. To prevent inappropriate long-term use, require prior approval for exceeding 4 weeks on newly started patients only. (no history within the last 100 days)
2. Approval would be granted in any of the following situations:
    i. Clinical Rationale to support long-term BZO use for supplided indication(s)
    ii. No concurrent sedative / hypnotic or opioid
    iii. Dose <3 mg diazepam equivalents

Recommendations to OHA:

1. Approve amended prior approval and bring back more data and information. Consider targeted education to those at high risk of mortality and piloting these interventions at a high risk clinic.
2. Bring back a policy evaluation after the first quarter of implementation.
3. Change "evidence to support" to Clinical Rationale.

ACTION: Motion, 2nd, All in Favor. Approved.

VII. PREFERRED DRUG LIST OLD BUSINESS

a. Diabetes Class Clarification (Pages 52 -80)
Mr. Citron gave the following updates:
   1. In addition to requiring prior authorization as decided upon in the September P&T meeting, make the new combination products alogliptin / pioglitazone (Oseni®) and alogliptin / metformin (Kazano®) non-preferred.
   2. *(After executive session) - Keep the new combination products alogliptin / pioglitazone (Oseni®) and alogliptin / metformin (Kazano®) non-preferred.

***ACTION:** After Executive Session, all in favor.

VIII. PREFERRED DRUG LIST NEW BUSINESS (continued)

a. First Generation Antipsychotic Review (Pages 81-102)
Dr. Herink presented the following information:
   1. To reduce the copay burden, first generation antipsychotics should be included on the voluntary PDL list to promote the use of cost-effective and individualized treatment options for schizophrenia and bipolar disorder. Evaluate comparative costs in executive session.
   2. Further review the second generation antipsychotics at an upcoming meeting for comparative effectiveness and safety.
   3. *(After executive session) Add class to PDL and make all FGA preferred.

***ACTION:** After Executive Session, all in favor.

b. Chronic Obstructive Pulmonary Disease (COPD) (Pages 103-132)
Dr. Meeker presented the following information:
   1. Due to no evidence demonstrating clinical superiority of fluticasone / vilanterol over current agents, recommended making it non preferred.
   2. Recommend adding fluticasone / vilanterol to the LABA/ ICS prior authorization criteria and limiting to patients who have COPD.
   3. Due to strong comparative effectiveness of superiority between other agents, recommend comparing costs in executive session and maintaining tiotropium as preferred due to evidence of superiority over ipratropium.
   4. *(After executive session) – Guidelines to be amended to fit with new GOLD COPD classification.
   5. *(After executive session) – No changes to the PDL.

***ACTION:** After Executive Session, all in favor.

c. Parkinson's Disease Drugs (Pages 133-146)
Dr. Herink presented the following information:
   1. There is insufficient evidence that rotigotine (Neupro®) is more efficacious or safer than other oral dopamine agonists in the treatment of Parkinson's Disease. Evaluate in executive session for relative cost.

2. *(After executive session) – No changes to the PDL.

***ACTION:** After Executive Session, all in favor.

d. Statin Medications (Pages 147-163)
Dr. Herink presented the following information:
1. There is insufficient comparative evidence on long term clinical outcomes or evidence that one agent is safer than another. Evaluate comparative costs in executive session.
2. *(After executive session) – No changes to the PDL.

***ACTION:** After Executive Session, all in favor.

e. Drug Class Scans
1. Newer Antiemetics (Pages 164-174)
Dr. Herink presented the following information:
i. There is evidence that palonsetron may be superior to other 5HT3 antagonists in the treatment of chemotherapy induced nausea and vomiting for moderately emetogenic chemotherapy and that ondansetron, dolasetron, and granisetron are equally effective.
ii. There is low quality evidence that the combination of doxylamine / pyridoxine led to significantly greater improvement in nausea vomiting symptoms as compared with placebo (-4.8 PUQE score vs 3.9; p=0.006) but insufficient comparative evidence compared to other available agents. Maintain as non-preferred.
iii. Evaluate comparative costs in executive session.
iv. *(After executive session) – No changes to the PDL.

***ACTION:** After Executive Session, all in favor.

2. Newer Drugs for Insomnia (Pages 175-200)
Dr. Herink presented the following information:
i. No further research or review needed at this time.
ii. Evaluate comparative costs in executive session.
iii. Consider DUR evaluation and safety edit for zolpidem.
iv. *(After executive session) – Bring back zolpidem DUE with potential safety recommendations. No PDL changes.

***ACTION:** After Executive Session, all in favor.

3. Nonsteroidal Antiinflammatory Drugs (Pages 201-216)
Dr. Herink presented the following information:
i. No further research or review needed at this time.
ii. Evaluate comparative costs in executive session.
iii. *(After executive session) – Bring back information to assess the safety of diclofenac. No PDL changes at this time.

***ACTION:** After Executive Session, all in favor.

4. Skeletal Muscle Relaxants (Pages 217-230)
Dr. Herink presented the following information:
i. No further research or review needed at this time.
ii. Evaluate comparative costs in executive session.
iii. *(After executive session) – No PDL changes at this time.

***ACTION:** After Executive Session, all in favor.

IX. EXECUTIVE SESSION

X. RECONVENE for PUBLIC RECOMMENDATIONS

Mr. Citron confirmed to the public of the next P & T meeting will be held in November.

VII. ADJOURN

Drug Use Research & Management Program
DHS - Division of Medical Assistance Programs
500 Summer Street NE, E35, Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Pharmacy Utilization Summary Report: July 2012 - June 2013

Eligibility	Jul-12	Aug-12	Sep-12	Oct-12	Nov-12	Dec-12	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Avg Monthly
Total Members (FFS & Encounter)	618,940	619,527	621,079	619,870	618,962	621,328	621,239	624,167	626,033	624,596	625,809	625,937	622,598
FFS Members	97,124	95,914	103,154	101,337	85,412	80,358	76,316	78,706	79,138	75,030	75,828	78,595	83,050
Encounter Members	521,816	523,613	517,925	518,533	533,550	540,970	544,923	545,461	546,895	549,566	549,981	547,342	539,548

Gross Cost Figures for Drugs	Jul-12	Aug-12	Sep-12	Oct-12	Nov-12	Dec-12	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	YTD Sum
Total Amount Paid (FFS & Encounter)	$33,131,399	$31,017,308	$28,840,606	$31,350,278	$29,726,982	$29,680,115	$34,452,651	$31,392,629	$32,505,280	$32,305,187	$33,016,518	$29,798,048	$377,217,000
Mental Health Carve-Out Drugs	$7,840,388	$7,915,794	$6,911,556	$7,647,322	$7,187,998	$6,952,372	$7,640,960	$7,087,457	$7,359,442	$7,665,770	$7,812,992	$7,133,052	$136,128,769
FFS Physical Health Drugs	$3,349,782	$3,390,199	$3,209,382	$3,605,313	$2,717,565	$2,592,390	$2,865,612	$2,379,322	$2,483,291	$2,400,213	$2,399,041	$2,118,511	$47,286,768
FFS Physician Administered Drugs	$1,392,349	$1,597,905	$1,538,693	$1,689,318	$1,433,951	$1,221,756	$1,422,679	$1,054,998	$1,196,733	$1,243,209	$1,335,463	$1,081,543	$16,208,597
Encounter Physical Health Drugs	$17,757,583	$14,770,692	$14,464,494	$15,261,689	$15,405,186	$15,446,045	$18,414,367	$17,141,000	$17,809,881	$17,489,238	$17,331,247	$16,065,669	$197,357,092
Encounter Physician Administered Drugs	$2,791,297	$3,342,718	$2,716,480	$3,146,636	$2,982,282	$3,467,552	$4,109,033	$3,729,851	$3,655,933	$3,506,758	$4,137,774	$3,399,273	$40,985,587

Quarterly Rebates Invoiced	2012-Q3	2012-Q4	2013-Q1	2013-Q2	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$37,268,783	$25,873,430	$47,019,853	$50,280,799	$203,062,978
CMS MH Carve-out	$10,981,703	$9,980,750	$11,358,595	$11,512,882	$55,802,731
SR MH Carve-out					$0
CMS FFS Drug	$5,189,951	$4,815,767	$4,619,949	$4,246,922	$23,023,574
SR FFS	$231,164	$265,759	$193,166	$135,650	$996,295
CMS Encounter	$20,715,594	$10,709,014	$30,634,759	$34,014,010	$122,274,015
SR Encounter	$150,370	$102,140	$213,385	$371,334	$966,363

Quaterly Net Drug Costs	2012-Q3	2012-Q4	2013-Q1	2013-Q2	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$55,720,530	$64,883,944	$51,330,707	$44,838,954	$204,310,396
Mental Health Carve-Out Drugs	$11,686,034	$11,806,941	$10,729,264	$11,098,932	$56,726,534
FFS Phys Health + PAD	$9,057,195	$8,178,767	$6,589,521	$6,195,408	$32,481,562
Encounter Phys Health + PAD	$34,977,301	$44,898,236	$34,011,922	$27,544,615	$115,102,301

PMPM Drug Costs (Excludes Rebate)	Jul-12	Aug-12	Sep-12	Oct-12	Nov-12	Dec-12	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$53.53	$50.07	$46.44	$50.58	$48.03	$47.77	$55.46	$50.30	$51.92	$51.72	$52.76	$47.61	$50.51
Mental Health Carve-Out Drugs	$12.64	$12.75	$11.10	$12.29	$11.57	$11.15	$12.26	$11.32	$11.72	$12.24	$12.46	$11.36	$12.11
FFS Physical Health Drugs	$34.49	$35.35	$31.11	$35.58	$31.82	$32.26	$37.55	$30.23	$31.38	$31.99	$31.64	$26.95	$31.51
FFS Physician Administered Drugs	$14.34	$16.66	$14.92	$16.67	$16.79	$15.20	$18.64	$13.40	$15.12	$16.57	$17.61	$13.76	$15.81
Encounter Physical Health Drugs	$34.03	$28.21	$27.93	$29.43	$28.87	$28.55	$33.79	$31.42	$32.57	$31.82	$31.51	$29.35	$27.95
Encounter Physician Administered Drugs	$5.35	$6.38	$5.24	$6.07	$5.59	$6.41	$7.54	$6.84	$6.68	$6.38	$7.52	$6.21	$6.35

Drug Use Research & Management Program
DHS - Division of Medical Assistance Programs
500 Summer Street NE, E35, Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Pharmacy Utilization Summary Report: July 2012 - June 2013

Claim Counts	Jul-12	Aug-12	Sep-12	Oct-12	Nov-12	Dec-12	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Avg Monthly
Total Claim Count (FFS & Encounter)	621,362	582,600	565,468	625,433	599,103	594,770	669,691	599,110	617,776	610,697	604,442	557,039	7,247,491
Mental Health Carve-Out Drugs	101,142	103,052	94,620	104,388	99,521	97,378	101,130	91,221	95,707	97,016	97,409	88,581	1,729,031
FFS Physical Health Drugs	79,043	81,377	78,459	88,144	71,174	67,289	70,130	63,309	65,303	65,076	63,196	58,156	1,214,767
FFS Physician Administered Drugs	9,701	9,665	8,875	10,229	8,516	7,751	9,230	8,270	8,158	8,122	8,138	7,407	104,062
Encounter Physical Health Drugs	401,382	358,024	354,508	390,508	386,535	389,654	449,883	402,230	414,130	405,867	399,455	370,624	5,904,629
Encounter Physician Administered Drugs	30,094	30,482	29,006	32,164	33,357	32,698	39,318	34,080	34,478	34,616	36,244	32,271	398,808

Amount Paid per Claim	Jul-12	Aug-12	Sep-12	Oct-12	Nov-12	Dec-12	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Avg Monthly
Average Paid / Claim (FFS & Encounter) (Rebates Excluded)	$53.30	$53.22	$50.98	$50.10	$49.60	$49.88	$51.38	$52.38	$52.60	$52.89	$54.61	$53.48	$52.04
Mental Health Carve-Out Drugs	$77.34	$76.67	$72.86	$73.00	$71.95	$71.11	$75.32	$77.45	$76.64	$78.80	$80.04	$80.30	$78.64
FFS Physical Health Drugs	$42.38	$41.66	$40.91	$40.90	$38.18	$38.53	$40.86	$37.58	$38.03	$36.88	$37.96	$36.43	$38.74
FFS Physician Administered Drugs	$143.53	$165.33	$173.37	$165.15	$168.38	$157.63	$154.14	$127.57	$146.69	$153.07	$164.10	$146.02	$155.41
Encounter Physical Health Drugs	$44.24	$41.26	$40.80	$39.08	$39.85	$39.64	$40.93	$42.61	$43.01	$43.09	$43.39	$43.35	$42.30
Encounter Physician Administered Drugs	$92.75	$109.66	$93.65	$97.83	$89.40	$106.05	$104.51	$109.44	$106.04	$101.30	$114.16	$105.34	$102.51

Amount Paid per Claim - Multi Source Drugs	Jul-12	Aug-12	Sep-12	Oct-12	Nov-12	Dec-12	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Avg Monthly
Multi-Source Drugs: Average Paid / Claim (FFS & Encounter)	$27.05	$24.89	$24.49	$23.33	$23.06	$22.85	$22.36	$22.71	$22.81	$22.85	$22.96	$22.54	$23.48
Mental Health Carve-Out Drugs	$41.50	$40.42	$36.46	$36.34	$34.70	$34.07	$34.96	$35.32	$35.14	$35.86	$36.02	$35.32	$37.14
FFS Physical Health Drugs	$23.17	$22.09	$22.11	$22.20	$20.54	$20.16	$20.46	$19.70	$20.30	$19.89	$20.42	$19.87	$20.73
Encounter Physical Health Drugs	$24.22	$21.12	$21.87	$20.14	$20.58	$20.54	$19.86	$20.38	$20.42	$20.29	$20.25	$19.98	$20.72

Amount Paid per Claim - Single Source Drugs	Jul-12	Aug-12	Sep-12	Oct-12	Nov-12	Dec-12	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Avg Monthly
Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$301.53	$309.12	$292.23	$289.00	$294.78	$293.73	$309.64	$326.93	$335.45	$342.89	$350.49	$352.29	$324.19
Mental Health Carve-Out Drugs	$433.83	$434.84	$435.39	$433.66	$434.36	$434.75	$461.97	$465.27	$462.09	$464.99	$477.04	$484.54	$462.44
FFS Physical Health Drugs	$248.01	$251.38	$242.16	$242.50	$232.17	$238.38	$256.65	$232.18	$233.11	$226.88	$233.82	$223.09	$236.20
Encounter Physical Health Drugs	$274.70	$280.70	$260.26	$255.70	$264.56	$262.62	$278.65	$303.75	$315.82	$324.31	$329.59	$332.07	$299.49

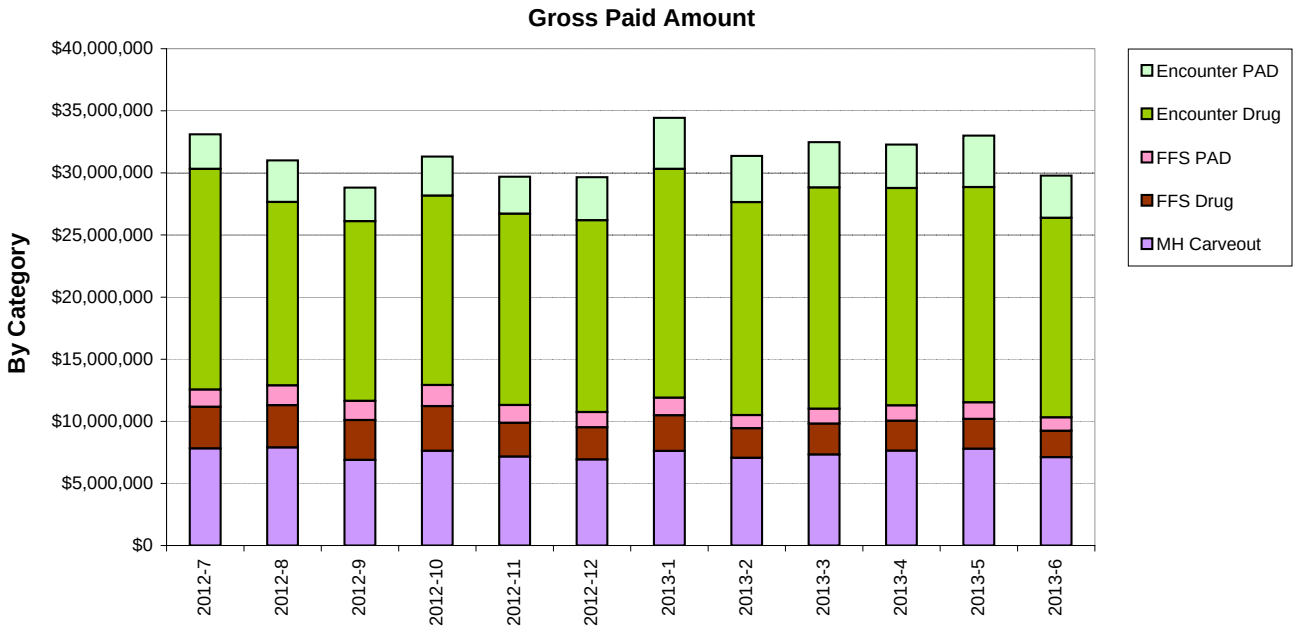
Multi-Source Drug Use Percentage	Jul-12	Aug-12	Sep-12	Oct-12	Nov-12	Dec-12	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Avg Monthly
Multi-Source Drug Use Percentage	91.7%	91.9%	91.8%	91.7%	91.8%	91.8%	91.6%	91.8%	91.9%	92.0%	92.0%	92.0%	91.8%
Mental Health Carve-Out Drugs	90.9%	90.8%	90.9%	90.8%	90.7%	90.8%	90.5%	90.2%	90.3%	90.0%	90.0%	90.0%	90.3%
FFS Physical Health Drugs	91.5%	91.5%	91.5%	91.5%	91.7%	91.6%	91.4%	91.6%	91.7%	91.8%	91.8%	91.9%	91.6%
Encounter Physical Health Drugs	92.0%	92.2%	92.1%	92.0%	92.1%	92.1%	91.9%	92.2%	92.4%	92.5%	92.5%	92.5%	92.2%

Preferred Drug Use Percentage	Jul-12	Aug-12	Sep-12	Oct-12	Nov-12	Dec-12	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Avg Monthly
Preferred Drug Use Percentage	87.35%	87.55%	86.89%	86.86%	86.75%	86.61%	86.91%	86.99%	87.05%	87.05%	84.97%	84.98%	86.3%
Mental Health Carve-Out Drugs	74.47%	73.59%	70.39%	70.28%	70.73%	70.74%	73.03%	73.08%	73.03%	73.04%	71.87%	71.14%	71.8%
FFS Physical Health Drugs	93.94%	94.21%	94.20%	94.12%	93.89%	93.66%	92.39%	92.50%	92.20%	92.29%	91.11%	91.38%	92.5%
Encounter Physical Health Drugs	90.52%	90.16%	90.10%	90.00%	89.81%	89.59%	89.73%	89.84%	90.00%	87.73%	87.89%	87.88%	89.0%

Last Updated: January 27, 2014

Drug Use Research & Management Program
DHS - Division of Medical Assistance Programs
500 Summer Street NE, E35, Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

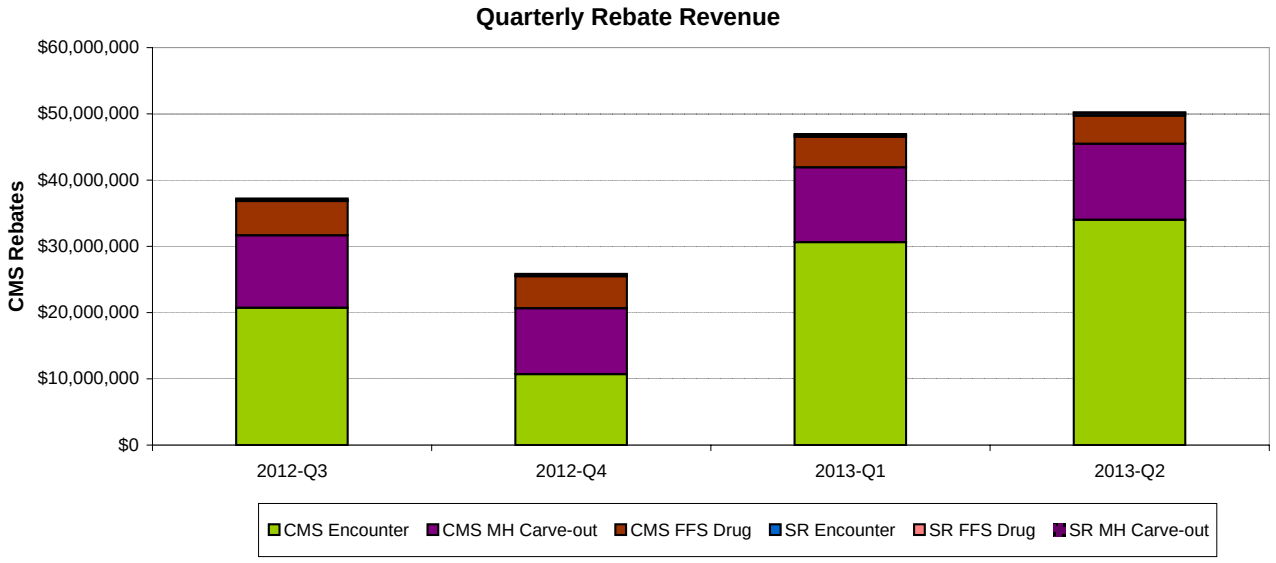
Pharmacy Utilization Summary Report: July 2012 - June 2013

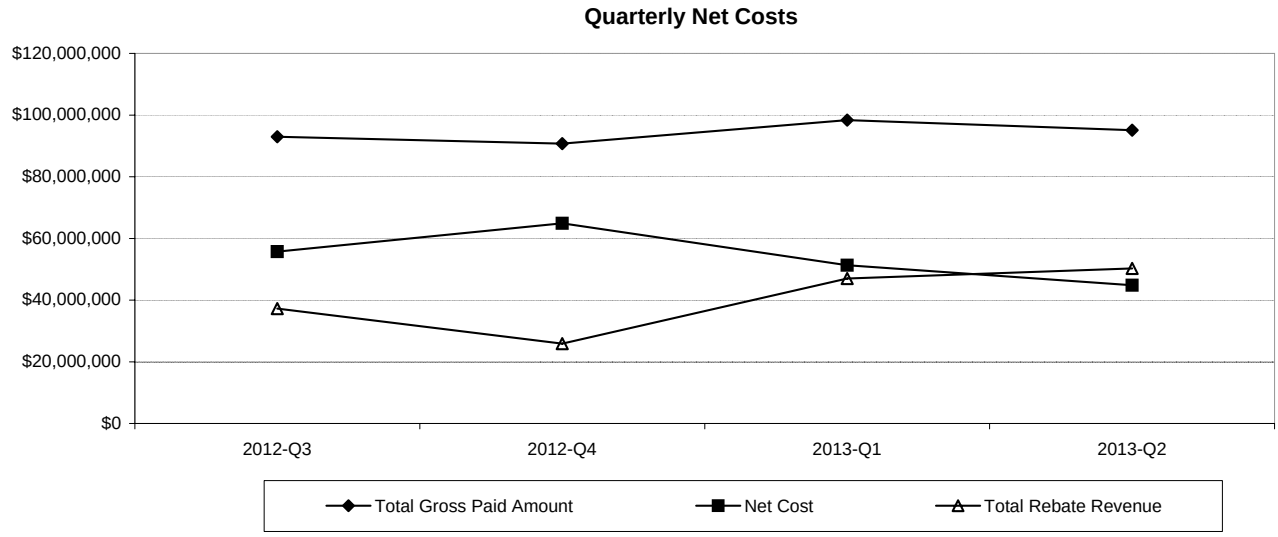


Last Updated: January 27, 2014

Drug Use Research & Management Program
DHS - Division of Medical Assistance Programs
500 Summer Street NE, E35, Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Pharmacy Utilization Summary Report: 2012 Q3 - 2013 Q2





Last Updated: January 27, 2014

Drug Use Research & Management Program
DHS - Division of Medical Assistance Programs
500 Summer Street NE, E35, Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Top 40 Drugs by Gross Amount Paid (FFS Only) - Fourth Quarter 2013

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	ABILIFY	Antipsychotics, 2nd Gen	$6,904,753	21.3%	9,702	$712	V
2	CYMBALTA	Antidepressants - 2nd Gen	$3,117,456	9.6%	11,178	$279	V
3	INTUNIV	ADHD Drugs	$1,245,936	3.8%	5,393	$231	V
4	SEROQUEL XR	Antipsychotics, 2nd Gen	$1,171,693	3.6%	2,349	$499	V
5	STRATTERA	ADHD Drugs	$1,000,068	3.1%	4,255	$235	V
6	INVEGA SUSTENNA	Antipsychotics, 2nd Gen	$803,161	2.5%	623	$1,289	V
7	LATUDA	Antipsychotics, 2nd Gen	$772,273	2.4%	1,211	$638	V
8	DIVALPROEX SODIUM ER	Antiepileptics	$608,061	1.9%	3,039	$200	Y
9	INVEGA	Antipsychotics, 2nd Gen	$575,763	1.8%	751	$767	V
10	ZIPRASIDONE HCL	Antipsychotics, 2nd Gen	$442,278	1.4%	2,851	$155	Y
11	RISPERDAL CONSTA	Antipsychotics, 2nd Gen	$425,050	1.3%	629	$676	V
12	Factor Viii Recombinant Nos	Physican Administered Drug	$424,659	1.3%	14	$30,333	
13	MODAFINIL	ADHD Drugs	$372,966	1.1%	536	$696	V
14	DULOXETINE HCL	Antidepressants - 2nd Gen	$285,667	0.9%	1,239	$231	V
15	SAPHRIS	Antipsychotics, 2nd Gen	$283,050	0.9%	621	$456	V
16	SERTRALINE HCL	Antidepressants - 2nd Gen	$235,759	0.7%	19,960	$12	Y
17	Xyntha Inj	Physican Administered Drug	$221,455	0.7%	7	$31,636	
18	PRISTIQ ER	Antidepressants - 2nd Gen	$218,668	0.7%	1,105	$198	V
19	BUPROPION XL	Antidepressants - 2nd Gen	$217,698	0.7%	7,509	$29	V
20	TRAZODONE HCL	STC 11 - Psychostimulants, Antidepressants	$214,619	0.7%	22,093	$10	
21	LAMOTRIGINE	Antiepileptics	$211,741	0.7%	774	$274	V
22	FLUOXETINE HCL	Antidepressants - 2nd Gen	$210,253	0.6%	17,605	$12	Y
23	CLOZAPINE	Antipsychotics, 2nd Gen	$196,952	0.6%	2,491	$79	Y
24	RISPERIDONE	Antipsychotics, 2nd Gen	$176,014	0.5%	10,150	$17	Y
25	LAMOTRIGINE	Antiepileptics	$173,140	0.5%	12,346	$14	Y
26	QUETIAPINE FUMARATE	Antipsychotics, 2nd Gen	$163,116	0.5%	8,062	$20	Y
27	METHYLPHENIDATE ER	ADHD Drugs	$159,977	0.5%	1,380	$116	N
28	Trastuzumab Injection	Physican Administered Drug	$158,352	0.5%	52	$3,045	
29	BUPROPION HCL SR	Antidepressants - 2nd Gen	$153,359	0.5%	6,437	$24	Y
30	CITALOPRAM HBR	Antidepressants - 2nd Gen	$147,743	0.5%	17,036	$9	Y
31	LANTUS	Insulins	$146,313	0.5%	578	$253	Y
32	VIIBRYD	Antidepressants - 2nd Gen	$141,859	0.4%	895	$159	V
33	LORAZEPAM	Benzodiazepine Anxiolytics	$141,688	0.4%	13,979	$10	
34	PROAIR HFA	Asthma Rescue	$138,633	0.4%	2,752	$50	Y
35	HUMIRA	Targeted Immune Modulators	$137,920	0.4%	62	$2,225	Y
36	CLOMIPRAMINE HCL	STC 11 - Psychostimulants, Antidepressants	$136,778	0.4%	263	$520	Y
37	OLANZAPINE ODT	Antipsychotics, 2nd Gen	$124,428	0.4%	841	$148	V
38	VENLAFAXINE HCL ER	Antidepressants - 2nd Gen	$123,924	0.4%	6,863	$18	Y
39	SYNAGIS	STC 33 - Antivirals	$123,545	0.4%	54	$2,288	
40	DIVALPROEX SODIUM	Antiepileptics	$122,109	0.4%	4,615	$26	Y
		Aggregate	**$32,450,982**		**472,997**	**$262**	

Notes
- FFS Drug Costs only, no rebate excluded
- PDL Key: Y=Preferred, N=Non-Preferred, V=Voluntary, Blank=Non PDL Class

Last updated: January 27, 2014

ProDUR Report for October 2013- December 2013

High Level Summary by DUR Alert

DUR Alert	Disposition	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts
DA (Drug/Allergy Interaction)	Set alert/Pay claim	57	20	0	37	0.07%
DC (Drug/Inferred Disease Interaction)	Set alert/Pay claim	1,219	379	1	837	1.41%
DD (Drug/Drug Interaction)	Set alert/Pay claim	614	200	0	414	0.71%
ER (Early Refill)	**Set alert/Deny claim**	57,889	12,070	39	34,774	66.75%
ID (Ingredient Duplication)	Set alert/Pay claim	14,824	4,102	4	10,709	17.09%
LD (Low Dose)	Set alert/Pay claim	1,023	222	0	798	1.18%
LR (Late Refill/Underutilization)	Set alert/Pay claim	131	91	8	32	0.15%
MC (Drug/Disease Interaction)	Set alert/Pay claim	2,057	850	1	1,187	2.37%
MX (Maximum Duration of Therapy)	Set alert/Pay claim	561	187	0	372	0.65%
PA (Pediatric and Geriatric Age Limits)	Set alert/Pay claim	2	0	0	2	0.00%
PG (Pregnancy/Drug Interaction)	**Set alert/Deny claim**	2,419	1,561	6	841	2.79%
TD (Therapeutic Duplication)	Set alert/Pay claim	5,929	1,872	1	4,050	6.84%
	Totals	**86,725**	**21,554**	**60**	**54,053**	**100.00%**

ProDUR Report for October 2013- December 2013							
Top Drugs in Each DUR Alerts							
DUR Alert	**Drug Name**	**# Alerts**	**# Overrides**	**# Cancellations & Non-Response**	**# Claims Screened**	**% Alerts/Total Claims**	**% Alerts Overridden**
DA	Tramadol	15	4	11	1,260	1.2%	26.7%
	Hydrocodone Bit/APAP	15	2	13	6,024	0.2%	13.3%
	Oxycodone HCl	17	9	8	2,821	0.6%	52.9%
DC	Haloperidol	190	62	128	2,267	8.4%	32.6%
	Wellbutrin (Bupropion)	313	56	257	21,391	1.5%	17.9%
	Diazepam	85	21	64	9,194	0.9%	24.7%
DD	Geodon (Ziprasidone)	393	136	257	4,348	9.0%	34.6%
	Celexa (Citalopram)	41	17	24	23,937	0.2%	41.5%
	Trazodone	32	6	26	29,279	0.1%	18.8%
ER	Lorazepam	1,509	352	1,157	18,808	8.0%	23.3%
	Alprazolam	1,078	198	880	14,504	7.4%	18.4%
	Lamictal (Lamotrigine)	2,309	469	1,840	19,589	11.8%	20.3%
	Abilify (Aripiprazole)	1,860	391	1,469	14,180	13.1%	21.0%
	Risperdal (Risperidone)	2,154	514	1,640	15,354	14.0%	23.9%
	Seroquel (Quetiapine)	2,108	510	1,598	15,301	13.8%	24.2%
	Wellbutrin (Bupropion)	2,047	328	1,719	21,391	9.6%	16.0%
	Zoloft (Sertraline)	3,061	585	2,475	27,015	11.3%	19.1%
	Prozac (Fluoxetine)	2,383	366	2,017	23,876	10.0%	15.4%
	Celexa (Citalopram)	2,125	334	1,791	23,937	8.9%	15.7%
	Trazodone	3,414	612	2,802	29,279	11.7%	17.9%
	Cymbalta (Duloxetine)	1,677	268	1,409	17,989	9.3%	16.0%
ID	Lamictal (Lamotrigine)	899	213	686	19,589	4.6%	23.7%
	Seroquel (Quetiapine)	865	254	611	15,301	5.7%	29.4%
	Risperdal (Risperidone)	815	270	544	15,354	5.3%	33.1%
	Zoloft (Sertraline)	715	200	514	27,015	2.6%	28.0%
	Prozac (Fluoxetine)	644	129	514	23,876	2.7%	20.0%
LD	Trazodone	172	28	144	29,279	0.6%	16.3%
	Intuniv (Guanfacine HCl)	135	23	111	8,010	1.7%	17.0%
	Ergocalciferol (Vitamin D2)	215	48	167	3,963	5.4%	22.3%
LR	Coumadin (Warfarin Sodium)	10	1	9	613	1.6%	10.0%
	Lithium Carbonate	18	17	1	6,134	0.3%	94.4%
	Paxil (Paroxetine)	23	15	8	8,194	0.3%	65.2%
MC	Wellbutrin (Bupropion)	175	40	135	21,391	0.8%	22.9%
	Ibuprofen	253	188	63	3,497	7.2%	74.3%
	Trazodone	164	40	124	29,279	0.6%	24.4%

MX	Haloperidol	47	22	25	396	11.9%	46.8%
	Z-Pack (Azithromycin)	20	7	13	1,652	1.2%	35.0%
	Progesterone, Micronized	29	21	8	133	21.8%	72.4%
PA	Provigil (Modafinil)	2	0	2	807	0.2%	0.0%
PG	Lorazepam	246	194	52	18,808	1.3%	78.9%
	Alprazolam	240	202	38	14,504	1.7%	84.2%
	Ibuprofen	530	391	138	3,497	15.2%	73.8%
TD	Lamictal (Lamotrigine)	404	111	292	19,589	2.1%	27.5%
	Depakote (Divalproex Sodium)	308	101	207	11,413	2.7%	32.8%
	Seroquel (Quetiapine)	488	149	339	15,301	3.2%	30.5%
	Zyprexa (Olanzapine)	447	170	277	9,473	4.7%	38.0%
	Risperdal (Risperidone)	399	143	256	15,354	2.6%	35.8%

ProDUR Report for October 2013- December 2013

Top Drugs in Early Refill- Requirement of Clarification Code began 1/13/2013

DUR Alert	Drug Name	CC-3 Vacation Supply	CC-4 Lost Rx	CC-5 Therapy Change	CC-6 Starter Dose	CC-7 Medically Necessary	CC-14 LTC Leave of Absence
ER	Remeron (Mirtazapine)	6	11	44	3	64	1
	Hydrocodone Bit/APAP	1	3	31	0	21	0
	Oxycodone HCl	3	0	34	2	36	0
	Lorazepam	13	11	113	4	153	0
	Alprazolam	6	12	71	0	65	0
	Diazepam	6	5	52	0	54	0
	Buspar (Buspirone)	2	7	52	0	62	0
	Lamictal (Lamotrigine)	7	14	153	2	176	0
	Depakote (Divalproex Sodium)	8	12	89	4	196	1
	Clonazepam	0	5	18	0	32	0
	Gabapentin	1	4	30	2	16	0
	Abilify (Aripiprazole)	13	14	103	7	176	1
	Seroquel (Quetiapine)	11	15	135	8	211	0
	Risperdal (Risperidone)	7	21	147	5	209	0
	Zyprexa (Olanzapine)	9	14	54	2	133	0
	Geodon (Ziprasidone)	2	5	18	1	60	0
	Albuterol	1	3	10	0	31	0
	Lithium Carbonate	3	4	64	0	63	0
	Wellbutrin (Bupropion)	9	26	62	2	143	0
	Prilosec (Omeprazole)	3	3	17	1	30	0
	Zoloft (Sertraline)	14	27	204	6	188	0
	Celexa (Citalopram)	9	15	85	7	144	0
	Prozac (Fluoxetine)	18	16	119	2	137	0
	Lexapro (Escitaloprim)	6	8	49	3	67	0
	Paxil (Paroxetine)	1	8	29	2	53	0
	Trazodone	18	24	193	8	258	0
	Cymbalta (Duloxetine)	13	12	68	5	101	0
	Effexor (Venlafaxine)	5	5	55	2	57	0
	Amitriptyline	8	13	64	2	71	0
	Straterra (Atomoxetine)	3	6	23	1	34	0
	TOTALS	**206**	**323**	**2186**	**81**	**3041**	**3**

Drug Use Research & Management Program
Oregon State University
500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | Fax 503-947-1119

Retro-DUR Intervention History by Quarter FFY 2013 - 2014

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Apr - Jun
Profile Review	Children under age 12 antipsychotic	Profiles Reviewed	122			
	Children under age 18 on 3 or more psychotropics	Profiles Reviewed	33			
	Children under age 18 on any psychotropic	Profiles Reviewed	195			
	Children under age 6 on any psychotropic	Profiles Reviewed	5			
	Lock-In	Profiles Reviewed	21			
		Letters Sent To Providers	2			
		Provider Responses	0			
		Provider Agreed / Found Info Useful	0			
		Locked In	12			

THE OREGON STATE DRUG REVIEW©
AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug_policy/newsletter
November 2013 Volume 3, Issue 5

Update on the New Oral Anticoagulants with a Focus on Apixaban

By Kathy Sentena, Pharm.D., Oregon State University College of Pharmacy – Drug Use Research and Management Group

Since the approval of dabigatran (Pradaxa®) in 2011, two additional new oral anticoagulants (NOA), rivaroxaban (Xarelto®) and apixaban (Eliquis®), are offered as alternatives to warfarin.[1,2,3,4] All the NOAs are approved by the US Food and Drug Administration (FDA) for use in non-valvular atrial fibrillation (NVAF).[1,2,3] Rivaroxaban is the only NOA which has obtained approval for the additional indications of deep vein thrombosis (DVT) and pulmonary embolism (PE) prophylaxis and treatment. While no direct comparisons between the NOAs have been studied, emerging data, guideline updates and systematic reviews can help to navigate the best options for patients requiring anticoagulation. This review will present the evidence for apixaban and provide guidance on the use of oral anticoagulants.

Apixaban

Apixaban joins rivaroxaban as a factor Xa inhibitor approved to reduce the risk of stroke and systemic embolism in patients with NVAF.[4] Apixaban has also been studied in additional indications, as shown in Table 1.

Table 1 - Summary of Apixaban Studies [5-13]

Primary Endpoint	Results
Atrial Fibrillation	
ARISTOTLE: Apixaban 5 mg twice daily (A5) vs. warfarin (W) (INR 2-3)	
Apixaban superior to warfarin for the incidence of stroke and systemic embolism.	A5 :1.27% / W:1.60% HR: 0.79 (95% CI, 0.66 to 0.95, p= 0.01 for superiority
AVERROES: Apixaban 5 mg twice daily (A5) vs. aspirin 81-324 mg (ASA) daily	
Apixaban superior to aspirin for the incidence of stroke and systemic embolism.	A5: 1.6% / ASA: 3.7% HR: 0.45 (95% CI, 0.32 to 0.62, p<0.001)
Total Knee Replacement Prophylaxis	
ADVANCE-1 & 2: Apixaban 2.5 mg twice daily (A2.5) vs. enoxaparin (E)	
Apixaban inferior to enoxaparin 30mg twice daily (E30) and superior to enoxaparin 40mg daily (E40) for composite endpoints (DVT, non-fatal PE or death from any cause).	Advance-1 A2.5: 9.0% / E30: 8.8% RR 1.02 (95% CI 0.78 to 1.32, p=0.06 for noninferiority) Advance-2 A2.5: 15.1% / E40: 24.4% RR: 0.62 (95% CI 0.51 to 0.74, p<0.0001 for superiority)
Total Hip Replacement Prophylaxis	
ADVANCE-3: Apixaban 2.5 mg twice daily (A2.5) vs. enoxaparin 40 mg daily (E)	
Apixaban superior to enoxaparin for composite endpoints (DVT, non-fatal PE or death from any cause).	A2.5: 1.4% / E: 3.9% RR: 0.36 (95% CI 0.22 to 0.54, p<0.001 for noninferiority and superiority)
Acute Coronary Syndrome	
APPRAISE-2: Apixaban 5 mg twice daily (A5) vs. placebo (P)	
Similar rates of ischemic events in both groups.	A5: 7.5% / P: 7.9% HR: 0.95 (95% CI 0.80 to 1.11, p=0.51)
Prophylaxis in Medically Ill Patients	
ADOPT: Apixaban 2.5 mg twice daily (A2.5) vs. enoxaparin 40mg daily (E)	
Similar rates of death due to a clotting event.	A2.5: 2.71% / E: 3.06% RR: 0.87 (95% CI 0.62 to 1.23, p=0.44)
Treatment of Venous thromboembolism	
AMPLIFY: Apixaban 10mg x 7 days then 5 mg twice daily (A) vs. conventional tx (CT)	
Apixaban non-inferior to conventional tx (enoxaparin + warfarin) for recurrent VTE or death.	A: 2.3% / CT: 2.7% RR: 0.84 (95% CI 0.60 to 1.18, p<0.001)
AMPLIFY-EXT: Apixaban 2.5mg (A2.5) or 5mg (A5) twice daily vs. placebo (P)	
Apixaban doses superior to placebo for recurrent VTE or death from VTE.	A2.5: 0.2% / A5: 0.1% / P: 0.5% A2.5 vs. P: RR 0.49 (95% CI 0.09 to 2.64) A5 vs. P: RR: 0.25 (95% CI 0.03 to 2.24)
Pulmonary embolism-PE, venous thromboembolism-VTE, deep vein thrombosis- DVT, HR-hazard ratio, RR-relative risk	

For the prevention of stroke in patients with NVAF, apixaban was shown to be superior to warfarin (1.3% for apixaban vs.1.6% for warfarin, HR 0.69 [95% CI, 0.66 to 0.95, p=0.01]) for the primary endpoint, which was primarily driven by the reductions in hemorrhagic strokes.[5] All-cause mortality rates were also significantly lower for apixaban. The rate of major bleeding was higher with warfarin (3.1%) compared to apixaban (2.1%).[5] Apixaban was also found to be superior to aspirin (ASA). The applicability of these findings are limited due to 64% of patients having taken 81mg of ASA in the study. ASA 325mg daily has the most robust evidence for stroke prevention.[14]

Off-label Uses

Evidence to support the use of apixaban use in total knee replacement (TKR) prophylaxis is mixed, with data showing inferiority and superiority to enoxaparin (Table 1).[7,8] One study of apixaban use in total hip replacement (THR) prophylaxis shows superiority to enoxaparin[9] Apixaban use in the treatment of venous thromboembolism (VTE) proved to be non-inferior to traditional therapies (enoxaparin and warfarin) with less bleeding.[12] The reduction in ischemic events did not outweigh the increased risk of bleeding with apixaban in patients with acute coronary syndrome (ACS), causing the trial to be stopped early. In patients who are medically ill, apixaban and enoxaparin death rates were similar but treatments were given for different durations.[11]

Role of New Oral Anticoagulants

Studies of NOAs in NVAF have shown apixaban and dabigatran 150mg twice daily to be slightly more effective for the prevention of strokes compared to warfarin.[5,15] The number-needed-to -treat (NNT) to avoid 1 stroke during 1 year of treatment is 167 patients for dabigatran and 303 for apixaban. In the ROCKET-AF trial, rivaroxaban was shown to be non-inferior to warfarin.[16] Dabigatran was the only NOA to decrease both hemorrhagic and ischemic strokes compared to warfarin.[15] Apixaban was the only NOA found to be associated with lower all-cause mortality than warfarin (HR 0.89, (95% CI, 0.80 to 0.998, p=0.047).[5] A systematic review done by the Drug Effectiveness Review Project (DERP) found NOAs to be of similar efficacy for NVAF, based on indirect comparisons.[17] Subgroup analysis found NOAs not to be superior to warfarin, when international normalized ratios (INR) were therapeutic at least 66% of the time.[17] The FDA analysis of the RE-LY data also found warfarin and dabigatran efficacy to be similar in patients with well controlled INRs.[18] The Canadian Agency for Drugs and Technologies in Health (CADTH) recommends NOAs as an option for patients with NVAF if they have a $CHAD_2$ score ≥1and whom are not suitable candidates for warfarin.[19] Guidelines for AF are conflicted, with some preferring NOAs over warfarin, while others recommend NOAs only in patients who aren't suitable for warfarin therapy.[20-22]

In AF studies, the risk of intracranial bleeds are lower with NOAs compared to warfarin, irrespective of INR.[5,15,16] In indirect comparisons, apixaban was associated with less major bleeding than the other NOAs.[17] These findings were repeated when apixaban was directly compared to warfarin.[5] Studies have found less risk of gastrointestinal bleeding (GIB) with warfarin compared to dabigatran and rivaroxaban.[15,16] A systematic review and meta-analysis found an overall increased risk of GIB with the NOAs.[23] Myocardial infarction risk was also less with warfarin compared to dabigatran.[15]

The NOAs have been studied in multiple conditions requiring anticoagulation including orthopedic prophylaxis. The DERP Report found NOAs to have comparable efficacy in reducing the risk of VTEs with no differences in rates of bleeding.[17] Event and bleeding rates in a pooled analysis done by CADTH showed dabigatran and enoxaparin efficacy and bleeding rates to be similar.[24] Rivaroxaban was found to be superior to enoxaparin (40mg daily dose) with comparable rates of bleeding.[24] ACCP guidelines support the use of low molecular weight heparins (LMWH) over NOAs for this indication.[25] For the treatment of acute VTE NOAs were compared to standard care (enoxaparin and vitamin K antagonists) and were found to be non-inferior.[12,26,27]

Rivaroxaban and dabigatran were found to have similar rates of bleeding. Apixaban was shown to have statistically significantly less of the composite outcome of major bleeds and nonmajor bleeds (relative risk, 0.44 (95% CI, 0.36 to 0.55; p<0.001).[12]

New trials are examining the use of NOAs in the extended treatment of VTE.[13,27,28] These studies look at patients who could generally stop therapy but may be at higher risk of VTE recurrence or whom physicians are uncertain about the continuing need for anticoagulation. A study with dabigatran found it to be non-inferior to warfarin but only by a small margin.[28] All the other studies have been placebo comparisons. Apixaban was shown to have no increase risk of bleeding compared to placebo, while the other NOAs were shown to have a higher risk of bleeding.[13,27,28] Appropriate patient selection is important, as patients in these studies were younger and healthier with less risk of recurrent VTE than those seen in other studies.

Considerations

Study limitations and unanswered questions complicate selection of optimal anticoagulation treatment. RE-LY (dabigatran in AF) and EINSTEIN-DVT (rivaroxaban in VTE tx) were open-label studies, which may introduce bias inherent to this study design.[14,27] Rivaroxaban has only been studied in AF patients with a $CHAD_2$ score of ≥2, leaving efficacy in patients with lower $CHAD_2$ scores unknown .[16] Orthopedic prophylaxis studies in patients undergoing TKR have shown NOAs to have inferior efficacy when compared to the US approved enoxaparin doses of 30mg twice daily.[3,29] The inability to monitor the degree of anticoagulation and reverse treatment if necessary is also a concern with NOAs. All NOAs have black box warnings of increased risk of thrombosis upon drug discontinuation. Dabigatran was found to be inferior to warfarin in patients with mechanical heart valves and is therefore not recommended.[23]

Experts believe that without head-to-head studies there is insufficient evidence to recommend one NOA over another. Evidence suggests that NOAs are an appropriate option for oral anticoagulation in some patients. However, careful consideration of the data and patient specific characteristics needs to be taken into account when choosing an anticoagulant regimen. Limited widespread use, lack of long-term evidence, the inability to reverse anticoagulation and relatively small treatment differences, when compared to traditional agents, should not be overlooked.

Peer Reviewed By: Jack McAnulty, MD, Cardiologist, Legacy Health and Colleen Colley, Pharm.D., Anticoagulation Program Manager, Portland VA Medical Center.

References

1. Boehringer Ingelheim Pharmaceuticals, Inc. Pradaxa Label. US Food and Drug Administration. 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022512s016lbl.pdf. Accessed November 12, 2012.
2. Janssen Pharmaceuticals, Inc. Xarelto Label. US Food and Drug Administration. 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022406s001s002s003lbl.pdf. Accessed September 25, 2012
3. Bristol-Meyers Squibb. Eliquis Label. US Food and Drug Administration. 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202155s000lbl.pdf. Accessed September 25, 2012.
4. Bristol-Meyers Squibb. Coumadin Label. US Food and Drug Administration. 2011. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/009218s107lbl.pdf. Accessed September 25, 2013.
5. Granger C, Alexander J, McMurray J, et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med 2011; 365:981-92.
6. Connolly S, Eikelboom J, Joyner C, et al. Apixaban in Patients with Atrial Fibrillation. N Engl J Med. 2011;364:806-817.
7. Lassen M, Raskob G, Gallus A, et al. Apixaban or Enoxaparin for Thromboprophylaxis after Knee Replacement. NEJM 2009; 361 (6):594-604.
8. Lassen M, Raskob G, Gallus A, et al. Apixaban versus Enoxaparin for Thromboprophylaxis after Knee Replacement (ADVANCE-2): a Randomized Double-Blind Trial. The Lancet 2010; 375:807-815.
9. Lassen M, Gallus A, Raskob G, et al. Apixaban versus Enoxaparin for Thromboprophylaxis after Hip Replacement. NEJM 2010; 363 (26):2487-2498.
10. Alexander J, Lopes R, James S, et al. Apixaban with Antiplatelet Therapy after Acute Coronary Syndrome. NEJM 2011; 365 (8):699-708.
11. Goldhaber S, Leizorovicz A, Kakkar A, et al. Apixaban versus Enoxaparin for Thromboprophylaxis in Medically Ill Patients. NEJM 2011; 365 (23):2167-2177.
12. Agnelli G, Buller H, Cohen A, et al. Oral Apixaban for the Treatment of Acute Venous Thromboembolism. NEJM 2013;369:799-808.
13. Agnelli G, Buller H, Cohen A, et al. Apixaban for Extended Treatment of Venous Thromboembolism. NEJM 2012. Epub ahead of print. Available at:www.nejm.org.liboff.ohsu.edu/doi/pdf/10.1056/NEJMoa1207541. Accessed February 1, 2013.
14. American Heart Association. Stroke Prevention in Atrial Fibrillation. Final results. Circulation 1991;84:527-539. Available online at: http://circ.ahajournals.org/content/84/2/527.long. Accessed November 4, 2014.
15. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation (RE-LY). N Engl J Med. 2009;361:1139-51.
16. Patel M, Mahaffey K, Garg J, et al. Rivaroxaban Versus Warfarin In Nonvalvular Atrial Fibrillation. N Engl J Med 2011;365:883-891.
17. Carson S, Selph S, Thakurta S. Summary Review: Newer Oral Anticoagulant Drugs. Final original report. Drug Effectiveness Review Project 2013. Available at http://derp.ohsu.edu/about/final-document-display.cfm.
18. Dabigatran, FDA Center for Drug Evaluation and Research. Summary Review Document. October 19, 2010. Accessed 6/13/11. ww.accessdata.fda.gov/drugsatfda_docs/nda/2010/022512Orig1s000SumR.pdf
19. Canadian Agency for Drugs and Technologies in Health (CADTH). Recommendations for antithrombotic agents for the prevention of stroke and systemic embolism in patients with atrial fibrillation. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health (CADTH); 2013 Mar. 16. Available at: http://www.cadth.ca/media/pdf/TR0003_AntithromboticAgents-AF_RecsReport-e.pdf. Assessed October 7, 2013.
20. Camm A, Lip G, De Canterina R, et al. 2012 Focused Update of the 2010 ESC Guidelines for the Management of Atrial Fibrillation. Eur Heart J 2012;33:2719-2747.
21. Anderson J, Halperin J, Alber N, et al. Management of Patients with Atrial Fibrillation (compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS guideline recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:1935-44.
22. Eikelboom J, Connolly S, Brueckmann M, et al. Dabigatran versus Warfarin in Patients with Mechanical Heart Valves. NEJM 2013;369(13):1206-14.
23. Holster Lisanne, Valkhoff V, Kuipers, et al. New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis. J Gastro 2013;145:105-112.
24. Ndegwa S, Moulton K, Argaez C. Dabigatran or Rivaroxaban Versus Other Anticoagulants for Thromboprophylaxis After Major Orthopedic Surgery: Systematic Review of Comparative Clinical-Effectiveness and Safety. Canadian Agency for Drugs and Technologies in Health. 2009. Available at: http://www.cadth.ca/media/pdf/M0006_Rivaroxaban_and_Dabigatran_L3_e.pdf.
25. Guyatt G, Akl E, Crowther M, et al. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines: Executive Summary. CHEST 2012; 141(2)(Suppl):7S-47S.
26. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009;361(24):2342-52.
27. The EINSTEIN Investigators. Oral Rivaroxaban for the Symptomatic Venous Thromboembolism. NEJM 2010; 363 (26):2499-2510.
28. Schulman S, Kearon C, Kakkar A, et al. Extended use of Dabigatran, Warfarin, or Placebo in Venous Thromboembolism. NEJM 2013;368:709-18.
29. RE-MOBILIZE Writing Committee, Ginsberg JS, Davidson BL, Comp PC et al. Oral thrombin inhibitor dabigatran etexilate vs. North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. J Arthroplasty. 2009;24(1):1-9.

Oregon DUR Board Newsletter Produced by OSU COLLEGE of PHARMACY
DRUG USE RESEARCH & MANAGEMENT
Managing Editor: Kathy Sentena
sentenak@ohsu.edu

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Abbreviated Drug Evaluation: Omega-3 Fatty Acids

Month/Year of Review: November 2013
Generic Name: Omega-3 Fatty Acid
Dossier Received: NA
PDL CLASS: Other Lipid Lowering Agents

End date of literature search: September 30, 2013
Brand Name (Manufacturer): Varies

Research Questions:

- Are omega-3 fatty acids effective in reducing cardiovascular mortality or stroke, cancer prevention, decreasing cognitive decline or as adjunctive therapy for mood disorders such as depression and bipolar?
- Are omega-3 fatty acids safe?
- Are there subpopulations that will benefit from omega-3 fatty acids in terms of effectiveness or harms compared to other therapies for the treatment of cardiovascular conditions, cancer, dementia or mood disorders.
- Is there evidence of improved efficacy or safety of one product over another?

Conclusions:

- There is moderate level evidence from 4 of 5 meta-analyses that omega-3 fatty acids do not reduce cardiovascular events (mostly myocardial infarction, stroke and cardiovascular death) in primary or secondary prevention.[1–5]
- There is moderate level evidence from 3 meta-analyses that omega-3 fatty acids have no significant beneficial effect in controlling atrial fibrillation.[6-8]
- There is low level evidence from 1 meta-analysis[9] omega-3 fatty acids improve cardiac function in patients with chronic heart failure and low level evidence they lower blood pressure.[10]
- There is moderate level evidence from 3 systematic reviews including observational studies that omega-3 fatty acids are of no benefit for cancer prevention.
- There is low level evidence from a Cochrane review that omega-3 fatty acids when used for 6-40 months do not prevent dementia in healthy participants over the age of 60 years who were cognitively healthy.[11]
- There is moderate level evidence of no benefit of omega-3 fatty acids on cognitive function in cognitively healthy older people and patients with Alzheimer's disease but there was a small benefit for immediate recall and attention and processing speed in subjects with cognitive impairment no dementia.[12]
- There is low level evidence that omega-3 fatty acids have mixed results for the treatment of bipolar symptoms[70,71] and depression.[13–15]
- There is moderate level of evidence that omega-3 fatty acids are safe and well tolerated.[2,11,12,16]
- There are numerous dietary fish oil supplements available and the amount of EPA and DHA per serving is highly variable. There are not strong recommendations on which supplements are preferred. Adherence, pill burden, and cost should be considered when choosing appropriate supplements.

Recommendations

- Keep omega-3 fatty acids as non-preferred agent on PDL, requiring the "Non-preferred drugs in PDL classes" prior authorization criteria.
- Consider listing all over-the-counter fish oil products as non-preferred.

Reason for Review:

Omega-3 fatty acids (i.e. fish oil) have been postulated to have a number of beneficial effects in patients at risk for vascular disease, including: 1)the treatment of hypertriglyceridemia, prevention of stroke, sudden cardiac death and heart failure, 2) used as adjunctive therapy for the treatment mood disorders such as major depression and bipolar disorders, 3) prevention of cognitive decline and dementia in Alzheimer's patient and 4) its possible role in cancer prevention. This review will exam the effectiveness and safety of fish oil in above settings by reviewing the high quality meta-analyses, systematic reviews and relevant treatment guidelines.

Background/Current landscape

Omega-3 and omega-6 fatty acids are considered essential fatty acids. They are not endogenously synthesized and must be obtained from the diet. Omega-6 fatty acids include linoleic, gamma-linolenic, and arachidonic acids. The typical Western diet is rich in omega-6 fatty acids due to the abundance of linoleic acid in corn, sunflower, and sunflower oils.[17] Omega-3 fatty acids typically include the long chain eicosapentaenoic (EPA), dicisapentanoic (DPA) and docosahexanoic (DHA), and the plant oil derived alpha linolenic acid (ALA). Omega-3 fatty acids account for only a small percentage of the dietary sources – plants and fish.[18] EPA and DHA are absorbed from the gastrointestinal tract. Consumption of fish oil increases the concentration of EPA and DHA in plasma lipids and membrane phospholipids within days, with maximal incorporation at about two weeks. Increases are dose-dependent but nonlinear, with a larger increase at lower doses and then smaller increments with increasing dose.[19]

The physiologic effects of fish oil occur within weeks of habitual consumption and may result from altered cell membrane fluidity and receptor responses following incorporation of omega-3 fatty acids into cell membranes and direct binding of omega-3 fatty acids to cytosolic receptors that regulate gene transcription. Consequently, this affects metabolic or signaling pathways associated with coronary heart disease, depression, and bipolar disorder.[20–22]

The interest in the therapeutic use of omega-3 fatty acids to prevent and treat cardiovascular disease began after a report showed that high consumption of fish oil in people living in Greenland was associated with a decreased risk of cardiovascular disease.[23] The protective component was suggested to be the long chain n-3 fatty acids consumed in very high amounts as a result of the regular intake of seal meat and whale blubber.[23] Additional epidemiological work has found similar patterns of low cardiovascular disease in populations that consume a diet rich in seafood, in Japan, Norway, Holland, and India.[24–27] However, not all epidemiological studies agree and a meta-analysis of cohort data has found no clear effect of long-chain and shorter-chain n-3 fats (from both fish and vegetable oils) on cardiovascular events.[28] The Gruppo Italiano per lo Studio della Sopravvivenza mell'Infarto (GISSI) – Prevenzion trial of 11,324 patients randomized into a mixture of omega-3 fatty acids EPA and DHA or placebo showed a significant reduction in all cause mortality and death from cardiovascular causes over 3.5 years of follow- ups. However, results from other clinical trials showed conflicting results.[29–31] The most recent large scale randomized controlled trial Rischio and Prevenzione (R & P) Study showed daily treatment with n-3 fatty acids did not reduce cardiovascular mortality and morbidity.[32] Of the 12,513 patients enrolled, 6244 were randomly assigned to n-3 fatty acids and 6269 to placebo. With a median of 5 years of follow-up, the primary end point occurred in 1478 of 12,505 patients included in the analysis (11.8%), of whom 733 of 6239 (11.7%) had received n-3 fatty acids and 745 of 6266 (11.9%) had received placebo (adjusted

hazard ratio with n-3 fatty acids, 0.97; 95% confidence interval, 0.88 to 1.08; P=0.58).[32] Experimental and epidemiological studies indicated that fish oil could improve cardiac function and functional capacity in patients with CHF[33,34] and in prevention of atrial fibrillation (AF).[35,36] However, clinical trials have shown inconsistent results in CHF[37–43] and in preventing postoperative AF.[44–48]

It was observed in migrant studies that changes in food patterns are more often associated with an increased incidence of cancers.[49] Several epidemiological studies have shown a risk reduction of some cancers associated with long chain omega-3 fatty acids or fish intake.[50] A role of fish intake and prostate cancer has been studied in several settings. Populations with a high consumption of fish, such as in populations in Japan and in Alaskan Eskimos, have lower rates of prostate cancer than populations with Western diets, in which fish intake is generally lower.[51,52]

The Epidemiological and animal studies suggested that omega-3 fatty acid could be protective against cognitive decline and dementia. Omega-3 fatty acids constitute 60% of the membrane fatty acids in neurons.[53] An ecological study of diet and Alzheimer's disease[54], and a study in Japanese with Japanese lifestyle had lower rates of cognitive decline[55] suggested that consumption of fish might be protective. While the literature suggests promise, findings have not shown consistent beneficial effects in population examined.

Evidence from ecological, cross-sectional and case-control studies suggest that fish consumption and omega-3 fatty acids intake may affect the prevalence of major depressive disorder (MDD). There is a strong negative correlation between fish consumption and national rates of MDD.[56] Cross-sectional studies have demonstrated higher rates of MDD in individuals who rarely consume fish.[57] Although some randomized clinical studies found positive effects associated with the supplementation, others did not find this benefit. [58–60]

EPA and DHA Products on the Market

There are numerous dietary fish oil supplements available. However they are not regulated by the Food and Drug Administration (FDA). The concentrations of EPA and DHA in omega-3 fatty acid supplements range from a modest level of less than 20% to more than of 80%.[61] Reports regarding the accuracy of the stated amount of EPA and DHA in supplement labels have been inconsistent. There are two FDA approved prescription agents Lovaza® and Vescepa®. Lovaza® contains high-purity omega-3 acid ethyl esters and is FDA approved as adjunctive therapy to diet to reduce very high triglyceride levels (500mg/dL or higher) in adults. Vescepa® is a high-purity form of EPA ethyl ester, like Lovaza® it is indicated as an adjunct to diet to reduce triglyceride levels in adults with severe hyperglyceridemia (500mg/dL or higher). Both of these agents are non-preferred under the Oregon Health Plan and require non-PDL prior authorization criteria due to their use as an alternative to a fibric acid derivative and niacin for hypertriglyceridemia.

Some preliminary evidence suggested that EPA and DHA affects the serum fatty acids and hemodynamics, such as heart rate differently.[62–64] A meta-analysis of randomized placebo-controlled trials of monotherapy with EPA (n=10), DHA (n=17), or EPA versus DHA (n=6) in 2011 examined the effects of EPA versus DHA on serum lipids.[65] The results showed that compared with placebo, DHA raised LDL 7.23 mg/dL (95% CI, 3.98–10.5) whereas EPA non-significantly reduced LDL. In direct comparison studies, DHA raised LDL 4.63 mg/dL (95% CI, 2.15–7.10) more than EPA. Both EPA and DHA reduced triglycerides, with a greater reduction by DHA in direct comparison studies. DHA also raised high-density lipoprotein (4.49 mg/dL; 95% CI, 3.50–5.48) compared with placebo, whereas EPA did not. A More recent exploratory, hypothesis-generating literature review evaluated potentially differential effects of EPA and DHA on LDL, HDL and triglycerides, and non-HDL-C in published studies of omega-3 fatty acid supplementation or prescription omega-3 fatty acid ethyl esters. Placebo-adjusted changes in mean lipid parameters were compared in randomized, controlled trials in subjects treated for ≥ 4 weeks with DHA or EPA. Of 22 studies identified, 6 compared DHA with

EPA directly, 12 studied DHA alone (including 14 DHA-treated groups), and 4 examined EPA alone. In studies directly comparing EPA with DHA, a net increase in LDL-C of 3.3% was observed with DHA (DHA: +2.6%; EPA: -0.7%). In such head-to-head comparative studies, DHA treatment was associated with a net decrease in TG by 6.8% (DHA: -22.4%; EPA: -15.6%); a net increase in non-HDL-C by 1.7% (DHA: -1.2%; EPA -2.9%); and a net increase in HDL-C by 5.9% (DHA: +7.3%; EPA: +1.4%). Increases in LDL-C were also observed in 71% of DHA-alone groups [with demonstrated statistical significance ($P < .05$) in 67% (8 of 12) DHA-alone studies] but not in any EPA-alone studies. Changes in LDL-C significantly correlated with baseline TG for DHA-treated groups. The range of HDL-C increases documented in DHA-alone vs. EPA-alone studies further supports the fact that HDL-C is increased more substantially by DHA than EPA. In total, these findings suggest that DHA-containing supplements or therapies were associated with more significant increases in LDL-C and HDL-C than were EPA-containing supplements or therapies. The authors concluded future prospective, randomized trials are warranted to confirm these preliminary findings, determine the potential effects of these fatty acids on other clinical outcomes, and evaluate the generalizability of the data to larger and more heterogeneous patient populations.[66]

Methods:
A MEDLINE Ovid search was conducted using key words: omega-3 fatty acids, EPA, DHA, cancers, cardiovascular disease, prevention, stroke, hypertension, cardiac outcomes, hyperlipidemia, hypertriglyceridemia, dementia, cognitive function, Alzheimer's disease, depression, bipolar disorder, and psychiatric disorders. The search was limited to meta-analysis, systematic reviews in English language, and to studies conducted in humans in the last ten years. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, Oregon Evidence-based Practice Center, National Institute for Health and Clinical Excellence (NICE), and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality and relevant systematic reviews. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

Systematic Reviews: (See Appendix A for Abstract)

<u>Cardiovascular Disease</u>
The effect of omega-3 fatty acids was most studied in cardiovascular (CV) disease. Below is the summary of the most recent systematic review and meta-analyses on its effect on the overall CV outcomes and selected CV events related to heart failure, arrhythmias including atrial fibrillation, stroke and hypertension.

Overall Cardiovascular Disease (CVD) Outcomes
Kotwal et al.[2]published a meta-analysis in 2012 that examined the effects of omega-3 fatty acids on cardiovascular and other important outcomes. The authors reviewed the randomized controlled trials using dietary supplements, dietary interventions or both. The primary outcome was a composite of cardiovascular events (mostly myocardial infarction, stroke, and cardiovascular death). Secondary outcomes were arrhythmia, cerebrovascular events, hemorrhagic stroke, ischemic stroke, coronary revascularization, heart failure, total mortality, nonvascular mortality, and end-stage kidney disease. Twenty studies including 63,030 participants were included. There was no overall effect of Omega-3 fatty acids on composite cardiovascular events (relative risk [RR]=0.96; 95% confidence interval [CI], 0.90-1.03; P=0.24) or on total mortality (RR=0.95; 95% CI, 0.86-1.04; P=0.28). Omega-3 fatty acids did protect against vascular death (RR=0.86; 95% CI, 0.75-0.99; P=0.03), but not coronary events (RR=0.86; 95% CI, 0.67-1.11; P=0.24). There was no effect on arrhythmia (RR=0.99; 95% CI, 0.85-1.16; P=0.92) or cerebrovascular events (RR=1.03; 95% CI, 0.92-1.16; P=0.59). Adverse events were more common in the treatment group than the placebo group (RR=1.18, 95% CI, 1.02-1.37; P=0.03), predominantly because of an excess of gastrointestinal side effects. A key strength of this overview is the attempt to extract data on all

commonly reported vascular outcomes from all trials and to systematically report the summary estimates of effect in each case. However, the reporting of outcomes across studies is inconsistent and in part because there is significant heterogeneity between the trials' results for several of the outcomes studied. The authors acknowledge the heterogeneity may also contribute to the absence of positive findings in this meta-analysis. They concluded that the beneficial effects of omega 3 fatty acids are not as large as previously implied and recommendations for widespread use should be tempered.

Kwak SM et al.[4] conducted a meta-analysis on the effects of omega-fatty acids in the secondary prevention of CV disease. The analysis included 14 randomized, double-blind, placebo-controlled trials involving 20,485 patients with a history of CVD. Supplementation with omega-3 fatty acids did not reduce the risk of overall cardiovascular events (relative risk, 0.99; 95% CI, 0.89-1.09; I^2 = 27.1%), all-cause mortality, sudden cardiac death, myocardial infarction, congestive heart failure, or transient ischemic attack and stroke. There was a small reduction in cardiovascular death (relative risk, 0.91; 95% CI, 0.84-0.99), which disappeared when a study with major methodological problems was excluded. Furthermore, no significant preventive effect was observed in subgroup analyses by the following: country location, inland or coastal geographic area, history of CVD, concomitant medication use, type of placebo material in the trial, methodological quality of the trial, duration of treatment, dosage of eicosapentaenoic acid or docosahexaenoic acid, or use of fish oil supplementation only as treatment. This analysis showed moderate evidence of no secondary preventive effect of omega-3 fatty acid supplements against overall CV events among patients with a history of CV disease.

Similar results were observed by another recent meta-analysis conducted by Rizois EC et al.[5] The analysis included 20 randomized clinical trials with total of 68,680 patients. There were 7,044 reported deaths in these trials, 3,993 cardiac deaths, 1,150 sudden deaths, 1,837 myocardial infarctions, and 1,490 strokes. No statistically significant association was observed with all-cause mortality (RR, 0.96; 95% CI, 0.91 to 1.02; p = 0.17;I^2 = 12%; risk reduction [RD] -0.004, 95% CI, -0.01 to 0.02; p = 0.19; I^2 = 38%), cardiac death (RR, 0.91; 95% CI, 0.85 to 0.98; p = 0.01; I^2 = 6%) and a non-significant absolute risk reduction of -0.01(95% CI, -0.02 to 0.00; p = 0.09; I^2 = 78%), sudden death (RR, 0.87; 95% CI, 0.75 to 1.01; RD, -0.003; 95% CI, -0.012 to 0.006), myocardial infarction (RR, 0.89; 95% CI, 0.76 to 1.04; RD, -0.002; 95% CI, -0.007 to 0.002), and stroke (RR, 1.05; 95% CI, 0.93 to 1.18; RD, 0.001; 95% CI, -0.002 to 0.004) when all supplement studies were considered. Omega-3 fatty acids are not statistically significantly associated with major cardiovascular outcomes across various patient populations. The authors concluded the findings from this analysis do not justify the use of omega-3 fatty acids as a structured intervention in everyday clinical practice or guidelines supporting dietary omega-3 fatty acids administration.

Unlike three meta-analyses mentioned above, another recent meta-analysis by Delgado-Lista J et al.[3] showed different findings on several endpoints compared with the above analyses. This meta-analysis included clinical trials and randomized controlled trials of omega-3 fatty acids either in capsules or in dietary intake, compared to placebo or usual diet, equal to or longer than 6 months, and written in English. Most of the studies analyzed included persons with high cardiovascular risk. The primary outcome was a cardiovascular event of any kind and secondary outcomes were all-cause mortality, cardiac death and coronary events. The analysis included 21 of the 452 pre-selected studies. The results showed an overall decrease of risk of suffering a cardiovascular event (N = 45,285) of any kind of 10 % (OR 0·90; [0·85-0·96], p = 0·001; I^2 = 53%), a 9 % decrease of risk of cardiac death (OR 0·91; [0·83-0·99]; p = 0·03; I^2 = 32%), a decrease of coronary events (fatal and non-fatal) of 18 % (OR 0·82; [0·75-0·90]; $p < 1 \times 10^{-4}$;I^2 0%), and a trend to lower total mortality (5 % reduction of risk; OR 0·95; [0·89-1·02]; p = 0·15. Based on these findings, the authors concluded marine omega-3 fatty acids are effective in preventing cardiovascular events, cardiac death and coronary events, especially in persons with high cardiovascular risk. However, the trials included for various endpoints with exception of coronary events all showed heterogeneity. Results should be interpreted with caution.

Arrhythmias

Leon H et al.[6] conducted a meta-analysis focusing on the effects of fish oil (DHA and EPA) on mortality and arrhythmias and explore dose response and formulation effects. The primary outcomes of interest were the arrhythmic end points of appropriate implantable cardiac defibrillator intervention and sudden cardiac death. The secondary outcomes were all cause mortality and death from cardiac causes. Subgroup analyses included the effect of formulations of EPA and DHA on death from cardiac causes and effects of fish oil in patients with coronary artery disease or myocardial infarction. 12 studies totaling 32,779 patients met the inclusion criteria. A neutral effect was reported in three studies (n=1,148) for appropriate implantable cardiac defibrillator intervention (odds ratio (OR) 0.90, 95% confidence interval (CI) 0.55 to 1.46) and in six studies (n=31,111) for sudden cardiac death (0.81, 0.52 to 1.25). 11 studies (n=32,439 and n=32,519) provided data on the effects of fish oil on all cause mortality (OR: 0.92; CI: 0.82 to 1.03) and a reduction in deaths from cardiac causes (OR: 0.80; CI: 0.69 to 0.92). The dose-response relation for DHA and EPA on reduction in deaths from cardiac causes was not significant. The conclusions from the analysis were that fish oil supplementation was associated with a significant reduction in deaths from cardiac causes but had no effect on arrhythmias or all cause mortality. Evidence to recommend an optimal formulation of EPA or DHA to reduce these outcomes is insufficient. Fish oils are a heterogeneous product, and the optimal formulations for DHA and EPA remain unclear.

Liu T et al[7] reviewed the role of omega-3 fatty acids in AF prevention. This meta-analysis included 10 randomized clinical trials with total of 1,955 patients. The results showed omega-3 fatty acids had no significant effect on the prevention of AF (OR 0.81, 95% CI 0.57 to 1.15; p=0.24). There was significant heterogeneity among the studies (p=0.002, I^2=65.0%). Subgroup analysis showed no significant beneficial effect of fish oils in any subset of population.

Armaganijan L et al.[8] conducted meta-analysis to examine the role of omega-3 fatty acids preventing AF after open heart surgery. Four randomized studies (3 double blind, one open-label) that enrolled 538 patients were identified. The use of omega-3 fatty acids was not associated with a reduction in the occurrence of postoperative AF in the patients undergoing cardiac surgery compared to the untreated patients (odds ratio, 0.79; 95% confidence interval, 0.56 - 1.13; p = 0.195). Similar results were observed when the open-label study was excluded from the analyses (odds ratio, 0.99; 95% confidence interval, 0.65 - 1.49; p = 0.963).

Chronic Heart Failure (CHF)

Xin W et al.[9] published a meta-analysis to evaluate effects fish oil on cardiac function and related parameters in CHF patients. Randomised controlled trials of fish oil supplementation on cardiac function in patients with CHF were identified. Seven trials with 825 participants were included. Meta-analysis results showed that left ventricular ejection fraction was significantly increased (weighted mean difference (WMD) = 2.25%, 95% CI 0.66 to 3.83, p = 0.005) and left ventricular end-systolic volume was significantly decreased (WMD = 7.85 ml, 95% CI -15.57 to -0.12, p = 0.05) in the fish oil group compared with the placebo group, although left ventricular end-diastolic volume was not significantly affected. Meta-regression and subgroup analysis indicated that the improvement in left ventricular systolic function was more remarkable in patients with non-ischemic heart failure. Fish oil supplementation also improved the New York Heart Association functional classification and peak oxygen consumption in patients with non-ischemic heart failure. Although this analysis suggested that improvements in cardiac function, remodeling and functional capacity may be important mechanisms underlying the potential therapeutic role of fish oil for patients with CHF and these effects might be more remarkable in patients with non-ischemic heart failure, it was noted that the number of studies and patients included in this analysis was small, the results of estimations should be interpreted with caution.

Hypertension

Campell F et al.[10] in 2012 published a meta-analysis that reviewed the randomized controlled trials and crossover trials that evaluated the effectiveness of fish oil supplements in lowering blood pressure. The analysis included trials enrolling adults who were given fish oil supplements with at least 8 weeks' follow-up. There were 17 studies with a total of 1,524 participants were included in the analysis. The analysis examined the effects of fish oil supplements in both normotensive and hypertensive participants with blood pressure of 140/85 mmHg at least. Meta-analysis was performed using the inverse-variance method. Data from eight studies in hypertensive participants found a statistically significant reduction in systolic and diastolic BP; 2.56 mmHg (95% CI 0.58 to 4.53) and 1.47 mmHg (95% CI 0.41 to 2.53), respectively. Nine studies in normotensive participants showed a non-significant reduction in both systolic and diastolic BP. Meta-regression showed no significant relationship between dose of fish oil and the effect on blood pressure. The analysis concluded the small but statistically significant effects of fish-oil supplements in hypertensive participants in this review have important implications for population health and lowering the risk of stroke and ischemic heart disease. Their modest effects, however, mean that they should not be recommended as an alternative to BP-lowering drugs where guidelines recommend treatment.

Stroke

Larsson SC et al.[1] conducted a meta-analysis of prospective studies to summarize available evidence regarding the relation between long-chain omega-3 fatty acids intake and stroke. Prospective studies that provided relative risks (RRs) with 95 % confidence intervals (CIs) for the association between dietary long-chain omega-3 fatty acids intake and stroke were eligible. A random-effects model was used to combine study-specific results. Eight prospective studies, with 5,238 stroke events among 242,076 participants, were included in the meta-analysis. The combined RR of total stroke was 0.90 (95 % CI, 0.81-1.01) for the highest versus lowest category of long-chain omega-3 fatty acids intake, without heterogeneity among studies (P = 0.32). Results were similar for ischemic (RR, 0.82; 95 % CI, 0.71-0.94) and hemorrhagic stroke (RR, 0.80; 95 % CI, 0.55-1.15). A statistically significant reduction in total stroke risk was observed in women (RR, 0.80; 95 % CI, 0.65-0.99). This meta-analysis showed no overall association between omega-3 fatty acids intake and stroke, but suggests that women might benefit from a higher intake of these PUFAs.

<u>Cancer</u>

Gerber M[67] published an updated systematic review in 2012 on omega-3 fatty acids and cancers. The review included all prospective and case-control observational studies since the ones reported in the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) expert consultation. Studies included in this review were prospective and case-control observational studies, intervention studies and randomised controlled trials were also considered. The specific validity criteria and evaluation of the level of evidence were defined in the review. The author concluded a probable level of evidence that fish oil is neither a risk factor nor a beneficial factor with regards to cancers. Observational studies on colorectal, prostate and breast cancers only provided limited evidence suggesting a possible role of fish oil in cancer prevention due to insufficient homogeneity of the observations.

Additionally Szmanski KM et. al.[68] performed a meta-analysis on fish intake and prostate cancer by focusing on the incidence of prostate cancer and prostate cancer-specific mortality and included subgroup analyses based on race, fish type, method of fish preparation, and high-grade and high stage cancer. Case-control and cohort studies were included in the analysis. The results showed no association between fish consumption and a significant reduction in prostate cancer incidence based on 12 case-control studies (n = 5,777cases and 9,805 control subjects), odds ratio: 0.85; 95% CI: 0.90, 1.14). The meta-analysis was not performed on high-grade disease, locally advanced disease and metastatic disease due to only one case-control study available for each subgroup. However,

there was an association between fish consumption and a significant 63% reduction in prostate cancer-specific mortality based on 4 cohort studies (n= 49,661, RR: 0.37; 95 CI: 0.18, 0.74). The authors concluded that there was no strong evidence of protective association of fish consumption with prostate cancer incidence but there is a significant 63% reduction on prostate cancer-specific mortality. The analysis was based on cohort case-control studies not randomized control clinical trials.

Ries A et al[16] also examines the role of fish oil in patients with cachexia due to advanced cancer. The analysis included only clinical studies and systematic reviews evaluating clinical studies. There were three systematic reviews included, 10 controlled trials, 11 uncontrolled/case series included in the review. Two out three systematic reviews found no clear advantage of treatment with fish oil; four of the six-high-quality randomized controlled trials found no significant benefit from fish oil supplementation. The authors concluded insufficient evidence to support a net benefit of fish oil in cachexic patients with advanced cancer. However, adverse effects were infrequent with no severe adverse effects.

Cognitive Function and Dementia

Cochrane Review[11] *(2012)*
The authors of this review included studies where healthy participants over the age of 60 years who were cognitively healthy at the start of the study were randomly assigned to receive extra omega-3 fatty acids in their diet or a placebo (such as olive oil).Three randomized clinical trials were included in the analysis. Information on cognitive function at the start of a study was available on 4,080 participants randomised in three trials. Cognitive function data were available on 3,536 participants at final follow-up. In two studies participants received gel capsules containing either omega-3 fatty acids (the intervention) or olive or sunflower oil (placebo) for six or 24 months. In one study, participants received margarine spread for 40 months; the margarine for the intervention group contained omega-3 fatty acids. Two studies had cognitive health as their primary outcome; one study of cardiovascular disease included cognitive health as an additional outcome. None of the studies examined the effect of omega-3 fatty acids on incident dementia. In two studies involving 3,221 participants there was no difference between the omega-3 and placebo group in mini-mental state examination score at final follow-up (following 24 or 40 months of intervention); MD-0.07 (95%CI -0.25 to 0.10). In two studies involving 1043 participants, other tests of cognitive function such as word learning, digit span and verbal fluency showed no beneficial effect of omega-3 fatty acids supplementation. Participants in both the intervention and control groups experienced either small or no cognitive declines during the studies.
The main reported side-effect of omega-3 fatty acids supplementation was mild gastrointestinal problems. Overall, minor adverse events were reported by fewer than 15%of participants, and reports were balanced between intervention groups. Adherence to the intervention was on average over 90% among people who completed the trials. All three studies included in this review are of high methodological quality. The review concluded evidence on the effect of omega-3 fatty acids on incident dementia is lacking. The available trials showed no benefit of omega-3 fatty acids supplementation on cognitive function in cognitively healthy older people. Omega-3 fatty acids supplementation is generally well tolerated with the most commonly reported side-effect being mild gastrointestinal problems.
The authors suggested further studies of longer duration are required. Longer-term studies may identify greater change in cognitive function in study participants which may enhance the ability to detect the possible effects of omega-3 fatty acids supplementation in preventing cognitive decline in older people.

The above Cochrane review only included the healthy elderly patients. Alternatively Mazereeuw G et al.[12] conducted a meta-analysis examined the neuropsychological benefit of omega-3 fatty acids in randomized double-blinded placebo-controlled studies including healthy, cognitive impairment no

dementia (CIND), or Alzheimer's Disease (AD) subjects. Ten randomized clinical trials were combined quantitatively. Treatment effects were summarized across cognitive sub-domains, and effect sizes were estimated using Hedge's g and random effects modeling. All of the included studies scored above the suggested cutoff for high quality (5 points) according to the PEDro scale. Scores ranged from 6 to 10 with a mean of 8.85. Hedge's g was used to represent effect sizes between treatment and placebo groups for continuous neuropsychological outcomes in each study. The results suggested no effect of omega-3 fatty acids on composite memory (g = 0.04 [95% CI: -0.06 – 0.14], N = 934/812, *p* = 0.452). When examined by domain, no overall benefit for immediate recall (0.04 [-0.05 – 0.13], N = 934/812, *p* = 0.358) was detected; however, an effect in CIND subjects (0.16 [0.01 – 0.31], N= 349/327, *p* = 0.034) was found. A benefit for attention and processing speed was also detected in CIND (0.30 [0.02 – 0.57], N = 107/86, *p* = 0.035), but not healthy subjects. Benefits for delayed recall, recognition memory, or working memory and executive function were not observed. Treatment did not benefit AD patients as measured by the Mini-Mental State Examination (MMSE) or Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS–cog). No differences in adverse events (AE), dropout, or dropout due to AE between groups were observed. The authors concluded omega-3 fatty acid treatment was associated with a small, but significant benefit for immediate recall and attention and processing speed in subjects with CIND but not in healthy subjects or those with AD. There was high degree of safety and tolerability observed in these RTCs. However the findings suggest the effects of omega-3 fatty acids on cognitive decline are not uniform, and that there is a need to identify potentially responsive populations.

Psychiatric Disorders

In 2012 Ortega RM et al[69] conducted a systematic review of effects of omega-3 fatty acids supplementation in behavior and non-neurodegenerative neuropsychiatric disorders. The review included 38 published randomized, controlled clinical trials up to April 2011. There were 23 studies examined the influence of omega-3 fatty acid supplementation on the prevention /treatment of depression, 6 on perinatal depression and 9 were on attention deficit hyperactivity disorder (ADHD). Great heterogeneity was noticed in terms of study design, sample size, the doses of omega-3 fatty acids and study duration. Some benefit was noted with respect to the treatment of hyperactivity and depression in over half the examined studies, although the evidence was not conclusive. For any firm conclusions to be drawn, further studies will be needed that take into account the initial omega-3 fatty acids status of the subjects.

Bipolar Disorder

Sarris J et al.[70] published a review article in 2011 that examined the clinical trials using nutrient-based nutraceuticals, such as omega-3 fatty acids, N-acetyl cysteine, inositol, and vitamins and minerals in combination with standard pharmacotherapies to treat bipolar disorder (BD). Specifically for omega-3 fatty acids, the review included 9 clinical trials. Seven were randomized, double blinded and placebo controlled design with total 341 patients. Study duration ranges between 4 to 16 weeks. Only three out of seven RCTs showed omega-3 fatty acids statistically positive results on depression. No omega-3 study revealed a statistically significant finding on the outcome of mania. The meta-analytic comparison between DHA and EPA found that DHA monotherapy was not significant, whereas in studies using supplements containing greater than 50% EPA, a significant effect occurred in favor of omega-3 [standardized mean difference = 0.446; 95%confidence interval (CI): 0.753 to 0.138; z =2.843; p = 0.005]. The authors acknowledge that limitation specific to this review is that a meta-analysis could not be conducted as the varied types of nutraceuticals covered in this review provide too much heterogeneity. Caution should be extended in interpreting the large effects of several isolated studies, as they have not yet been replicated in larger trials.

In 2006 Turnbull et al.[71] reviewed the level of evidence regarding the efficacy of omega-3 fatty acid supplementation in improving bipolar disorder symptoms. Of 99 articles meeting initial search criteria, 5 randomized control trials and 2 quasi-experimental studies were selected for review. Omega-3 fatty acid

supplementation was effective in 4 of 7 studies. Those using an omega-3 combination of eicosapentaenoic acid and docosahexanoic acid demonstrated a statistically significant improvement in bipolar symptoms, whereas those using a single constituent did not. Dosage variations did not demonstrate statistically significant differences. The authors concluded due to its benign side effect profile and some evidence supporting its usefulness in bipolar illness, omega-3 may be a helpful adjunct in treatment of selected patients. Future studies are needed to conclusively confirm the efficacy of omega-3 fatty acids in bipolar disorder, uncovering a new well-tolerated treatment option. It was noted five studies had a sample size less than 45. In two of the seven studies, nearly 50% of the participants failed to complete the trial, thereby diminishing confidence in study outcomes. Of these two studies, only one performed an ITT analysis; neither found a significant reduction in symptoms. Due to major concern of internal validity of the review studies, specifically small sample size and high level of attrition rate, the conclusion should be interpreted with caution.

Depression

There are several meta-analyses were published in the past decade.[13–15] The most recent one was conducted by Bloch MH et. al[13] in 2012. This review included randomized, placebo-controlled trials of omega-3 fatty acid treatment of major depressive disorder. Review's primary outcome measure was standardized mean difference in a clinical measure of depression severity. In stratified meta-analysis, the review examined the effects of trial duration, trial methodological quality, baseline depression severity, diagnostic indication, dose of eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA) in omega-3 preparations, and whether omega-3 fatty acids was given as monotherapy or augmentation. In 13 randomized, placebo-controlled trials examining the efficacy of omega-3 fatty acids involving 731 participants, meta-analysis demonstrated no significant benefit of omega-3 fatty acids treatment compared with placebo (standard mean difference (SMD) = 0.11, 95% confidence interval (CI): 0.04, 0.26). Meta-analysis demonstrated significant heterogeneity and publication bias. Nearly all evidence of omega-3 benefit was removed after adjusting for publication bias using the trim-and-fill method (SMD = 0.01, 95% CI: 0.13, 0.15). Secondary analyses suggested a trend toward increased efficacy of omega-3 fatty acids in trials of lower methodological quality, trials of shorter duration, trials which utilized completers rather than intention-to-treat analysis, and trials in which study participants had greater baseline depression severity. Current published trials suggest a small, non-significant benefit of omega-3 fatty acids for major depression. Nearly all of the treatment efficacy observed in the published literature may be attributable to publication bias. The authors concluded that although there is still strong evidence based on the epidemiological and cellular literature that omega-3/omega-6 fatty acids balance may have an important role in the pathogenesis of depression, there is limited evidence for omega-3 fatty acids supplementation being an effective acute treatment for it.

Earlier meta-analysis by Sublette ME et al.[14] in 2011 on omega-3 fatty acids in treatment of depression reviewed 15 randomized clinical trials involving 916 participants. The results indicated that supplements with EPA ≥ 60% showed benefit on standardized mean depression scores (effect size = 0.532; 95% CI, 0.277–0.733; t = 4.195; P < .001) versus supplements with EPA < 60% (effect size = −0.026; 95% CI, −0.200 to 0.148; t = −0.316; P = .756), with negligible contribution of random effects or heteroscedasticity and with no effects of treatment duration or age. Supplements with EPA < 60% were ineffective. Exploratory analyses supported a nonlinear model, with improvement determined by the dose of EPA in excess of DHA, within the range of 200 to 2,200 mg/d of EPA. The authors concluded supplements containing EPA ≥ 60% of total EPA + DHA, in a dose range of 200 to 2,200 mg/d of EPA in excess of DHA, were effective against primary depression. Translational studies are needed to determine the mechanisms of EPA's therapeutic benefit. Several limitations were noted by the authors: 1) the number of potential moderators examined was limited by considerations of statistical power and inconsistent information in the source articles; 2) unexamined covariates that might be relevant include baseline level of depression, presence of stabilizing antioxidant in the supplement, response by sex or ethnicity, baseline plasma PUFA levels, and dietary intakes; 3) the selection of a diagnostic phenotype for study was limited by the relatively small number of clinical trials

primarily focusing on depression, and by a lack of diagnostic clarity in some of the studies. Thus no inferences can be made about depressive episodes occurring within Major Depressive Disorder as opposed to Bipolar Disorder.

Similarly Appleton KM et al.[15] conducted a systematic review and meta-analysis on effects of omega-3 fatty acids in treatment of depressed mood. Thirty-five randomized controlled trials were identified, and twenty-nine were included in the meta-analyses. The pooled standardized difference in mean outcome of the 29 trials that provided data to allow pooling (fixed-effects model) was 0.10 SD (95% CI: 0.02, 0.17) in those who received omega-3 fatty acids compared with placebo, with strong evidence of heterogeneity (I^2 = 65%, P < 0.01). The presence of funnel plot asymmetry suggested that publication bias was a likely source of this heterogeneity. Depressive symptom severity and participant diagnosis also explained some of the observed heterogeneity. Greater effects of omega-3 fatty acids were found in individuals with more-severe depressive symptoms. In trials that enrolled individuals with a diagnosed depressive disorder, the combined mean difference was 0.41 (95% CI: 0.26, 0.55), although evidence of heterogeneity was also found (I^2= 71%). In trials that enrolled individuals without a depressive diagnosis, no beneficial effects of omega-3 fatty acids were found (largest combined mean difference: 0.22; 95% CI: -0.01, 0.44; I^2= 0%). In summary, although trial evidence of the effects of omega-3 fatty acids on depressed mood has increased but remains difficult to summarize because of considerable heterogeneity. The evidence available provides some support of a benefit of omega-3 fatty acids in individuals with diagnosed depressive illness but no evidence of any benefit in individuals without a diagnosis of depressive illness.

Treatment Guidelines

The European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of Acute and Chronic Heart Failure 2012 listed omega-3 fatty acids as one of the recommended treatments for potentially all patients with systolic heart failure.[72] The guidelines did recognize evidence of omega-3 fatty acids after myocardial infarction is uncertain. The small treatment effect of omega-3 fatty acids was based on the Gruppo Italiano per lo Studio della Sopravvivenza mell'Infarto micocardico-heart failure (GISSI-HF)[73] trial was only detected after covariate adjustment in the statistical analysis and there was no effect on HF hospitalization. In addition, the guidelines for specialized nutritional and metabolic support in the critically – ill patients in Spain also recommended administer at least 1gm/day EPA plus DHC (level C) in patients with acute coronary syndrome who require enteral nutrition.[74]

American Heart Association (AHA) published a scientific statement on Triglyceride and Cardiovascular disease in May 2011.[75] The statement stated "As monotherapy, fibrates offer the most TG reduction, followed by immediate-release niacin, omega-3 methyl esters, extended-release niacin, statins, and ezetimibe". It recommends 2 to 4 grams of eicosapentaenoic acid (EPA) plus docosahexanoic acid (DHA) per day for patients who need to lower their TG level.

Canadian Network for Mood and Anxiety Treatment (CANMAT) Clinical guidelines for the management of major depressive disorder in adults under section "Complementary and alternative medicine treatments"[76] has Level 1 recommendation of using omega-3 fatty acids as second line monotherapy and adjunctive therapy in patients with mild to moderate severity of major depressive disorder in 2009.

In November of 2013, the American Heart Association (AHA) and the American College of Cardiology (ACC) released four clinical practice guidelines for the prevention of CV disease.[77] . The objective of the second guideline was to update the clinical practice recommendations for the treatment of blood cholesterol levels to reduce atherosclerotic cardiovascular disease (ASCVD) risk using data from RCTs and systematic reviews. The panel could find no data supporting the routine use of nonstatin drugs combined with statin therapy to reduce further coronary events. There were no RCTs that assessed clinical outcomes in statin-

intolerant patients. It was recommended based on expert opinion only that: Clinicians treating high-risk patients who have a less than anticipated response to statins, who are unable to tolerate a recommended intensity of a statin, or who are completely statin intolerant may consider the addition of a nonstatin cholesterol-lowering therapy. The panel also recommends (C recommendation; weak evidence) that if EPA and/or DHA are used for the management of severe hypertriglyceridemia, it is reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding.

On-going Randomized Clinical Trials Scan

The above reviews further the uncertainty of the effects of omega-3 fatty acids' role in the treatment of hypertriglyceridemia, prevention of stroke, sudden cardiac death and heart failure; being used in as adjunctive therapy for the treatment mood disorders such as major depression and bipolar disorders; and the prevention of cognitive decline and dementia in Alzheimer's patient and its possible role in cancer prevention. The following table summarizes the current on-going randomized clinical trials that might bring more evidence to current practice.

RCTs	Study Population	Number of Participants/Estimated Completion Date	Primary Endpoints
A *S*tudy of **C**ardiovascular **E**vents i**N** **D**iabetes (ASCEND)[78]	Type I or II diabetic subjects with no known vascular disease allocated to take either 100mg aspirin daily or placebo and 1 gram capsules containing naturally occurring omega-3 fatty acids or placebo capsules containing olive oil.	15,480/2017	"Log rank" analyses of serious vascular events during the scheduled treatment period (5-7 years) among all those allocated omega-3 fatty acid capsules versus all those allocated placebo capsules.
Reduction of Cardiovascular Events With EPA - Intervention Trial (REDUCE-IT)[79]	High risk patients with hypertriglyceridemia and on statin.	8,000/2016	Evaluate whether EPA, combined with a statin therapy, will be superior to the statin therapy alone, when used as a prevention in reducing long-term cardiovascular events measured as composite endpoint of CV death, MI, stroke, coronary revascularization, and hospitalization for unstable angina, in high-risk patients with mixed dyslipidemia.
Inositol and Omega-3 Fatty Acids in Pediatric Mania[80]	Children ages 6-12 years old with bipolar spectrum disorders.	60/2014	Improvement in mania symptoms by change in Young Mania Rating Scale (YMRS)
Omega 3 FA Supplements as Augmentation in the Treatment of Depression[81]	Adult patients with select medical conditions (cancer, cardiovascular diseases and diabetes). Patients were randomized to receive Omega 3 Fatty acid augmentation of desvenlafaxine (DVS) or placebo augmentation of DVS.	90/2015	Hospital Anxiety and Depression Scale

References

1. Larsson SC, Orsini N, Wolk A. Long-chain omega-3 polyunsaturated fatty acids and risk of stroke: a meta-analysis. *European Journal of Epidemiology*. 2012;27(12):895–901. doi:10.1007/s10654-012-9748-9.

2. Kotwal S, Jun M, Sullivan D, Perkovic V, Neal B. Omega 3 Fatty Acids and Cardiovascular Outcomes Systematic Review and Meta-Analysis. *Circ Cardiovasc Qual Outcomes*. 2012;5(6):808–818. doi:10.1161/CIRCOUTCOMES.112.966168.

3. Delgado-Lista J, Perez-Martinez P, Lopez-Miranda J, Perez-Jimenez F. Long chain omega-3 fatty acids and cardiovascular disease: a systematic review. *British Journal of Nutrition*. 2012;107(Supplement S2):S201–S213. doi:10.1017/S0007114512001596.

4. Kwak S, Myung S, Lee Y, Seo H, Korean Meta-analysis Study Group f. Efficacy of omega-3 fatty acid supplements (eicosapentaenoic acid and docosahexaenoic acid) in the secondary prevention of cardiovascular disease: A meta-analysis of randomized, double-blind, placebo-controlled trials. *Arch Intern Med*. 2012;172(9):686–694. doi:10.1001/archinternmed.2012.262.

5. Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: A systematic review and meta-analysis. *JAMA*. 2012;308(10):1024–1033. doi:10.1001/2012.jama.11374.

6. Leon H, Shibata MC, Sivakumaran S, Dorgan M, Chatterley T, Tsuyuki RT. Effect of fish oil on arrhythmias and mortality: systematic review. *BMJ*. 2008;337(dec23 2):a2931–a2931. doi:10.1136/bmj.a2931.

7. Liu T, Korantzopoulos P, Shehata M, Li G, Wang X, Kaul S. Prevention of atrial fibrillation with omega-3 fatty acids: a meta-analysis of randomised clinical trials. *Heart*. 2011;97(13):1034–1040. doi:10.1136/hrt.2010.215350.

8. Armaganijan L, Lopes RD, Healey JS, Piccini JP, Nair GM, Morillo CA. Do Omega-3 fatty acids prevent atrial fibrillation after open heart surgery? A meta-analysis of randomized controlled trials. *Clinics*. 2011;66(11):1923–1928. doi:10.1590/S1807-59322011001100012.

9. Xin W, Wei W, Li X. Effects of fish oil supplementation on cardiac function in chronic heart failure: a meta-analysis of randomised controlled trials. *Heart*. 2012;98(22):1620–1625. doi:10.1136/heartjnl-2012-302119.

10. Campbell F, Dickinson HO, Critchley JA, Ford GA, Bradburn M. A systematic review of fish-oil supplements for the prevention and treatment of hypertension. *European Journal of Preventive Cardiology*. 2013;20(1):107–120. doi:10.1177/2047487312437056.

11. Sydenham E, Dangour AD, Lim W-S. Omega 3 fatty acid for the prevention of cognitive decline and dementia. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 1996. Available at: http://onlinelibrary.wiley.com.liboff.ohsu.edu/doi/10.1002/14651858.CD005379.pub3/abstract. Accessed September 9, 2013.

12. Mazereeuw G, Lanctôt KL, Chau SA, Swardfager W, Herrmann N. Effects of omega-3 fatty acids on cognitive performance: a meta-analysis. *Neurobiology of Aging*. 2012;33(7):1482.e17–1482.e29. doi:10.1016/j.neurobiolaging.2011.12.014.

13. Bloch MH, Hannestad J. Omega-3 fatty acids for the treatment of depression: systematic review and meta-analysis. *Mol Psychiatry*. 2012;17(12):1272–1282. doi:10.1038/mp.2011.100.

14. Sublette ME, Ellis SP, Geant AL, Mann JJ. Meta-Analysis of the Effects of Eicosapentaenoic Acid (EPA) in Clinical Trials in Depression. *The Journal of Clinical Psychiatry*. 2011;72(12):1577–1584. doi:10.4088/JCP.10m06634.

15. Appleton KM, Rogers PJ, Ness AR. Updated systematic review and meta-analysis of the effects of n−3 long-chain polyunsaturated fatty acids on depressed mood. *Am J Clin Nutr*. 2010;91(3):757–770. doi:10.3945/ajcn.2009.28313.

16. Ries A, Trottenberg P, Elsner F, et al. A systematic review on the role of fish oil for the treatment of cachexia in advanced cancer: An EPCRC cachexia guidelines project. *Palliat Med*. 2012;26(4):294–304. doi:10.1177/0269216311418709.

17. James MJ, Gibson RA, Cleland LG. Dietary polyunsaturated fatty acids and inflammatory mediator production. *Am J Clin Nutr*. 2000;71(1 Suppl):343S–8S.

18. Nettleton JA. Omega-3 fatty acids: comparison of plant and seafood sources in human nutrition. *J Am Diet Assoc*. 1991;91(3):331–337.

19. Masson S, Latini R, Tacconi M, Bernasconi R. Incorporation and washout of n-3 polyunsaturated fatty acids after diet supplementation in clinical studies. *J Cardiovasc Med (Hagerstown)*. 2007;8 Suppl 1:S4–10. doi:10.2459/01.JCM.0000289269.98105.65.

20. Vanden Heuvel JP. Diet, fatty acids, and regulation of genes important for heart disease. *Curr Atheroscler Rep*. 2004;6(6):432–440.

21. Clandinin MT, Cheema S, Field CJ, Garg ML, Venkatraman J, Clandinin TR. Dietary fat: exogenous determination of membrane structure and cell function. *FASEB J*. 1991;5(13):2761–2769.

22. Chang C-Y, Ke D-S, Chen J-Y. Essential fatty acids and human brain. *Acta Neurol Taiwan*. 2009;18(4):231–241.

23. Bang HO, Dyerberg J, Hjøorne N. The composition of food consumed by Greenland Eskimos. *Acta Med Scand*. 1976;200(1-2):69–73.

24. Bulliyya G. Fish intake and blood lipids in fish eating vs non-fish eating communities of coastal south India. *Clin Nutr*. 2000;19(3):165–170. doi:10.1054/clnu.1999.0092.

25. Kromhout D, Bosschieter EB, de Lezenne Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. *N Engl J Med*. 1985;312(19):1205–1209. doi:10.1056/NEJM198505093121901.

26. Engler MB. Vascular effects of omega-3 fatty acids: possible therapeutic mechanisms in cardiovascular disease. *J Cardiovasc Nurs*. 1994;8(3):53–67.

27. Yano K, MacLean CJ, Reed DM, et al. A comparison of the 12-year mortality and predictive factors of coronary heart disease among Japanese men in Japan and Hawaii. *Am J Epidemiol*. 1988;127(3):476–487.

28. Hooper L, Thompson RL, Harrison RA, et al. Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. *BMJ*. 2006;332(7544):752–760. doi:10.1136/bmj.38755.366331.2F.

29. Kromhout D, Giltay EJ, Geleijnse JM, Alpha Omega Trial Group. n-3 fatty acids and cardiovascular events after myocardial infarction. *N Engl J Med*. 2010;363(21):2015–2026. doi:10.1056/NEJMoa1003603.

30. Brouwer IA, Katan MB, Zock PL. Effects of n-3 fatty acids on arrhythmic events and mortality in the SOFA implantable cardioverter defibrillator trial. *Am J Clin Nutr*. 2006;84(6):1554; author reply 1554–1555.

31. Leaf A, Albert CM, Josephson M, et al. Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake. *Circulation*. 2005;112(18):2762–2768. doi:10.1161/CIRCULATIONAHA.105.549527.

32. Risk and Prevention Study Collaborative Group, Roncaglioni MC, Tombesi M, et al. n-3 fatty acids in patients with multiple cardiovascular risk factors. *N Engl J Med*. 2013;368(19):1800–1808. doi:10.1056/NEJMoa1205409.

33. Duda MK, O'Shea KM, Stanley WC. omega-3 polyunsaturated fatty acid supplementation for the treatment of heart failure: mechanisms and clinical potential. *Cardiovasc Res*. 2009;84(1):33–41. doi:10.1093/cvr/cvp169.

34. Marchioli R, Silletta MG, Levantesi G, Pioggiarella R, Tognoni G. N-3 polyunsaturated fatty acids in heart failure: mechanisms and recent clinical evidence. *Cell Mol Biol (Noisy-le-grand)*. 2010;56(1):110–130.

35. Kang JX, Leaf A. Protective effects of free polyunsaturated fatty acids on arrhythmias induced by lysophosphatidylcholine or palmitoylcarnitine in neonatal rat cardiac myocytes. *Eur J Pharmacol*. 1996;297(1-2):97–106.

36. Kang JX, Leaf A. Antiarrhythmic effects of polyunsaturated fatty acids. Recent studies. *Circulation*. 1996;94(7):1774–1780.

37. Zhao YT, Shao L, Teng LL, et al. Effects of n-3 polyunsaturated fatty acid therapy on plasma inflammatory markers and N-terminal pro-brain natriuretic peptide in elderly patients with chronic heart failure. *J Int Med Res*. 2009;37(6):1831–1841.

38. Nodari S, Triggiani M, Campia U, et al. Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in patients with dilated cardiomyopathy. *J Am Coll Cardiol*. 2011;57(7):870–879. doi:10.1016/j.jacc.2010.11.017.

39. Skou HA, Toft E, Christensen JH, Hansen JB, Dyerberg J, Schmidt EB. N-3 fatty acids and cardiac function after myocardial infarction in Denmark. *Int J Circumpolar Health*. 2001;60(3):360–365.

40. Radaelli A, Cazzaniga M, Viola A, et al. Enhanced baroreceptor control of the cardiovascular system by polyunsaturated Fatty acids in heart failure patients. *J Am Coll Cardiol*. 2006;48(8):1600–1606. doi:10.1016/j.jacc.2006.05.073.

41. Ghio S, Scelsi L, Latini R, et al. Effects of n-3 polyunsaturated fatty acids and of rosuvastatin on left ventricular function in chronic heart failure: a substudy of GISSI-HF trial. *Eur J Heart Fail*. 2010;12(12):1345–1353. doi:10.1093/eurjhf/hfq172.

42. Moertl D, Hammer A, Steiner S, Hutuleac R, Vonbank K, Berger R. Dose-dependent effects of omega-3-polyunsaturated fatty acids on systolic left ventricular function, endothelial function, and markers of inflammation in chronic heart failure of nonischemic origin: a double-blind, placebo-controlled, 3-arm study. *Am Heart J*. 2011;161(5):915.e1–9. doi:10.1016/j.ahj.2011.02.011.

43. Nodari S, Metra M, Milesi G, et al. The role of n-3 PUFAs in preventing the arrhythmic risk in patients with idiopathic dilated cardiomyopathy. *Cardiovasc Drugs Ther*. 2009;23(1):5–15. doi:10.1007/s10557-008-6142-7.

44. Calò L, Bianconi L, Colivicchi F, et al. N-3 Fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a randomized, controlled trial. *J Am Coll Cardiol*. 2005;45(10):1723–1728. doi:10.1016/j.jacc.2005.02.079.

45. Saravanan P, Bridgewater B, West AL, O'Neill SC, Calder PC, Davidson NC. Omega-3 fatty acid supplementation does not reduce risk of atrial fibrillation after coronary artery bypass surgery: a randomized, double-blind, placebo-controlled clinical trial. *Circ Arrhythm Electrophysiol*. 2010;3(1):46–53. doi:10.1161/CIRCEP.109.899633.

46. Mariscalco G, Sarzi Braga S, Banach M, et al. Preoperative n-3 polyunsatured fatty acids are associated with a decrease in the incidence of early atrial fibrillation following cardiac surgery. *Angiology*. 2010;61(7):643–650. doi:10.1177/0003319710370962.

47. Heidt MC, Vician M, Stracke SKH, et al. Beneficial effects of intravenously administered N-3 fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a prospective randomized study. *Thorac Cardiovasc Surg*. 2009;57(5):276–280. doi:10.1055/s-0029-1185301.

48. Heidarsdottir R, Arnar DO, Skuladottir GV, et al. Does treatment with n-3 polyunsaturated fatty acids prevent atrial fibrillation after open heart surgery? *Europace*. 2010;12(3):356–363. doi:10.1093/europace/eup429.

49. Nelson NJ. Migrant studies aid the search for factors linked to breast cancer risk. *J Natl Cancer Inst*. 2006;98(7):436–438. doi:10.1093/jnci/djj147.

50. Gerber M. Background Review Paper on Total Fat, Fatty Acid Intake and Cancers. *Annals of Nutrition and Metabolism*. 2009;55(1-3):140–161. doi:10.1159/000229000.

51. Dewailly E, Mulvad G, Sloth Pedersen H, Hansen JC, Behrendt N, Hart Hansen JP. Inuit are protected against prostate cancer. *Cancer Epidemiol Biomarkers Prev*. 2003;12(9):926–927.

52. Nutting PA, Freeman WL, Risser DR, et al. Cancer incidence among American Indians and Alaska Natives, 1980 through 1987. *Am J Public Health*. 1993;83(11):1589–1598.

53. Lukiw WJ, Bazan NG. Docosahexaenoic Acid and the Aging Brain. *J Nutr*. 2008;138(12):2510–2514. doi:10.3945/jn.108.096016.

54. Grant WB. Dietary Links to Alzheimer's Disease: 1999 Update. *Journal of Alzheimer's Disease*. 1999;1(4):197–201.

55. Graves AB, Rajaram L, Bowen JD, McCormick WC, McCurry SM, Larson EB. Cognitive decline and Japanese culture in a cohort of older Japanese Americans in King County, WA: the Kame Project. *J Gerontol B Psychol Sci Soc Sci*. 1999;54(3):S154–161.

56. Hibbeln JR. Fish consumption and major depression. *Lancet*. 1998;351(9110):1213. doi:10.1016/S0140-6736(05)79168-6.

57. Tanskanen A, Hibbeln JR, Hintikka J, Haatainen K, Honkalampi K, Viinamäki H. Fish consumption, depression, and suicidality in a general population. *Arch Gen Psychiatry*. 2001;58(5):512–513.

58. Marangell LB, Martinez JM, Zboyan HA, Kertz B, Kim HFS, Puryear LJ. A double-blind, placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. *Am J Psychiatry*. 2003;160(5):996–998.

59. Grenyer BFS, Crowe T, Meyer B, et al. Fish oil supplementation in the treatment of major depression: a randomised double-blind placebo-controlled trial. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31(7):1393–1396. doi:10.1016/j.pnpbp.2007.06.004.

60. Silvers KM, Woolley CC, Hamilton FC, Watts PM, Watson RA. Randomised double-blind placebo-controlled trial of fish oil in the treatment of depression. *Prostaglandins Leukot Essent Fatty Acids*. 2005;72(3):211–218. doi:10.1016/j.plefa.2004.11.004.

61. Zargar A, Ito MK. Long chain omega-3 dietary supplements: a review of the National Library of Medicine Herbal Supplement Database. *Metab Syndr Relat Disord*. 2011;9(4):255–271. doi:10.1089/met.2011.0004.

62. Grimsgaard S, Bonaa KH, Hansen JB, Nordøy A. Highly purified eicosapentaenoic acid and docosahexaenoic acid in humans have similar triacylglycerol-lowering effects but divergent effects on serum fatty acids. *Am J Clin Nutr*. 1997;66(3):649–659.

63. Grimsgaard S, Bønaa KH, Hansen JB, Myhre ES. Effects of highly purified eicosapentaenoic acid and docosahexaenoic acid on hemodynamics in humans. *Am J Clin Nutr*. 1998;68(1):52–59.

64. Woodman RJ, Mori TA, Burke V, Puddey IB, Watts GF, Beilin LJ. Effects of purified eicosapentaenoic and docosahexaenoic acids on glycemic control, blood pressure, and serum lipids in type 2 diabetic patients with treated hypertension. *Am J Clin Nutr*. 2002;76(5):1007–1015.

65. Wei MY, Jacobson TA. Effects of eicosapentaenoic acid versus docosahexaenoic acid on serum lipids: a systematic review and meta-analysis. *Curr Atheroscler Rep*. 2011;13(6):474–483. doi:10.1007/s11883-011-0210-3.

66. Jacobson TA, Glickstein SB, Rowe JD, Soni PN. Effects of eicosapentaenoic acid and docosahexaenoic acid on low-density lipoprotein cholesterol and other lipids: a review. *J Clin Lipidol*. 2012;6(1):5–18. doi:10.1016/j.jacl.2011.10.018.

67. Gerber M. Omega-3 fatty acids and cancers: a systematic update review of epidemiological studies. *British Journal of Nutrition*. 2012;107(Supplement S2):S228–S239. doi:10.1017/S0007114512001614.

68. Szymanski KM, Wheeler DC, Mucci LA. Fish consumption and prostate cancer risk: a review and meta-analysis. *Am J Clin Nutr*. 2010;92(5):1223–1233. doi:10.3945/ajcn.2010.29530.

69. Ortega RM, Rodríguez-Rodríguez E, López-Sobaler AM. Effects of omega 3 fatty acids supplementation in behavior and non-neurodegenerative neuropsychiatric disorders. *British Journal of Nutrition*. 2012;107(Supplement S2):S261–S270. doi:10.1017/S000711451200164X.

70. Sarris J, Mischoulon D, Schweitzer I. Adjunctive nutraceuticals with standard pharmacotherapies in bipolar disorder: a systematic review of clinical trials. *Bipolar Disorders*. 2011;13(5-6):454–465. doi:10.1111/j.1399-5618.2011.00945.x.

71. Turnbull T, Cullen-Drill M, Smaldone A. Efficacy of Omega-3 Fatty Acid Supplementation on Improvement of Bipolar Symptoms: A Systematic Review. *Archives of Psychiatric Nursing*. 2008;22(5):305–311. doi:10.1016/j.apnu.2008.02.011.

72. McMurray JJV, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012 The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2012;33(14):1787–1847. doi:10.1093/eurheartj/ehs104.

73. GISSI-HF investigators. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *The Lancet*. 4;372(9645):1223–1230. doi:10.1016/S0140-6736(08)61239-8.

74. Jiménez Jiménez FJ, Cervera Montes M, Blesa Malpica AL. Guidelines for specialized nutritional and metabolic support in the critically-ill patient: Update. Consensus SEMICYUC-SENPE: Cardiac patient. *Nutrición Hospitalaria*. 2011;26:76–80.

75. Miller M, Stone NJ, Ballantyne C, et al. Triglycerides and Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation*. 2011;123(20):2292–2333. doi:10.1161/CIR.0b013e3182160726.

76. Ravindran AV, Lam RW, Filteau MJ, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults.: V. Complementary and alternative medicine treatments. *Journal of Affective Disorders*. 2009;117, Supplement 1:S54–S64. doi:10.1016/j.jad.2009.06.040.

77. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013. doi:10.1161/01.cir.0000437738.63853.7a.

78. ASCEND. A Study of Cardiovascular Events in Diabetes. Available at: http://www.ctsu.ox.ac.uk/ascend/. Accessed November 25, 2013.

79. A Study of AMR101 to Evaluate Its Ability to Reduce Cardiovascular Events in High Risk Patients With Hypertriglyceridemia and on Statin. The Primary Objective is to Evaluate the Effect of 4 g/Day AMR101 for Preventing the Occurrence of a First Major Cardiovascular Event. - Full Text View - ClinicalTrials.gov. Available at: http://clinicaltrials.gov/ct2/show/NCT01492361?term=REDUCE-IT&rank=1. Accessed December 5, 2013.

80. ClinicalTrials.Gov. Inositol and Omega-3 Fatty Acids in Pediatric Mania - Full Text View - ClinicalTrials.gov. Available at: http://clinicaltrials.gov/ct2/show/study/NCT01396486?term=fish+oil+randomized+control+trials&no_unk=Y&type=Intr&rank=40. Accessed November 25, 2013.

81. ClinicalTrials.Gov. Omega 3 FA Supplements as Augmentation in the Treatment of Depression - Full Text View - ClinicalTrials.gov. Available at: http://clinicaltrials.gov/ct2/show/NCT01803711?term=fish+oil+randomized+control+trials&no_unk=Y&type=Intr&rank=64. Accessed November 25, 2013.

Appendix A: Abstract of Systematic Reviews

1. **Omega 3 Fatty acids and cardiovascular outcomes: systematic review and meta-analysis.** Kotwal S, Jun M, Sullivan D, Perkovic V, Neal B. *Circ Cardiovasc Qual Outcomes*. 2012;5(6):808–818. doi:10.1161/CIRCOUTCOMES.112.966168.

   Abstract

   BACKGROUND: Early trials evaluating the effect of omega 3 fatty acids (ω-3 FA) reported benefits for mortality and cardiovascular events but recent larger studies trials have variable findings. We assessed the effects of ω-3 FA on cardiovascular and other important clinical outcomes.

   METHODS AND RESULTS: We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials for all randomized studies using dietary supplements, dietary interventions, or both. The primary outcome was a composite of cardiovascular events (mostly myocardial infarction, stroke, and cardiovascular death). Secondary outcomes were arrhythmia, cerebrovascular events, hemorrhagic stroke, ischemic stroke, coronary revascularization, heart failure, total mortality, nonvascular mortality, and end-stage kidney disease. Twenty studies including 63030 participants were included. There was no overall effect of ω-3 FA on composite cardiovascular events (relative risk [RR]=0.96; 95% confidence interval [CI], 0.90-1.03; P=0.24) or on total mortality (RR=0.95; 95% CI, 0.86-1.04; P=0.28). ω-3 FA did protect against vascular death (RR=0.86; 95% CI, 0.75-0.99; P=0.03) but not coronary events (RR=0.86; 95% CI, 0.67-1.11; P=0.24). There was no effect on arrhythmia (RR=0.99; 95% CI, 0.85-1.16; P=0.92) or cerebrovascular events (RR=1.03; 95% CI, 0.92-1.16; P=0.59). Adverse events were more common in the treatment group than the placebo group (RR=1.18, 95% CI, 1.02-1.37; P=0.03), predominantly because of an excess of gastrointestinal side effects.

   CONCLUSIONS: ω-3 FA may protect against vascular disease, but the evidence is not clear-cut, and any benefits are almost certainly not as great as previously believed.

2. **Efficacy of omega-3 fatty acid supplements (eicosapentaenoic acid and docosahexaenoic acid) in the secondary prevention of cardiovascular disease: a meta-analysis of randomized, double-blind, placebo-controlled trials**. Kwak SM, Myung SK, Lee YJ, Seo HG; Korean Meta-analysis Study Group**.** *Arch Intern Med*. 2012;172(9):686–694. doi:10.1001/archinternmed.2012.262.

   Abstract

   BACKGROUND: Although previous randomized, double-blind, placebo-controlled trials reported the efficacy of omega-3 fatty acid supplements in the secondary prevention of cardiovascular disease (CVD), the evidence remains inconclusive. Using a meta-analysis, we investigated the efficacy of eicosapentaenoic acid and docosahexaenoic acid in the secondary prevention of CVD.

   METHODS: We searched PubMed, EMBASE, and the Cochrane Library in April 2011. Two of us independently reviewed and selected eligible randomized controlled trials.

   RESULTS: Of 1007 articles retrieved, 14 randomized, double-blind, placebo-controlled trials (involving 20 485 patients with a history of CVD) were included in the final analyses. Supplementation with omega-3 fatty acids did not reduce the risk of overall cardiovascular events (relative risk, 0.99; 95% CI, 0.89-1.09), all-cause mortality, sudden cardiac death, myocardial infarction, congestive heart failure, or transient ischemic attack and stroke. There was a small reduction in cardiovascular death (relative risk, 0.91; 95% CI, 0.84-0.99), which disappeared when we excluded a study with major methodological problems. Furthermore, no significant preventive effect

was observed in subgroup analyses by the following: country location, inland or coastal geographic area, history of CVD, concomitant medication use, type of placebo material in the trial, methodological quality of the trial, duration of treatment, dosage of eicosapentaenoic acid or docosahexaenoic acid, or use of fish oil supplementation only as treatment.

CONCLUSION: Our meta-analysis showed insufficient evidence of a secondary preventive effect of omega-3 fatty acid supplements against overall cardiovascular events among patients with a history of cardiovascular disease.

3. **Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis.** Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. *JAMA*. 2012;308(10):1024–1033. doi:10.1001/2012.jama.11374.

Abstract

CONTEXT: Considerable controversy exists regarding the association of omega-3 polyunsaturated fatty acids (PUFAs) and major cardiovascular end points.

OBJECTIVE: To assess the role of omega-3 supplementation on major cardiovascular outcomes.

DATA SOURCES: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials through August 2012.

STUDY SELECTION: Randomized clinical trials evaluating the effect of omega-3 on all-cause mortality, cardiac death, sudden death, myocardial infarction, and stroke.

DATA EXTRACTION: Descriptive and quantitative information was extracted; absolute and relative risk (RR) estimates were synthesized under a random-effects model. Heterogeneity was assessed using the Q statistic and I2. Subgroup analyses were performed for the presence of blinding, the prevention settings, and patients with implantable cardioverter-defibrillators, and meta-regression analyses were performed for the omega-3 dose. A statistical significance threshold of .0063 was assumed after adjustment for multiple comparisons.

DATA SYNTHESIS: Of the 3635 citations retrieved, 20 studies of 68,680 patients were included, reporting 7044 deaths, 3993 cardiac deaths, 1150 sudden deaths, 1837 myocardial infarctions, and 1490 strokes. No statistically significant association was observed with all-cause mortality (RR, 0.96; 95% CI, 0.91 to 1.02; risk reduction [RD] -0.004, 95% CI, -0.01 to 0.02), cardiac death (RR, 0.91; 95% CI, 0.85 to 0.98; RD, -0.01; 95% CI, -0.02 to 0.00), sudden death (RR, 0.87; 95% CI, 0.75 to 1.01; RD, -0.003; 95% CI, -0.012 to 0.006), myocardial infarction (RR, 0.89; 95% CI, 0.76 to 1.04; RD, -0.002; 95% CI, -0.007 to 0.002), and stroke (RR, 1.05; 95% CI, 0.93 to 1.18; RD, 0.001; 95% CI, -0.002 to 0.004) when all supplement studies were considered.

CONCLUSION: Overall, omega-3 PUFA supplementation was not associated with a lower risk of all-cause mortality, cardiac death, sudden death, myocardial infarction, or stroke based on relative and absolute measures of association.

4. **Long chain omega-3 fatty acids and cardiovascular disease: a systematic review.** Delgado-Lista J, Perez-Martinez P, Lopez-Miranda J, Perez-Jimenez F. *British Journal of Nutrition*. 2012;107(Supplement S2):S201–S213. doi:10.1017/S0007114512001596.

Abstract

Introduction: Cardiovascular disease remains the commonest health problem in developed countries, and residual risk after implementing all current therapies is still high. The use of marine omega-3 fatty acids (DHA and EPA) has been recommended to reduce cardiovascular risk by multiple mechanisms.

Objectives: To update the current evidence on the influence of omega-3 on the rate of cardiovascular events.

Review Methods: We used the MEDLINE and EMBASE databases to identify clinical trials and randomized controlled trials of omega-3 fatty acids (with quantified quantities) either in capsules or in dietary intake, compared to placebo or usual diet, equal to or longer than 6 months, and written in English. The primary outcome was a cardiovascular event of any kind and secondary outcomes were all-cause mortality, cardiac death and coronary events. We used RevMan 5·1 (Mantel-Haenszel method). Heterogeneity was assessed by the I2 and Chi2 tests. We included 21 of the 452 pre-selected studies.

Results: We found an overall decrease of risk of suffering a cardiovascular event of any kind of 10 % (OR 0·90; [0·85-0·96], p = 0·001), a 9 % decrease of risk of cardiac death (OR 0·91; [0·83-0·99]; p = 0·03), a decrease of coronary events (fatal and non-fatal) of 18 % (OR 0·82; [0·75-0·90]; $p < 1 \times 10^{-4}$), and a trend to lower total mortality (5 % reduction of risk; OR 0·95; [0·89-1·02]; p = 0·15. Most of the studies analyzed included persons with high cardiovascular risk.

Conclusions: marine omega-3 fatty acids are effective in preventing cardiovascular events, cardiac death and coronary events, especially in persons with high cardiovascular risk.

5. **Effect of fish oil on arrhythmias and mortality: systematic review.** León H, Shibata MC, Sivakumaran S, Dorgan M, Chatterley T, Tsuyuki RT. *BMJ*. 2008;337(dec23 2):a2931–a2931. doi:10.1136/bmj.a2931.

Abstract

OBJECTIVE: To synthesise the literature on the effects of fish oil-docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)-on mortality and arrhythmias and to explore dose response and formulation effects.

DESIGN: Systematic review and meta-analysis.

DATA SOURCES: Medline, Embase, the Cochrane Library, PubMed, CINAHL, IPA, Web of Science, Scopus, Pascal, Allied and Complementary Medicine, Academic OneFile, ProQuest Dissertations and Theses, Evidence-Based Complementary Medicine, and LILACS. Studies reviewed Randomised controlled trials of fish oil as dietary supplements in humans.

DATA EXTRACTION: The primary outcomes of interest were the arrhythmic end points of appropriate implantable cardiac defibrillator intervention and sudden cardiac death. The secondary outcomes were all cause mortality and death from cardiac causes. Subgroup analyses included the effect of formulations of EPA and DHA on death from cardiac causes and effects of fish oil in patients with coronary artery disease or myocardial infarction.

DATA SYNTHESIS: 12 studies totalling 32 779 patients met the inclusion criteria. A neutral effect was reported in three studies (n=1148) for appropriate implantable cardiac defibrillator intervention (odds ratio 0.90, 95% confidence interval 0.55 to 1.46) and in six studies (n=31 111) for sudden cardiac death (0.81, 0.52 to 1.25). 11 studies (n=32 439 and n=32 519) provided data on the effects of fish oil on all cause mortality (0.92, 0.82 to 1.03) and a reduction in deaths from cardiac causes (0.80, 0.69 to 0.92). The dose-response relation for DHA and EPA on reduction in deaths from cardiac causes was not significant.

CONCLUSIONS: Fish oil supplementation was associated with a significant reduction in deaths from cardiac causes but had no effect on arrhythmias or all cause mortality. Evidence to recommend an optimal formulation of EPA or DHA to reduce these outcomes is insufficient. Fish oils are a heterogeneous product, and the optimal formulations for DHA and EPA remain unclear.

6. **Prevention of atrial fibrillation with omega-3 fatty acids: a meta-analysis of randomised clinical trials**. Liu T, Korantzopoulos P, Shehata M, Li G, Wang X, Kaul S. *Heart*. 2011;97(13):1034–1040. doi:10.1136/hrt.2010.215350.

Abstract

CONTEXT: Previous randomised controlled trials (RCT) regarding n-3 PUFA supplementation for atrial fibrillation (AF) prevention have yielded conflicting results.

OBJECTIVE: A systematic review and meta-analysis of RCT was conducted to examine the role of n-3 PUFA in AF prevention.

DATA SOURCES: MEDLINE, Web of Science and Cochrane clinical trials database were searched until November 2010.

STUDY SELECTION: Of 127 initially identified studies, 10 RCT with 1955 patients were finally analysed.

DATA EXTRACTION: Two blinded reviewers extracted data independently to a predefined form. Disagreements were resolved through discussion and consensus.

RESULTS: n-3 PUFA had no significant effect on the prevention of AF (OR 0.81, 95% CI 0.57 to 1.15; p=0.24). There was significant heterogeneity among the studies (p=0.002, I(2)=65.0%). Subgroup analysis showed no significant beneficial effect of fish oils in any subset of population.

CONCLUSIONS: No significant effects of n-3 PUFA supplementation on AF prevention were observed in this meta-analysis. A large-scale trial with higher doses and longer follow-up might be required to rule out the possibility of any treatment benefit.

7. **Do omega-3 fatty acids prevent atrial fibrillation after open heart surgery? A meta-analysis of randomized controlled trials.** Armaganijan L, Lopes RD, Healey JS, Piccini JP, Nair GM, Morillo CA. *Clinics*. 2011;66(11):1923–1928. doi:10.1590/S1807-59322011001100012.

Abstract

OBJECTIVES: N-3 polyunsaturated fatty acids have been proposed as a novel treatment for preventing postoperative atrial fibrillation due to their potential anti-inflammatory and anti-arrhythmic effects. However, randomized studies have yielded conflicting results. The objective of this study is to review randomized trials of N-3 polyunsaturated fatty acid use for postoperative atrial fibrillation.

METHODS: Using the CENTRAL, PUBMED, EMBASE, and LILACS databases, a literature search was conducted to identify all of the studies in human subjects that reported the effects of N-3 polyunsaturated fatty acids on the prevention of postoperative atrial fibrillation in cardiac surgery patients. The final search was performed on January 30, 2011. There was no language restriction, and the search strategy only involved terms for N-3 polyunsaturated fatty acids (or fish oil), atrial fibrillation, and cardiac surgery. To be included, the studies had to be randomized (open or blinded), and the enrolled patients had to be ≥18 years of age.

RESULTS: Four randomized studies (three double-blind, one open-label) that enrolled 538 patients were identified. The patients were predominantly male, the mean age was 62.3 years, and most of the patients exhibited a normal left atrial size and ejection fraction. N-3 polyunsaturated fatty acid use was not associated with a reduction in postoperative atrial fibrillation. Similar results were observed when the open-label study was excluded.

CONCLUSIONS: There is insufficient evidence to suggest that treatment with N-3 polyunsaturated fatty acids reduces postoperative atrial fibrillation. Therefore, their routine use in patients undergoing cardiac surgery is not recommended.

8. **Effects of fish oil supplementation on cardiac function in chronic heart failure: a meta-analysis of randomised controlled trials.** Xin W, Wei W, Li X. *Heart*. 2012;98(22):1620–1625. doi:10.1136/heartjnl-2012-302119.

Abstract

CONTEXT: The effects of fish oil on cardiac function, ventricular remodelling and functional capacity in patients with chronic heart failure (CHF) remain controversial.

OBJECTIVE: The aim of this meta-analysis was to evaluate effects of fish oil on cardiac function and related parameters in CHF patients.

DATA SOURCES: Medline, Embase, the Cochrane Library and references cited in related reviews and studies.

STUDY SELECTION: Randomised controlled trials of fish oil supplementation on cardiac function in patients with CHF were identified.

DATA EXTRACTION: Two investigators read all papers and extracted all relevant information. A fixed effect or, in the presence of heterogeneity, a random effect model, was used to estimate the combined effects.

RESULTS: 7 trials with 825 participants were included. Meta-analysis results showed that left ventricular ejection fraction was significantly increased (weighted mean difference (WMD) = 2.25%, 95% CI 0.66 to 3.83, p = 0.005) and left ventricular end-systolic volume was significantly decreased (WMD = 7.85 ml, 95% CI -15.57 to -0.12, p = 0.05) in the fish oil group compared with the placebo group, although left ventricular end-diastolic volume was not significantly affected. Meta-regression and subgroup analysis indicated that the improvement in left ventricular systolic function was more remarkable in patients with nonischaemic heart failure. Fish oil supplementation also improved the New York Heart Association functional classification and peak oxygen consumption in patients with non-ischaemic heart failure.

CONCLUSIONS: Improvement in cardiac function, remodelling and functional capacity may be important mechanisms underlying the potential therapeutic role of fish oil for patients with CHF. These effects might be more remarkable in patients with non-ischaemic heart failure.

9. **A systematic review of fish-oil supplements for the prevention and treatment of hypertension.** Campbell F, Dickinson HO, Critchley JA, Ford GA, Bradburn M. *European Journal of Preventive Cardiology*. 2013;20(1):107–120. doi:10.1177/2047487312437056.

Abstract

AIMS: Fish oils are widely believed to promote cardiovascular health by lowering blood pressure (BP) but the evidence supporting this is not conclusive. We aimed to systematically review existing evidence.

METHOD: We undertook a systematic review of randomized controlled trials and crossover trials that evaluated the effectiveness of fish-oil supplements. We included trials enrolling adults who were given fish-oil supplements with at least 8 weeks' follow up. Effects on systolic and diastolic BP were assessed using meta-analysis. Meta-regression was undertaken to explore the relationship between dose of fish oil and BP outcomes.

RESULTS: We included 17 studies, with a total of 1524 participants. We explored the effects of fish-oil supplements in both normotensive and hypertensive participants with BP 140/85 mmHg at least. Meta-analyses were performed using the inverse-variance method. Data from eight studies in hypertensive participants found a statistically significant reduction in systolic and diastolic BP; 2.56 mmHg (95% CI 0.58 to 4.53) and 1.47 mmHg (95% CI 0.41 to 2.53), respectively. Nine studies in normotensive participants showed a non-significant reduction in both systolic and diastolic BP. Meta-regression showed no significant relationship between dose of fish oil and the effect on BP.

CONCLUSION: The small but statistically significant effects of fish-oil supplements in hypertensive participants in this review have important implications for population health and lowering the risk of stroke and ischaemic heart disease. Their modest effects, however, mean that they should not be recommended as an alternative to BP-lowering drugs where guidelines recommend treatment.

10. **Long-chain omega-3 polyunsaturated fatty acids and risk of stroke: a meta-analysis**. Larsson SC, Orsini N, Wolk A. *European Journal of Epidemiology*. 2012;27(12):895–901. doi:10.1007/s10654-012-9748-9.

Abstract

Prospective studies of long-chain omega-3 polyunsaturated fatty acids (PUFA) in relation to stroke have yielded inconsistent results. The authors conducted a meta-analysis of prospective studies to summarize available evidence regarding the relation between long-chain omega-3 PUFA intake and stroke. Pertinent studies were identified by searching PubMed and Embase databases to November 1, 2012 and by reviewing the reference lists of relevant publications. Prospective studies that provided relative risks (RRs) with 95 % confidence intervals (CIs) for the association between dietary long-chain omega-3 PUFA intake and stroke were eligible. A random-effects model was used to combine study-specific results. Eight prospective studies, with 5238 stroke events among 242,076 participants, were included in the meta-analysis. The combined RR of total stroke was 0.90 (95 % CI, 0.81-1.01) for the highest versus lowest category of long-chain omega-3 PUFA intake, without heterogeneity among studies (P = 0.32). Results were similar for ischemic (RR, 0.82; 95 % CI, 0.71-0.94) and hemorrhagic stroke (RR, 0.80; 95 % CI, 0.55-1.15). A statistically significant reduction in total stroke risk was observed in women (RR, 0.80; 95 % CI, 0.65-0.99). This meta-analysis showed no overall association between omega-3 PUFA intake and stroke, but suggests that women might benefit from a higher intake of these PUFAs.

11. **Adjunctive nutraceuticals with standard pharmacotherapies in bipolar disorder: a systematic review of clinical trials**
Sarris, J., Mischoulon, D. and Schweitzer, I. (2011), Adjunctive nutraceuticals with standard pharmacotherapies in bipolar disorder: a systematic review of clinical trials. Bipolar Disorders, 13: 454–465. doi: 10.1111/j.1399-5618.2011.00945.x

Objective: Studies using augmentation of pharmacotherapies with nutraceuticals in bipolar disorder (BD) have been conducted and preliminary evidence in many cases appears positive. To date, however, no specialized systematic review of this area has been conducted. We present the first systematic review of clinical trials using nutrient-based nutraceuticals in combination with standard pharmacotherapies to treat BD. A subsequent aim of this report was to discuss posited underlying mechanisms of action.

Methods: PubMed, CINAHL, Web of Science, and Cochrane Library databases, and grey literature were searched during mid-2010 for human clinical trials in English using nutraceuticals such as omega-3, N-acetyl cysteine (NAC), inositol, and vitamins and minerals, in combination with pharmacotherapies to treat bipolar mania and bipolar depression. A review of the results including an effect size analysis (Cohen's *d*) was subsequently conducted.

Results: In treating bipolar depression, positive evidence with large effect sizes were found for NAC (*d* = 1.04) and a chelated mineral and vitamin formula (*d* = 1.70). On the outcome of bipolar mania, several nutraceuticals reduced mania with strong clinical effects: a chelated mineral formula (*d* = 0.83), L-tryptophan (*d* = 1.47), magnesium (*d* = 1.44), folic acid (*d* = 0.40), and branched-chain amino acids (*d* = 1.60). Mixed, but mainly positive, evidence was found for omega-3 for bipolar depression, while no evidentiary support was found for use in mania. No significant effect on BD outcome scales was found for inositol (possibly due to small samples).

Conclusions: BD treatment outcomes may potentially be improved by additional use of certain nutraceuticals with conventional pharmacotherapies. However, caution should be extended in interpreting the large effects of several isolated studies, as they have not yet been replicated in larger trials.

12. **Efficacy of Omega-3 Fatty Acid Supplementation on Improvement of Bipolar Symptoms: A Systematic Review.**
Teresa Turnbull, Mary Cullen-Drill, and Arlene Smaldone; *Archives of Psychiatric Nursing*. 2008;22(5):305–311. doi:10.1016/j.apnu.2008.02.011.

Abstract

The purpose of this review was to examine the current level of evidence regarding the efficacy of omega-3 fatty acid supplementation in improving bipolar disorder symptoms. Of 99 articles meeting initial search criteria, 5 randomized control trials and 2 quasi-experimental studies were selected for review. Omega-3 fatty acid supplementation was effective in 4 of 7 studies. Those using an omega-3 combination of eicosapentaenoic acid and docosahexanoic acid demonstrated a statistically significant improvement in bipolar symptoms, whereas those using a single constituent did not. Dosage variations did not demonstrate statistically significant differences. Due to its benign side effect profile and some evidence supporting its usefulness in bipolar illness, omega-3 may be a helpful adjunct in treatment of selected patients. Future studies are needed to conclusively confirmthe efficacy of omega-3s in bipolar disorder, uncovering a newwell-tolerated treatment option.

13. **Effects of omega 3 fatty acids supplementation in behavior and non-neurodegenerative neuropsychiatric disorders.** R. M. Ortega[a1a2] [c1], E. Rodríguez-Rodríguez[a2a3] and A. M. López-Sobaler; British Journal of Nutrition / Volume 107 / Supplement S2 / June 2012, pp S261-S270; Published online: 17 May 2012

Abstract

This work provides a systematic review of all published randomised, controlled clinical trials (RCT) investigating the effects of *n*-3 PUFA intake on the prevention and treatment of non-neurodegenerative neuropsychiatric disorders. Five databases (PubMed, EMBASE, LILACS, CINAHL and The Cochrane Database) were searched for RCT in this area published up to April 2011. The selected studies all involved human participants and included a comparison group. Thirty eight studies were identified, which examined the influence of *n*-3 PUFA supplementation on the prevention/treatment of depression (non-perinatal) (*n* 23), perinatal depression (*n* 6) and attention deficit hyperactivity disorder (ADHD) (*n* 9). Great heterogeneity was noticed in terms of study design, the doses of *n*-3 PUFA administered, and study duration. Some benefit was noted with respect to the treatment of hyperactivity and depression in over half the examined studies, although the evidence was not conclusive. For any firm conclusions to be drawn, further studies will be needed that take into account the initial *n*-3 PUFA status of the subjects. Excessive *n*-3 PUFA intakes might be associated with a greater risk of peroxidation events and therefore neuropsychiatric deterioration. Indeed, some studies only recorded benefits when lower doses were administered. It is therefore important that the dose required to achieve any potential benefit be determined.

14. **Omega-3 fatty acids for the treatment of depression: systematic review and meta-analysis.** Bloch MH, Hannestad J. Omega-3 fatty acids for the treatment of depression: systematic review and meta-analysis. *Mol Psychiatry*. 2012;17(12):1272–1282. doi:10.1038/mp.2011.100.

Abstract

We conducted a meta-analysis of randomized, placebo-controlled trials of omega-3 fatty acid (FA) treatment of major depressive disorder (MDD) in order to determine efficacy and to examine sources of heterogeneity between trials. PubMed (1965-May 2010) was searched for randomized, placebo-controlled trials of omega-3 FAs for MDD. Our primary outcome measure was standardized mean difference in a clinical measure of depression severity. In stratified meta-analysis, we examined the effects of trial duration, trial methodological quality, baseline depression severity, diagnostic indication, dose of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in omega-3 preparations, and whether omega-3 FA was given as monotherapy or augmentation. In 13 randomized, placebo-controlled trials examining the efficacy of omega-3 FAs involving 731 participants, meta-analysis demonstrated no significant benefit of omega-3 FA treatment compared with placebo (standard mean difference (SMD) = 0.11, 95% confidence interval (CI): _0.04, 0.26). Meta-analysis demonstrated significant heterogeneity and publication bias. Nearly all evidence of omega-3 benefit was removed after adjusting for publication bias using the trim-and-fill method (SMD = 0.01, 95% CI: _0.13, 0.15). Secondary analyses suggested a trend toward increased efficacy of omega-3 FAs in trials of
lower methodological quality, trials of shorter duration, trials which utilized completers rather than intention-to-treat analysis, and trials in which study participants had greater baseline depression severity. Current published trials suggest a small, non-significant benefit of omega-3 FAs for major depression. Nearly all of the treatment efficacy observed in the published literature may be attributable to publication bias.

15. **Meta-Analysis of the Effects of Eicosapentaenoic Acid (EPA) in Clinical Trials in Depression.** Sublette ME, Ellis SP, Geant AL, Mann JJ. Meta-Analysis of the Effects of Eicosapentaenoic Acid (EPA) in Clinical Trials in Depression. *The Journal of Clinical Psychiatry*. 2011;72(12):1577–1584. doi:10.4088/JCP.10m06634.

Abstract

Objective: Randomized trials of omega-3 polyunsaturated fatty acid (PUFA) treatment for depression have differed in outcome. Recent meta-analyses ascribe discrepancies to differential effects of eicosapentaenoic acid (EPA) versus docosahexaenoic acid (DHA) and to diagnostic heterogeneity. This meta-analysis tests the hypothesis that EPA is the effective component in PUFA treatment of major depressive episodes.

Data Sources: PubMed/MeSH was searched for studies published in English from 1960 through June 2010 using the terms fish oils (MeSH) AND (depressive disorder [MeSH] OR bipolar depression) AND randomized controlled trial (publication type). The search was supplemented by manual bibliography review and examination of relevant review articles.

Study Selection: The search yielded 15 trials involving 916 participants. Studies were included if they had a prospective, randomized, double-blinded, placebo-controlled study design; if depressive episode was the primary complaint (with or without comorbid medical conditions); if omega-3 PUFA supplements were administered; and if appropriate outcome measures were used to assess depressed mood.

Data Extraction: Extracted data included study design, sample sizes, doses and percentages of EPA and DHA, mean ages, baseline and endpoint depression ratings and standard deviations for PUFA and placebo groups, and P values. The clinical outcome of interest was the standardized mean difference in the change from baseline to endpoint scores on a depression rating scale in subjects taking PUFA supplements versus subjects taking placebo.

Data Synthesis: In a mixed-effect model, percentage of EPA in the supplements was the fixed-effect predictor, dichotomized into 2 groups: EPA < 60% or EPA ≥ 60% of the total EPA + DHA. Secondary analyses explored the relevance of treatment duration, age, and EPA dose.

Results: Supplements with EPA ≥ 60% showed benefit on standardized mean depression scores (effect size = 0.532; 95% CI, 0.277–0.733; t = 4.195; P < .001) versus supplements with EPA < 60% (effect size = −0.026; 95% CI, −0.200 to 0.148; t = −0.316; P = .756), with negligible contribution of random effects or heteroscedasticity and with no effects of treatment duration or age. Supplements with EPA < 60% were ineffective. Exploratory analyses supported a nonlinear model, with improvement determined by the dose of EPA in excess of DHA, within the range of 200 to 2,200 mg/d of EPA.

Conclusions: Supplements containing EPA ≥ 60% of total EPA + DHA, in a dose range of 200 to 2,200 mg/d of EPA in excess of DHA, were effective against primary depression. Translational studies are needed to determine the mechanisms of EPA's therapeutic benefit.

16. **Updated systematic review and meta-analysis of the effects of n-3 long-chain polyunsaturated fatty acids on depressed mood.** Appleton KM, Rogers PJ, Ness AR. Am J Clin Nutr. 2010 Mar;91(3):757-70. doi: 10.3945/ajcn.2009.28313. Epub 2010 Feb 3.

Abstract

BACKGROUND: The debate over a role for n-3 long-chain polyunsaturated fatty acids (n-3 PUFAs) in depressed mood continues.

OBJECTIVE: The objective was to update a previous systematic review and meta-analysis of published randomized controlled trials investigating the effects of n-3 PUFAs on depressed mood and to explore potential sources of heterogeneity.

DESIGN: Eight databases were searched for trials that randomly assigned participants to receive n-3 PUFAs/fish, measured depressed mood, used human participants, and included a comparison group up to April 2009.

RESULTS: Thirty-five randomized controlled trials were identified; 17 were not included in the previous review. The pooled standardized difference in mean outcome of the 29 trials that provided data to allow pooling (fixed-effects model) was 0.10 SD (95% CI: 0.02, 0.17) in those who received n-3 PUFAs compared with placebo, with strong evidence of heterogeneity ($I(2) = 65\%$, $P < 0.01$). The presence of funnel plot asymmetry suggested that publication bias was a likely source of this heterogeneity. Depressive symptom severity and participant diagnosis also explained some of the observed heterogeneity. Greater effects of n-3 PUFAs were found in individuals with more-severe depressive symptoms. In trials that enrolled individuals with a diagnosed depressive disorder, the combined mean difference was 0.41 (95% CI: 0.26, 0.55), although evidence of heterogeneity was also found ($I(2) = 71\%$). In trials that enrolled individuals without a depressive diagnosis, no beneficial effects of n-3 PUFAs were found (largest combined mean difference: 0.22; 95% CI: -0.01, 0.44; $I(2) = 0\%$).

CONCLUSIONS: Trial evidence of the effects of n-3 PUFAs on depressed mood has increased but remains difficult to summarize because of considerable heterogeneity. The evidence available provides some support of a benefit of n-3 PUFAs in individuals with diagnosed depressive illness but no evidence of any benefit in individuals without a diagnosis of depressive illness.

Drug Use Research & Management Program
Oregon State University
500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Drug Use Evaluation: Fish Oil / Omega – 3 Fatty Acids

Background: There is evidence of no efficacy for cardiovascular mortality or stroke, cancer prevention, or prevention of cognitive decline.[1] The results for adjunctive therapy for bipolar disease or depression are mixed from low level evidence.[1] This drug use evaluation describes the utilization of fish oil and omega-3 fatty acid (FO/O3) in the Oregon Health Plan (OHP) population to document costs, patient demographics and diagnostic distribution, and prescriber specialty distribution and geographic distribution.

Methods: Patients with a fee-for-service (FFS) paid drug claim for FO/O3 with a service date between July 1, 2012 and June 30, 2013 were included. FO/O3 claims are defined by the HICL Sequence Numbers in Appendix A. An "index" FO/O3 claim was defined as the first FO/O3 claim for a patient from July 1, 2012 to June 30, 2013. Patients with Medicare as defined by benefit packages BMM or BMD and patients with FFS eligibility of <75% of days in the study period were excluded. The study period was 1 year prior to the index FO/O3 claim thru June 30, 2013. Professional and outpatient claims from 1 year prior to the index FO/O3 claim thru June 30, 2013 were included for diagnostic information.

Results: There were 1,108 patients identified with a FFS FO/O3 claim. A significant number (n=695, 63%) were Medicare Part D patients (Table 1). Another 154 were excluded for <75% of days with FFS eligibility during the study period. The remaining 259 (23%) were analyzed. Table 2 describes the demographics of both the study population and the entire population on FO/O3. The study population is younger (mean age of 39 years versus 58 years) and more diverse ethnically (66% Caucasian versus 82%).

Table 1: Exclusions

	Count	Patients Left
Patients with FO/O3 claims – July 2012-June2013		1,108
Duals	695	413
<75% day eligibility during study period	154	259

Table 3 demonstrates that 52% of the total cost of claims comes from over-the-counter (OTC) products whereas when restricted to the study population this drops to just 15%. The legend product, omega-3 acid ethyl esters (i.e. Lovaza™), accounts for 48% of total claim costs but 84% of study population drug costs.

Table 2: Demographics

n=	259	%	1,108	%
Age on day of index claim				
Mean (Min - Max)	39.3 (7-74)		57.5 (7-101)	
< 13	13	5.0%	20	1.8%
13-18	41	15.8%	56	5.1%
19-64	201	77.6%	589	53.2%
> 64	4	1.5%	443	40.0%
Sex				
F	147	56.8%	660	59.6%
Ethnicity				
Caucasian	172	66.4%	913	82.4%

Table 3: Drugs Used July 2012-June2013

HSN - Generic Drug Name	Unique patient n=	%	Claim count	%	Total Amount Paid	%
Study Population n=	259		1,409		$73,771	
033347 - OMEGA-3 FATTY ACIDS/FISH OIL	189	73.0%	977	69.3%	$10,594	14.4%
026793 - OMEGA-3 ACID ETHYL ESTERS	67	25.9%	359	25.5%	$62,212	84.3%
035906 - PNV W-CA NO.37/IRON/FA/OMEGA-3	5	1.9%	14	1.0%	$306	0.4%
036020 - OMEGA-3/DHA/EPA/FISH OIL	4	1.5%	24	1.7%	$378	0.5%
034210 - SALMON OIL/OMEGA-3 FATTY ACIDS	4	1.5%	29	2.1%	$179	0.2%
033098 - PNV2/IRON B-G SUC-P/FA/OMEGA-3	1	0.4%	3	0.2%	$92	0.1%
002771 - OMEGA-3 FATTY ACIDS	1	0.4%	3	0.2%	$11	0.0%
Total Population n=	1,108		7,248		$147,617	
033347 - OMEGA-3 FATTY ACIDS/FISH OIL	925	83.5%	6121	84.5%	$67,771	45.9%
026793 - OMEGA-3 ACID ETHYL ESTERS	93	8.4%	411	5.7%	$70,580	47.8%
034210 - SALMON OIL/OMEGA-3 FATTY ACIDS	61	5.5%	455	6.3%	$4,730	3.2%
036020 - OMEGA-3/DHA/EPA/FISH OIL	21	1.9%	135	1.9%	$2,286	1.5%
035906 - PNV W-CA NO.37/IRON/FA/OMEGA-3	10	0.9%	22	0.3%	$615	0.4%
035602 - VIT C/VIT E/LUTEIN/MIN/OMEGA-3	9	0.8%	63	0.9%	$1,081	0.7%
002771 - OMEGA-3 FATTY ACIDS	6	0.5%	34	0.5%	$366	0.2%
033098 - PNV2/IRON B-G SUC-P/FA/OMEGA-3	4	0.4%	6	0.1%	$172	0.1%
036384 - PNV53/IRON B-G HCL-P/FA/OMEGA3	1	0.1%	1	0.0%	$15	0.0%

Table 4 reports the number of FO/O3 patients with selected diagnoses on a professional or outpatient claim in the year prior to the index claim and thru June 2013. Bipolar Disease was associated with the highest number of FO/O3 patients (n=47, 18%). Only 29 patients (11%) had a diagnosis of coronary artery disease or atherosclerosis. Excluding patients on the legend product (Lovaza™), this drops to 8%.

Table 4: Diagnoses associated with FO/O3 use (1 year prior to index FO/O3 claim)

Diagnosis	N=248	%
CAD or Atherosclerosis (410xx -414xx, 440xx)	29	11.2%
Heart Failure or Atrial Fibrillation (428xx, 4270x – 4273x)	26	10.0%
Bipolar (2961x, 2964x – 2969x)	47	18.1%
Depression (2962x-2963x)	26	10.0%
Dementia or Alzheimer's (290xx, 3310x)	1	0.4%

Table 5 represents the distribution of FO/O3 claims prescribed by various specialties. Family Practice, Internists and Family Nurse Practitioners account for 44% of all claims. Psychiatrists and Mental Health Nurse Practitioners account for 15% of all claims. Table 6 reveals Klamath, Yamhill, Lincoln and Union counties rank higher than expected relative to total OHP FFS population. Table 7 identifies two Family Nurse Practitioners in Klamath County as the highest prescribers but with less than 5% of total claims between them.

Table 5: Prescriber Specialty Distribution of all FO/03 claims July 2012-June2013

Prescriber Specialty	Unique Patients	%	Claim count	%	Total Amount Paid	%
n=	259		1,409		$73,771	
Family Practitioner	44	17.0%	251	17.8%	$16,662	22.6%
Psychiatrist	39	15.1%	187	13.3%	$2,952	4.0%
Family Nurse Practitioner	38	14.7%	152	10.8%	$6,215	8.4%
Internist	32	12.4%	216	15.3%	$17,870	24.2%
Nurse Practitioner	24	9.3%	105	7.5%	$2,866	3.9%
Physician Assistants	20	7.7%	63	4.5%	$3,717	5.0%
Pediatrics	17	6.6%	93	6.6%	$948	1.3%
Physician	16	6.2%	104	7.4%	$8,164	11.1%
UNKNOWN	10	3.9%	34	2.4%	$2,822	3.8%
Obstetrics & Gynecology	10	3.9%	26	1.8%	$217	0.3%
Certified Nurse Midwife	9	3.5%	33	2.3%	$491	0.7%
Advance Practice Nurse	6	2.3%	41	2.9%	$4,517	6.1%
Psychiatric Mental Health Nurse Practitioner	6	2.3%	31	2.2%	$975	1.3%
Indian Health Services 638 PPS	5	1.9%	11	0.8%	$247	0.3%
General Practitioner	5	1.9%	34	2.4%	$2,711	3.7%
Cardiologist	3	1.2%	23	1.6%	$1,197	1.6%
Naturopath	2	0.8%	16	1.1%	$181	0.2%
Optometrist	2	0.8%	13	0.9%	$252	0.3%
Physical Medicine and Rehabilitation Practitioner	2	0.8%	14	1.0%	$168	0.2%
Child & Adolescent Psychiatry	1	0.4%	2	0.1%	$21	0.0%
Billing Provider	1	0.4%	10	0.7%	$1,872	2.5%
Community Mental Health Center, Adult	1	0.4%	1	0.1%	$12	0.0%
FQHC - Community Health	1	0.4%	1	0.1%	$5	0.0%
Nephrologist	1	0.4%	4	0.3%	$794	1.1%
Neurological Surgeon	1	0.4%	1	0.1%	$7	0.0%
Neurologist	1	0.4%	1	0.1%	$10	0.0%
Nurse Practitioner Clinic	1	0.4%	2	0.1%	$15	0.0%
Osteopathic Physician	1	0.4%	1	0.1%	$190	0.3%
Primary Care - Federal Definition	1	0.4%	1	0.1%	$4	0.0%
Licensed Direct Entry Midwife (LDEM)	1	0.4%	6	0.4%	$3	0.0%

Table 6: Prescriber Geographic Distribution

Prescriber County	Unique Patients	%	Claim count	%	Total Amount Paid	%
n=	259		1,409		$73,771	
Multnomah County	67	25.9%	303	21.5%	$8,928	12.1%
Klamath County	26	10.0%	147	10.4%	$9,062	12.3%
Yamhill County	26	10.0%	146	10.4%	$6,771	9.2%
Lane County	18	6.9%	111	7.9%	$10,846	14.7%
UNKNOWN	29	11.2%	105	7.5%	$5,354	7.3%
Jackson County	17	6.6%	98	7.0%	$5,351	7.3%
Washington County	12	4.6%	74	5.3%	$3,927	5.3%
Lincoln County	18	6.9%	56	4.0%	$4,801	6.5%
Union County	6	2.3%	52	3.7%	$841	1.1%
Clatsop County	12	4.6%	51	3.6%	$1,562	2.1%
Marion County	8	3.1%	50	3.5%	$1,296	1.8%
Clackamas County	7	2.7%	43	3.1%	$628	0.9%
Josephine County	8	3.1%	32	2.3%	$986	1.3%
Douglas County	6	2.3%	26	1.8%	$1,508	2.0%
Tillamook County	3	1.2%	26	1.8%	$5,188	7.0%
Benton County	7	2.7%	14	1.0%	$385	0.5%
Wallowa County	1	0.4%	12	0.9%	$2,391	3.2%
Polk County	4	1.5%	12	0.9%	$569	0.8%
Malheur County	3	1.2%	13	0.9%	$612	0.8%
Deschutes County	1	0.4%	10	0.7%	$1,955	2.7%
Columbia County	1	0.4%	10	0.7%	$213	0.3%
Lake County	1	0.4%	7	0.5%	$96	0.1%
Crook County	1	0.4%	7	0.5%	$90	0.1%
Coos County	1	0.4%	1	0.1%	$193	0.3%
Curry County	1	0.4%	1	0.1%	$190	0.3%
Umatilla County	1	0.4%	2	0.1%	$26	0.0%

Table 7: Top 20 Prescribers by Claim Count

Rank	Specialty	County	Unique Patients	%	Claim Count	%	Total Amount Paid	%
		n=	259		1,409		$73,771	
1	Family Nurse Practitioner	Klamath County	5	1.9%	37	2.6%	$2,213	3.0%
2	Family Nurse Practitioner	Klamath County	8	3.1%	26	1.8%	$1,656	2.2%
3	Psychiatrist	Multnomah County	5	1.9%	25	1.8%	$258	0.3%
4	Internist	Lane County	3	1.2%	24	1.7%	$274	0.4%
5	Obstetrics & Gynecology	Multnomah County	9	3.5%	24	1.7%	$209	0.3%
6	Internist	Yamhill County	2	0.8%	23	1.6%	$4,510	6.1%
7	General Practitioner	Multnomah County	3	1.2%	22	1.6%	$655	0.9%
8	Physician (Default Spec)	Yamhill County	3	1.2%	22	1.6%	$163	0.2%
9	Physician (Default Spec)	Yamhill County	2	0.8%	21	1.5%	$215	0.3%
10	Physician	Multnomah County	3	1.2%	17	1.2%	$3,361	4.6%
11	Physician Assistants	Lincoln County	10	3.9%	17	1.2%	$226	0.3%
12	Psychiatrist	Josephine County	3	1.2%	16	1.1%	$759	1.0%
13	Physician (Default Spec)	Multnomah County	2	0.8%	16	1.1%	$218	0.3%
14	Family Practitioner	Union County	2	0.8%	16	1.1%	$194	0.3%
15	Internist	Lincoln County	1	0.4%	15	1.1%	$2,146	2.9%
16	Family Nurse Practitioner	Multnomah County	2	0.8%	15	1.1%	$179	0.2%
17	Nurse Practitioner (default Spec)	Yamhill County	5	1.9%	15	1.1%	$121	0.2%
18	Unknown	Unknown	5	1.9%	14	1.0%	$427	0.6%
19	Psychiatrist	Multnomah County	2	0.8%	14	1.0%	$213	0.3%
20	Physical Medicine and Rehabilitation Practitioner	Yamhill County	2	0.8%	14	1.0%	$168	0.2%

Discussion: There is little evidence to support the use of FO/O3 products for any indication but more than 1,100 patients had paid claims from July 2012 to June 2013 at a total cost of $147,617. Over 63% of these were Medicare patients who are associated with close to half the drug costs because OHP is paying for the over-the-counter products under Medicare Part D. It is difficult to draw conclusions about the Medicare population based upon available data.

Of the analyzed patients (n=259), the predominant product used was the over-the-counter fish oil supplements. The legend product (Lovaza™) is non-preferred in the Other Lipotropics PDL class and requires prior authorization to enforce step therapy with drugs of higher quality evidence of efficacy first. The legend product is indicated as adjunctive therapy for the treatment of hypertriglyceridemia (≥500 mg/dL). Only 11% of patients had a claim with a diagnosis of coronary artery disease or atherosclerosis while 26% of patients had a claim for the legend product. If patient on the legend product are excluded, only 8% of patients on the OTC products had a diagnosis for coronary artery disease or atherosclerosis. There is no evidence of wide-spread use of fish oil supplements in lieu of the legend product for this indication.

There is some evidence of significant use for psychiatric indications despite low level evidence and mixed results. Psychiatric specialties accounted for 15% of claims and 18% of patients had a bipolar disease diagnosis and 10% of patients a depression diagnosis.

There is no evidence of use of fish oil products for Alzheimer's disease or dementia in the study population though that can't be ruled out in the Medicare population.

The use of FO/O3 is not heavily concentrated in any geographic location although Klamath, Yamhill, Lincoln and Union counties rank higher than expected per capita.

This analysis is limited by the potential for missing diagnostic codes and the inability to determine what a drug is being prescribed for from administrative claims.

Recommendation:

1) Retain legend omega-3 acid ethyl esters (i.e. Lovanza™) as non-preferred.
2) Put all over-the-counter FO/O3 products on the "Excluded Drug List". Drugs on this list used for funded diagnoses will be approved through the administrative appeals process.
3) Publish an Oregon State Drug Review on FO/O3 detailing the lack of evidence and announcing the policy prior to implementation.

References:

1. Oregon Health Authority - Pharmacy and Therapeutics Committee. Abbreviated New Drug Evaluation: Omega - 3 Fatty Acids. Available at: http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/meetings/meetingdocs/2014_01_30/drafts/FishOil_CR.pdf. Accessed December 21, 2013.

Appendix A – Fish Oil or Omega-3 Fatty Acid Products Included

HICL Sequence Number	Generic Drug Name
16617	OMEGA-3 FATTY ACIDS/VITAMIN E
20648	OMEGA-3 FATTY ACIDS/VIT E MIX
25775	UBIDECARENONE/OMEGA-3/VIT E
26450	GLUC SU/OMEGA-3/VITAMIN E
26793	OMEGA-3 ACID ETHYL ESTERS
2771	OMEGA-3 FATTY ACIDS
32889	FISH OIL/DHA/EPA
33098	PNV2/IRON B-G SUC-P/FA/OMEGA-3
33347	OMEGA-3 FATTY ACIDS/FISH OIL
33561	FISH OIL/OM-3/DL-E/FA/B6-B12
33859	FISH OIL/VIT E/FAT NO.5/HC137
34210	SALMON OIL/OMEGA-3 FATTY ACIDS
34684	FISH OIL/OMEGA-3/VIT C/VIT E
34950	PNV NO10/IRON FUM&P/FA/OMEGA-3
35385	MV, MIN CMB#8/FA/CO Q10/OMEGA3
35602	VIT C/VIT E/LUTEIN/MIN/OMEGA-3
35708	FISH OIL/FAT NO.8/HRB COMB.137
35906	PNV W-CA NO.37/IRON/FA/OMEGA-3
35931	UBIDECAR/FISH OIL/OMEGA-3/VITE
35960	OM-3/EPA/DHA/FISH OIL/FLAX/E
36020	OMEGA-3/DHA/EPA/FISH OIL
36082	OMEGA-3/DHA/EPA/TUNA OIL
36166	PHYTOSTEROL/VIT D3/ FISH OIL
36202	FA/OMEGA-3/DHA/EPA/ST.JOHN
36320	FISH OIL/BORAGE/FLAX/OM3,6,9#1
36336	PNV17/IRON/FA/FISH OIL/DHA/OM
36384	PNV53/IRON B-G HCL-P/FA/OMEGA3
36386	PNV54/IRON B-G HCL-P/FA/OMEGA3
36394	PNV54/IRON B-G SUC-P/FA/OMEGA3
36395	PNV53/IRON B-G SUC-P/FA/OMEGA3
36398	OM-3/DHA/EPA/FISH OIL/VIT D3
36453	FISH,SAF,FLX,BRG OILS/O3,6,9#2
36932	MV-MN/FA/LYCOP/OMEGA 3,6,9 #3
37005	PNV#20/IRON/FA/DS/FISH/DHA/EPA
37006	OMEGA-3/DHA/EPA/LUT/ZEAXANTHIN
37058	OMEGA-3/DHA/EPA/FISH OIL/COQ10
37087	OM-3/DHA/EPA/FISH OIL/L. CASEI

HICL Sequence Number	Generic Drug Name
37167	OMEGA-3/DHA/CARBOHYDRATE SUPP
37169	OMEGA-3/DHA/ARA/CARBOHYDRATE
37181	KRILL OIL/OMEGA-3/DHA/EPA
37253	PNV82/FEPS/FA/OM3/DHA/EPA/FISH
37289	PN85/IRON CB&ASP G/FA/DHA/FISH
37292	MV/FA/DHA/EPA/FISH OIL/SAW/GNK
37302	MV/FA/DHA/EPA/FISH/CAL/D3/GINK
37332	OMEGA-3S/DHA/EPA/FISH OIL
37380	FLAXSEED/OMEGA3,6,9/FATTY ACID
37411	BORAGE &FISH OIL/FRUCT/SOY LEC
37423	MV-MINERALS/FA/OMEGA 3,6,9 #3
37424	MV-MN/IRON FUM/FA/OMEGA3,6,9#3
37554	PHOSPSERIN/OMEGA-3/DHA/EPA
37558	PHYTOSTEROL/OM-3/DHA/EPA/FISH
37714	PNV29/IRON CB&ASPG/FA/DHA/FISH
37747	OMEGA 3/DHA/EPA/VITAMIN D3
37751	OMEGA 3/DHA/EPA/OTHER OM3/D3
38143	OMEGA-3S/DHA/EPA/FISH OIL/D3
38496	MV-MIN/FA/D3/OM-3/DHA/EPA/FISH
38733	MV,FE/FA/D3/OM-3/DHA/EPA/FISH
38921	PNV100/IRON EDTA&PS/FA/OMEGA3
39204	PNV105/IRON/FA/OMEGA 3/DHA/EPA
39215	KRILL/OMEGA-3/DHA/EPA/LIPIDS
39350	OMEGA-3/DHA & EPA/ALA/VIT D3
39621	OMEGA-3/DHA/EPA/VIT E
39740	PNV110/IRON/FA/OMEGA 3/DHA/EPA
39804	GLUC/CHND/OM3/DHA/EPA/FISH/STR
39915	MV-MN/FE/FA/K/D3/CHOL/DHA/FISH
40264	MV/FA/D3/OM3/FISH/SAW PAL/ARG
40270	OMEGA-3/DHA/EPA/DPA/FISH OIL
40315	PNV113/IRON/FA/OMEGA-3/DHA/EPA
40321	FLAXSEED OIL/OMEGA 3,6,9
40329	PNV62/FA/OM3/DHA/EPA/FISH OIL
6184	BRAN/LECITHIN/OMEGA-3/MULTIVIT

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

New Drug Evaluation: Bedaquiline

Month/Year of Review: January 2014
Generic Name: Bedaquiline
PDL Class: None

End date of literature search: September 1, 2013
Brand Name (Manufacturer): Sirturo ™
Dossier Received: Yes

FDA Approved Indication:

Bedaquiline is indicated as part of combination therapy for the treatment of patients who are ≥ 18 years of age and have pulmonary multi-drug resistant tuberculosis (MDR-TB) when an effective treatment regimen cannot otherwise be provided. Bedaquiline is not indicated for latent, extra-pulmonary, or drug-sensitive TB.[1]

Research Questions:

- Is bedaquiline plus combination therapy for MDR-TB superior to combination therapy plus placebo (PLA) for preventing treatment failure, relapse, or death?
- Is there evidence bedaquiline is safer than other currently available agents for the treatment of MDR-TB?
- Are there subpopulations in which bedaquiline is either more effective or safer than other currently available agents?

Conclusions:

- At this time, the evidence supporting bedaquiline efficacy is low, due to the absence of phase 3 studies. Among the shortcomings of the phase 2 studies used as the basis for accelerated approval of bedaquiline are (1) small patient numbers, (2) short length of study, and (3) surrogate endpoints with limited specificity and sensitivity for predicting failure and relapse. Therefore, at this time, bedaquiline's ability to prevent treatment failure, relapse, or death remains largely uninvestigated. Accordingly, MDR-TB is intended for patients for whom other effective options for treating MDR-TB have been exhausted.

- Bedaquiline use comes with serious safety concerns, considerable monitoring, and several drug-drug interactions likely to be encountered in practice. Bedaquiline carries a black box warning for increased risk of death (NNH 11) and has been associated with QT prolongation and hepatic-related ADRs (NNH 20).

Unanswered safety questions include: What is the cause of or factors associated with increased risk of death in bedaquiline-treated patients? What is the safety profile of bedaquiline in pediatric, geriatric, and HIV patients as well as patients with severe renal or hepatic impairment and extrapulmonary TB? What is bedaquiline's safety profile when used beyond the limited number of patients within a phase 2 trial?

- Options for treating MDR-TB are limited; therefore, bedaquiline represents an important need, not only to affect a cure among infected individuals who may need another option to treat resistant strains but also to suppress the spread of the disease to others. Because increased risk of death among patients taking bedaquiline has been observed, the drug should only be used when an effective treatment regimen cannot otherwise be provided.

Recommendations:

- Currently no PDL class for antimycobacterial agents exists. However, for safety issues, prior authorize bedaquiline to limit its use to patients infected with active pulmonary MDR *M. tuberculosis* when
  - an effective antimycobacterial regimen cannot otherwise be provided and
  - the drug is used in association with an MDR-TB regimen that includes at least 3 drugs to which the patient's MDR-TB isolate is susceptible to *in vitro* or, if *in vitro* testing is unavailable, 4 other drugs to which the patient's isolate is likely susceptible.
- Documentation of the following should be provided:
  - diagnosis of active pulmonary MDR-TB (i.e., not latent or drug-sensitive TB)
  - resistance of the patient's isolate to at least isoniazid and rifampin
  - susceptibility of the patient's isolate to bedaquiline
  - prescriptions for 3 or 4 concomitant medications used to treat MDR-TB
  - the use of expert medical consultation
- Make bedaquiline non-preferred and consider reviewing the entire class in the future to identify preferred options.

Reason for Review:

Bedaquline, a recently approved agent for the treatment of MDR-TB, currently has no PDL class to manage either it or any other antimycobacterial agent. Prudence dictates bedaquiline should be used appropriately to ensure patient safety and prevention of further *M. tuberculosis* resistance to bedaquiline. Accordingly, this review will evaluate the evidence for bedaquiline's efficacy and focus on safety and appropriate use.

Background:

New drugs to treat MDR-TB are urgently needed, as treatment options are limited and an estimated one-third of the world's population is infected with *M. tuberculosis*. The overall mortality for MDR-TB is greater than 10% (range 8 to 21%) for patients in a good treatment program, and the case fatality rate of patients with MDR-TB and HIV is about 26%.[2]

In 2012, 61 verified cases of TB (1.6 cases per 100,000) occurred in Oregon, 74% of which were among foreign-born residents. About 8% of the isolates tested were resistant to isoniazid (INH), and one case of TB exhibited multidrug resistance (MDR). This compares to a TB rate of 3.2 cases per 100,000 nationally, with 98 cases of TB (1.3%) having MDR in 2011. About 83% of MDR-TB cases were foreign-born.[6]

Bedaquiline was developed to treat MDR-TB, which is defined as a strain resistant to at least isoniazid (INH) and rifampin (RMP). Extremely drug resistant (XDR) TB is a still rare type of TB that is resistant INH and RMP plus any fluoroquinolone (FQ) and at least one of three injectable second-line

drugs (i.e., amikacin, kanamycin, or capreomycin). Pre-XDR-TB is MDR-TB that has become resistant to at least one second-line injectable drug or to any fluoroquinolone [2,7]

The goals of TB therapy are to (1) cure patients and restore quality of life and productivity; (2) prevent death from active or the latent effects TB; (3) prevent TB relapse; (4) reduce the transmission of TB to others; and (5) prevent the development of and transmission of resistant organisms.[8]

Treatment for MDR-TB is complex and has a cure rate of 41-70%.[2] The general principles for designing MDR-TB treatment regimens are to use at least four drugs more certain to be effective. Effective drugs include those with known rare resistance, drug susceptibility tests (DST) showing susceptibility for drugs with good DST reliability (injectable agents and FQs, INH, and RMP), common use in the area, and no failure history in the patient or close contacts of the patient for whom the drugs are used. Drugs unsafe for the patient and drugs for which there is the possibility of cross-resistance should not be used.[8]

In the U.S., treatment of MDR-TB should be performed by or in consultation with an expert in its management. Treatment regimens employed are based on the pattern of drug resistance and typically include five drugs administered for durations up to 24 months. Patients should receive hospital-based or home-based DOT. Suggested regimens to treat MDR-TB include ethambutol and/or pyrazinamide; a fluoroquinolone (levofloxacin, ofloxacin, ciprofloxacin); an injectable (streptomycin, amikacin, kanamycin, capreomycin), and one or two alternative agents (cycloserine, ethionamide, p-aminosalicylic acid, clarithromycin, amoxicillin-clavulanate, linezolid).[7] However, the optimal use and contribution of individual drugs to MDR-TB regimens is unknown, and many second-line drugs are associated with toxicities. Few randomized–controlled trials have assessed the risk-benefit profile of MDR-TB regimens. [2,7]

In evaluating TB regimens in clinical trials, the phase 3 primary endpoint is a composite outcome of failure at the end of treatment or relapse after stopping the treatment. Failure to culture TB organisms does not necessarily indicate a cure. An effective regimen is one that not only converts patients to culture-negative by treatment's end but also prevents relapse. Therefore, clinical trials to evaluate new regimens commonly include follow-up beyond the end of 18 to 24 month's treatment. A systematic review of sputum monitoring for predicting outcome to TB treatment found the two-month culture had limited sensitivity and specificity for predicting failure and relapse.[9]

October 2013, the Centers for Disease Control and Prevention (CDC) published provisional guidelines for the use and safety of bedaquiline.[10] These guidelines state bedaquiline may be used:

- *for 24 weeks of treatment in adults with laboratory-confirmed pulmonary MDR TB (TB with an isolate showing genotypic or phenotypic resistance to both INH and RIF) when an effective treatment regimen cannot otherwise be provided. (Quality of evidence: low)*
- *on a case-by-case basis in children, HIV-infected persons, pregnant women, persons with extrapulmonary MDR TB, and patients with comorbid conditions on concomitant medications when an effective treatment regimen cannot otherwise be provided. (Quality of evidence: insufficient)*
- *on a case-by-case basis for durations longer than 24 weeks when an effective treatment regimen cannot be provided otherwise. (Quality of evidence: insufficient)*

With regard to the second and third recommendations, the CDC further states the effectiveness and safety of bedaquiline have not been studied adequately in these populations or beyond 24-weeks' duration; therefore, general guidance cannot be provide for or against its use. However, because MDR TB has a high mortality rate and limited treatment options, providers might consider bedaquiline in treating certain patients in the groups listed above or for longer durations in some patients.

Clinical Efficacy:

The FDA based accelerated approval of bedaquiline on two phase 2 clinical trials: a two-stage study called C208 and study C209. Study C208 stage 2 was considered the pivotal trial, while C208 stage 1 was considered exploratory and provided supportive evidence along with study C209. These studies assessed the ability of a bedaquiline MDR-TB regimen to reduce the time to sputum culture conversion after 8 or 24 weeks and increase the proportion of patients with negative sputum cultures vs an MDR-TB regimen plus placebo. A phase 3 trial is planned to further assess bedaquiline efficacy and safety.[2]

C208 was a multicenter, stratified, double-blind, randomized, placebo-controlled trial. The study's two stages were separate and consecutive. C208 stage 2 randomized subjects with sputum-positive pulmonary MDR-TB to receive a recommended 5-drug background regimen (BR) with either placebo (PLA) or bedaquiline for 24 weeks. After the bedaquiline and PLA treatment period, BR was continued to 72-96 weeks. Patients in the bedaquiline arm (n=21) received 400 mg daily weeks 1 and 2 and, then, bedaquiline 200 mg thrice weekly for weeks 3 through 24. The BR consisted of kanamycin, ofloxacin, ethionamide, pyrazinamide, and cycloserine or terizidone, with modifications allowed based on susceptibility test results during the course of the study, adverse events, or drug supply interruption. All treatment was administered via directly observed therapy (DOT). Stratification was by trial site and by the extent of lung cavitation: <2 cm, cavitation (≥2 cm) unilaterally, or ≥2 cm bilaterally. The primary endpoint was TSCC during treatment, which was defined as the time interval from initiation of bedaquiline or placebo treatment to the first of two consecutive negative cultures from sputa collected 25 days apart. [2]

The analysis population was predominantly male (64%), black (37%), and HIV negative (86%) with a median age of 33 years. At least 89% of patients had previous use of TB drug treatment and 83% had cavitary pulmonary disease. Differences in baseline characteristics between treatment groups included more HIV infected patients in the PLA group (21%) vs the bedaquiline group (8%), more $MDR_{H\&R}$-TB patients enrolled in the placebo group (68%) compared to the bedaquiline group (59%), and more pre-XDR TB isolates (a protocol violation) in the bedaquiline group (23%) vs the PLA group (18%). Analyses used a modified intent to treat (mITT) population that excluded patients with (1) DS-TB, XDR-TB, or unconfirmed MDR-TB or (2) no evidence of culture positivity prior to baseline or no results during the first 8 weeks after baseline. Analysis of the primary efficacy endpoint revealed a median TSCC at 24 weeks of 83 days for the bedaquiline group (CI: 56 to 97) and 125 days for the PLA group (CI: 98 to 168). Culture conversion rates at 24 weeks, the secondary endpoint, were 78% for the bedaquiline group and 58% for the placebo group for a NNT of 5. However, the difference in conversion rates were not significant at 72 weeks.[2]

C208 stage 1 was similarly designed to stage 2 but differed in that 44 subjects, randomized 1:1, comprised the mITT population and subjects were treated with bedaquiline or PLA plus BR for 8 weeks. The primary endpoint was TSCC during treatment, which was defined as the time interval from initiation of bedaquiline or placebo treatment to the first of two consecutive negative weekly cultures. In this study, the bedaquiline group again more quickly converted positive sputum cultures to negative: HR 11.8 (CI: 2.3 to 61.3, p=0.003). The actual mean TSCCs for each group were not provided. The rates of conversion were 48% (10/21) for the bedaquiline group and 9% (2/23) for the PLA group (difference 38.9%; CI: 12.3% to 63.1%; p=0.004) for a NNH of 3. However, no significant difference in conversion rates was evident at 24 and 104 weeks. [2–4]

Study C209 was a phase 2, single-arm, open-label study to evaluate the efficacy, safety, and tolerability of bedaquiline plus BR in the treatment of adults with pulmonary MDR-TB, including pre-XDR-TB and XDR-TB. The bedaquiline dose, treatment duration, primary efficacy endpoint, and main secondary endpoint were the same as C208 stage 2. The mean TSCC was 57 days (CI: 56 to 83). The culture conversion rate at 24 weeks was 79.5%.[2,5]

Among the shortcomings of the phase 2 studies used as the basis for accelerated approval of bedaquiline are small patient numbers, short length of study, and surrogate endpoints. At this time, bedaquiline's ability to prevent treatment failure, relapse, or death remains largely uninvestigated. Importantly, these studies leave open the following efficacy questions:
What is the efficacy of bedaquiline in phase 3 trials with treatment failure, relapse, and mortality as endpoints?
How will bedaquiline perform in the United States? These studies took place predominantly in South Africa, which has different demographics, resistance patterns, and drug availability from the United States and has endemic TB.
How will bedaquiline perform in HIV patients? Too few HIV patients were used in the trials to make this determination.

Clinical Safety:[1]

An increased risk of death was observed in the treatment group receiving bedaquiline plus BR versus the group receiving PLA plus BR: 11.4% (9/79) v. 2.5% (2/81); NNH 11. One death occurred during the 24-week bedaquiline treatment period, while the median time to death for the remaining decedents was 329 days after the last bedaquiline dose. The imbalance in deaths remains unexplained and, thus far, appears unrelated to sputum culture conversion, relapse, sensitivity to other TB drugs used, or disease severity. Bedaquiline also has been associated with QT prolongation. In a RCT, the largest mean increase in QTc was 15.7 ms for the bedaquiline group and 6.2 ms for the placebo group at week 18 of 24 weeks of treatment. These increases persisted after bedaquiline treatment ended.

More hepatic-related ADRs were observed in patients taking bedaquiline plus background therapy vs. those on other MDR-TB regimens. In two studies, 10.8% (11/102) of bedaquiline-treated patients versus 5.7% (6/105) of placebo-treated patients developed aminotransferase elevations at least 3 times the ULN (NNH 20). Limited data exist on the use of bedaquiline in patients with HIV (n=22), and these patients were not receiving antiretroviral therapy.

In a 24-week phase 2b study, adverse reactions occurring in ≥10% of subjects treated with bedaquiline (n=79) and at a frequency greater than placebo (n=81) were nausea (38% v 32.1%), arthralgia (32.9% v. 22.2%), headache (27.8% v. 12.3%), hemoptysis (17.7% v. 11.1%), and chest pain (11.4% v. 7.4%).

Unanswered safety questions include the following:
What is the cause of or factors associated with increased risk of death in bedaquiline-treated patients? What is the safety profile of bedaquiline in pediatric, geriatric, and HIV patients as well as patients with severe renal or hepatic impairment and extrapulmonary TB? What is bedaquiline's safety profile when used beyond the limited number of patients within a phase 2 trial?

COMPARATIVE CLINICAL EFFICACY[2–5]

Relevant Endpoints:

1) Failure at the end of treatment
2) Relapse after stopping treatment
3) Morbidity and mortality
4) Serious adverse effects

Primary Study Endpoint:

1) Time to sputum culture conversion (TSCC) from positive to negative, defined as the interval between the date of treatment initiation and the date of acquisition of the first of at least two consecutive negative weekly cultures.
2) Serious adverse effects

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (95% CI, p-values)	ARR NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
1. C208 Stage 2 Phase 2, DB, RCT, stratified, MC from FDA Medical Review	1. BED/BR: BED 400 mg QD + BR weeks 1-2 then BED 200 mg 3 times/wk + weeks 3-24 (then BR per guidelines) 2. PLA /BR weeks 1-24 (then BR alone per guidelines) Investigational duration: 24 weeks (final analysis at 120 weeks)	**Demographics (mITT):** Age (median): 34, 33 · Male: 68%, 61% · Race: Black: 36%, 38% White race: 9%, 12% Other race: 55%, 50% · HIV + : 8%, 21% (CD4+ cell count [median]: 463, 433) · Lung cavitation (%): ≥2 cm cavity bilaterally: 18%, 23% ≥2 cm cavity unilaterally: 64%, 62% no cavity ≥2 cm: 18%, 15% · Resistance extent: MDR-TB: 100%, 100% $MDR_{H\&R}$-TB: 59%, 68% Pre-XDR-TB: 23%, 18% · Any previous use of TB drug treatment: 91%, 88% **Inclusion Criteria:** · age 18–65 · newly diagnosed pulmonary TB resistant to INH and RMP · treatment naïve or first-	**mITT** 1. 67 2. 66	**Median TSCC at 24 weeks:** 1. BED/BR: 83 days (CI: 56 to 97) 2. PLA/BR: 125 days (CI: 98 to 168) Relative risk: 2.15 [1.39 to 3.31, p=0.0005] **Secondary endpoints: Culture conversion rates:** **at 24 weeks:** 1. BED/BR: 78% 2. PLA/BR: 58% (Difference 20% [CI: 4.5% to 35.6%, p=0.014]) **at 72 weeks**	NA 20/5	**Any SAEs overall treatment phase:** BED/BR: 24.1% PLA/BR: 18.5% **Deaths up to 120 weeks:** BED/BR: 11.4% PLA/BR: 2.5% (CI: 1.1 to 18.2, p=0.031) **TEAEs leading to D/C of study drug:** BED/BR: 9.1% PLA/BR: 7.6%	5.6/18 8.9/11 1.5/66	**Quality rating:** Poor **Internal Validity:** · This study possessed the shortcomings of a phase 2 study, including small, inadequate patient numbers, insufficient length of study, and the use of surrogate endpoints. · More HIV+ patients enrolled in the PLA group than BED group. More $MDR_{H\&R}$-TB patients enrolled in PLA group than BED group. Pre-XDR patients were enrolled in the study (protocol violation) More pre-XDR TB isolates in the BED group than the PLA group. The background regimen was modified in 39% of patients. **External Validity:** · Use of known CYP3A4 inducers and inhibitors and drugs with proarrhythmic potential were prohibited during the study. Many HIV antiviral regimens include CYP3A4 substrates, inducers, and inhibitors. · Performance of bedaquiline in a population with demographics the same or similar to the U.S. is unknown as trial participants were predominantly from South Africa (54%). Also, the numbers of HIV-positive patients in the study were insufficient to determine the efficacy and safety of bedaquiline in that population. · TB is endemic to the population used in this trial and most have previous experience with TB drugs. · Culture conversion rates may not be durable.

		line drug experience (INH, RMP, EMB, PZA, or SM) · able to produce sputum ≥10 mL nightly · D/C all TB meds 7 d before baseline assessment **Exclusion Criteria:** · pregnancy or breastfeeding · isolates not susceptible to aminoglycosides other than SM and FQs · HIV (+) w/ CD4 count <300 cells/µL or antifungal or antiretroviral therapy in previous 90 d · significant cardiac arrhythmia · alcohol/drug use that would compromise compliance · concomitant severe illness or deteriorating health, including immunodeficienc or GI disorder interfering with BED absorption · medical condition that would interfere with trial participation · at risk for QT/QTc prolongation · significant lab abnormalities · TB strain not susceptible to at least 3 of 5 drug classes for treating MDR-TB · chorioretinitis, optic neuritis, uveitis		1. BED/BR: 71% 2. PLA/BR: 56% (Difference 15% [CI: -1.1% to 31.4%, p=0.070])	NS			**Analysis:** · The results of this exploratory study suggest bedaquiline could successfully treat MDR-TB, but the effect over the full treatment duration may be no better than current regimens. Furthermore, the drug comes with serious safety concerns that may include death. Therefore, it should be considered a last-line therapy. Phase 3 trials are needed to fully assess its efficacy and safety. · The cause of imbalance in deaths between the bedaquiline and placebo arms is unknown.
2.Study C208 Stage Phase 2, DB, RCT, stratified, South Africa	1. BED/BR: BED 400 mg QD + BR weeks 1-2 then BED 200 mg 3 times/wk + BR weeks 3-8 (then BR per guidelines) *	**Demographics (ITT)**: (BED/BR, PLA/BR): · Age (median): 33, 33 · Male: 78%, 71%	**mITT** 1. 21 2. 23	**TSCC at 8 weeks:** HR 11.8 (CI: 2.3 to 61.3,		**SAEs DB treatment phase:** 1. BED/BR:		**Quality Rating:** Poor **Internal Validity:** · This study possessed the shortcomings of a phase 2 study, including small, inadequate patient numbers,

from Diacon et al (2009 and 2012) and FDA Medical Review	2. PLA /BR (then BR per guidelines) Investigational duration: 8 weeks Final analysis at 104 weeks *Subsequent intermittent doing of bedaquiline 200 mg thrice weekly was selected to maintain plasma concentrations above target average Css of 600 ng/µL	・Race Black: 56%, 54%・・ White: 0%, 4% Other: 44%, 42% ・HIV positive: 13%, 12% ・Lung cavitation (%): ≥2 cm cavity bilaterally: 26%, 29% ≥2 cm cavity unilaterally: 61%, 54% no cavity ≥2 cm: 13%, 17% ・Resistance results: pyrazinamide: 59%, 70% ethambutol: 65%, 55% kanamycin: 6%, 10% ofloxacin: 6%, 10% ethionamide: 12%, 5% ・Background Regimen: KAN or AMK, ETA, + PZA: 100%, 100% OFX: 100%, 96% EMB: 61%, 62% TZD or cycloserine: 52%, 67% **Inclusion criteria:** ・age 18−65 ・newly diagnosed pulmonary TB resistant to INH and RMP **Exclusion criteria:** ・isolates not susceptible to aminoglycosides (other than SM) and FQs or if previously treated for MDR-TB ・severe extrapulmonary manifestations of TB ・HIV+ with a CD4+ <300 or had received antiretroviral or antifungal meds in the previous 90 days		p=0.003) TSCC at 24 weeks: HR 2.25 (CI: 1.08 to 4.71, p=0.031) **Secondary endpoint: Culture conversion rates:** **at 8 weeks:** 1. BED/BR: 47.6% 2. PLA/BR: 8.7% (difference 38.9% [CI: 12.3% to 63.1%, p=0.004]) **at 24 weeks:** 1. BED/BR: 81% 2. PLA/BR: 65.2% (difference 14.8% [CI: -11.9% to 41.9%, p=0.29]) **at 104 weeks:** 1. BED/BR: 52.4% 2. PLA/BR: 47.8% (difference 4.6% [CI: -25.5% to 34.1%, p=0.76])	NA 39/3 NS NS	4.8% (n=1) 2. PLA/BR: 4.3% (n=1) **Deaths:** 0 **TEAEs leading to D/C of study drug:** 1. BED/PR: 0% 4. PLA/BR: 0%	NS NA NS	insufficient length of study, and the use of surrogate endpoints. ・The actual median TSCC was not reported. **External Validity:** ・Use of known CYP3A4 inducers and inhibitors and drugs with proarrhythmic potential were prohibited during the study. Many HIV antiviral regimens include CYP3A4 substrates, inducers, and inhibitors. ・Performance of bedaquiline in a population with demographics the same or similar to the U.S. is unknown as the trial location was South Africa and only one patient, in the PLA group, was Caucasian. Also, the numbers of HIV-positive patients in the study were insufficient to determine the efficacy and safety of bedaquiline in that population. ・TB is endemic to the population used in this trial and most have previous experience with TB drugs. ・Subsequent intermittent dosing of bedaquiline 200 mg thrice weekly was selected to maintain plasma concentrations above target average Css of 600 ng/µL. This protocol is not included in prescribing information for bedaquiline. ・Culture conversion rates may not be durable. **Analysis:** ・The results of this exploratory study suggest bedaquiline could successfully treat MDR-TB, but the effect over the full treatment duration may be no better than current regimens. Phase 3 trials are needed to fully assess its efficacy and safety. Therefore, it should be considered a last-line therapy.

		· Alcohol or drug abuse · Concomitant illness · Abnormal laboratory values · Pregnancy or breastfeeding						
3. C209 Phase 2, open-label, single-arm, MC from Clinicaltrials.gov (10/6/2013) and FDA Medical Review	BED/BR: BED 400 mg QD weeks 1-2 + BR then BED 200 mg 3 times/wk weeks 3-24 then BR (then BR per guidelines) Duration: 24 weeks	**Demographics (mITT):** Age (median): 32 · Male: 64% · Race: Black: 33% White race: 23% Asian: 41% Native American: 3% · HIV positive (%): 5% (CD4+ cell count [median]: 692, 656) · Lung cavitation (%): bilaterally: 13% unilaterally: 53% no cavity: 34% · Resistance extent: MDR-TB: 100% $MDR_{H\&R}$-TB: 45% Pre-XDR-TB: 22% XDR-TB: 18% · Any previous use of TB drug treatment: 91%, 88% **Inclusion Criteria:** · Females on contraception or abstaining · Pulmonary MDR-TB, including XDR-TB **Exclusion Criteria:** · Significant cardiac arrhythmias · Complicated or severe extrapulmonary TB · Certain QT/QTc characteristics · Pregnant or breastfeeding	**mITT** 205	**Median TSCC:** 57 days (CI: 56 to 83) **Secondary endpoints:** **Culture conversion rates at 24 weeks:** 79.5**%**	NA NA	**Any SAEs overall treatment phase:** 11.6%	NA	**Quality rating:** Poor As an open-label, single-arm study, this study does not constitute an adequate, well-controlled study.

		women						

BED: bedaquiline, BR: background regimen (standard five-drug, second-line TB regimen: kanamycin or amikacin, ofloxacin or ciprofloxacin, ethionamide or prothionamide, cycloserine or terizidone or ethambutol, or other substitutions indicated by susceptibility testing), AMK: amikacin, EMB: ethambutol, ETA: ethionamide, FQ: fluoroquinolone, INH: isoniazid, KAN: kanamycin, OFX: ofloxacin, PZA: pyrazinamide, RMP: rifampin, SM: streptomycin, TZD: terizidone, AEs: adverse events , DB: double blind, D/C: discontinuation, DS-TB: drug-susceptible TB, mITT: modified intent to treat, a subset of the ITT population that excludes patients with DS-TB, XDR-TB, or unconfirmed MDR-TB and patients with no evidence of culture positivity before baseline or no results during the first 8 weeks after baseline, NA: not applicable, PF: placebo-free, MC: multicenter, PLA: placebo, RCT: randomized controlled trial, SAE: serious adverse event, TEAE: treatment emergent adverse event

References:

1. Sirturo prescribing information. Titusville, NJ: Janssen Therapeutics. December 28, 2012.
2. Center for Drug Evaluation and Research. Medical Review Application Number: 204384Orig1s000. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Accessed July 19, 2013.
3. Diacon AH, Pym A, Grobusch M, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. *N. Engl. J. Med.* 2009;360(23):2397-2405.
4. Diacon AH, Donald PR, Pym A, et al. Randomized Pilot Trial of Eight Weeks of Bedaquiline (TMC207) Treatment for Multidrug-Resistant Tuberculosis: Long-Term Outcome, Tolerability, and Effect on Emergence of Drug Resistance. *Antimicrobial Agents and Chemotherapy*. 2012;56(6):3271-3276.
5. ClinicalTrials.gov. To Evaluate the Safety, Tolerability, and Efficacy of TMC207 as Part of an Individualized Multi-drug Resistant Tuberculosis (MDR-TB) Treatment Regimen in Participants With Sputum Smear-positive Pulmonary MDR-TB: ClinicalTrials.gov Identifier: NCT00910871. http://clinicaltrials.gov/ct2/show/NCT00910871?term=bedaquiline+C209&rank=1. Accessed October 6, 2013.
6. Oregon Health Authority. Epidemiology of TB in Oregon. http://public.health.oregon.gov/DiseasesConditions/CommunicableDisease/Tuberculosis/Pages/epi.aspx. Accessed October 7, 2013.
7. Treatment of tuberculosis: American Thoracic Society, CDC, and Infectious Diseases Society of America. *MMWR Recomm Rep*. 2003;52(RR-11):1-77. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm. Accessed July 19, 2013.
8. *Treatment of tuberculosis: Guidelines.* 4th ed. Geneva: World Health Organization; 2010. http://www.who.int/tb/publications/tb_treatmentguidelines/en/index.html. Accessed July 19, 2013.
9. Phillips PPJ, Fielding K, Nunn AJ. An evaluation of culture results during treatment for tuberculosis as surrogate endpoints for treatment failure and relapse. *PLoS ONE*. 2013;8(5):e63840.
10. Provisional CDC Guidelines for the Use and Safety Monitoring of Bedaquiline Fumrate (Sirturo) for the Treatment of Multidrug-Resistant Tuberculosis. *MMWR Recomm Rep*. 2013;62(9):1-12. http://www.cdc.gov/mmwr/pdf/rr/rr6209.pdf. Accessed December 21, 2013.
11. Center for Drug Evaluation and Research. Summary Review Application Number: 204384Orig1s000. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Accessed July 19, 2013.

Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY[1,11]

Bedaquiline is a diarylquinoline, a new class of antimycobacterial drug. Bedaquiline inhibits mycobacterial ATP (adenosine 5'-triphosphate) synthase 3 in *M. tuberculosis*. Bedaquiline is active against most isolates of *M. tuberculosis*. Resistance mechanisms that affect bedaquiline include modification of the mycobacterial *atpE* gene. However, at least one other as yet unknown resistance mechanism exists. No cross-resistance with other TB drugs has been identified.

PHARMACOKINETICS[1,11]

Parameter	Result
Oral Bioavailability	36 to 79%
Protein Binding	>99.9%
Elimination	Fecal*
Half-Life	5.5 months
Metabolism	CYP3A4 (major)

*Fecal elimination of bedaquiline predominates and urinary excretion is < 0.001%, indicating that renal clearance of unchanged drug is insignificant.

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
100 mg	oral	once daily weeks 1 and 2, then 3 times weekly weeks 3 to 24	400 mg daily week 1 and 2, then 200 mg 3 times weekly (at least 48 hours apart) weeks 3 to 24	None in patients with mild or moderate renal impairment. Not studied in patients with severe impairment or ESRD, so caution advised.	None in patients with mild or moderate hepatic impairment. Not studied in patients with severe impairment, so caution advised.	Safety and efficacy not established in patients <18 years old	Insufficient information on patients ≥65 years old	• Should be given in association with a MDR-TB regimen that includes at least 3 drugs to which the patient's MDR-TB isolate is susceptible to *in vitro* or, if *in vitro* testing is unavailable, 4 other drugs to which the patient's isolate is likely susceptible • Should be administered by directly observed therapy (DOT) • Take with food. • Swallow whole with water. • Avoid alcohol use while on therapy. • Re. a missed dose week 1 or 2: Continue the usual dosing schedule without making up the missed dose. • Re. a missed dose weeks 3 through 24: Take a missed 200-mg dose as soon as possible

								and resume the thrice weekly regimen.

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications):

BBW: An increased risk of death was observed in the treatment group receiving bedaquiline plus background regimen versus the group receiving placebo plus background regimen: 11.4% (9/79) v. 2.5% (2/81), respectively (NNH 11). One death occurred during the 24-week bedaquiline treatment period, while the median time to death for the remaining decedents was 329 days after the last bedaquiline dose. Five of the 9 deaths from the bedaquiline group and 2 from the placebo group were TB-related. The imbalance in deaths remains unexplained and, thus far, appears unrelated to sputum culture conversion, relapse, sensitivity to other TB drugs used, or disease severity. Therefore, bedaquiline should only be used when other regimens would be or are ineffective. Bedaquiline also has been associated with QT prolongation. In a RCT, the largest mean increase in QTc was 15.7 ms with bedaquiline treatment and 6.2 ms without at week 18 of 24 weeks of treatment. These increases persisted after bedaquiline treatment ended.

Warnings and Precautions: More hepatic-related ADRs were observed in patients taking bedaquiline. In two studies, 10.8% (11/102) of bedaquiline-treated patients versus 5.7% (6/105) of placebo-treated patients developed aminotransferase elevations at least 3 times the ULN (NNH 20). Therefore, alcohol and hepatotoxic drugs should be avoided, and bedaquiline discontinued if aminotransferase elevations are accompanied by total bilirubin elevation >2 times the ULN, aminotransferase elevations are >8 times the ULN or elevations persist >2 weeks. Limited data exist on the use of bedaquiline in patients with HIV (n=22), and these patients were not receiving antiretroviral therapy. Bedaquiline should be administered by DOT in combination with at least 3 drugs active against the TB isolate. Bedaquiline minimum inhibitory concentration should be determined for isolates from patients who fail to convert or relapse.

Monitoring: Baseline electrocardiogram should be obtained before treatment initiation and again at 12, 24, and 24 weeks initiating therapy. Baseline serum potassium, calcium, and magnesium should be measured and corrected if abnormal. ECGs also should be monitored when (1) administering bedaquiline concomitantly with other QT prolonging drugs, including fluoroquinolones, macrolides, and clofazimine, (2) patients have a history of tosades de pointes, congenital long QT syndrome, hypothyroidism, bradyarrhythmias, and uncompensated heart failure, and (3) below normal calcium, magnesium, and potassium levels. Baseline, monthly, and as-needed liver function tests should be obtained and monitoring for symptoms of liver dysfunction performed. If serum aminotranferase levels increase 3 times the ULN, a repeat test should be performed as well as a viral hepatitis test, and hepatotoxic drugs should be discontinued.

Drug-Drug interactions: One should avoid concomitant use of bedaquiline with strong CYP3A4 inducers used systemically, including rifampin, rifapentine, and rifabutin. Concomitant use of bedaquiline with strong CYP3A4 inhibitors used systemically for >14 days should be avoided. No clinical data on the combined use of antiretroviral agents and bedaquiline in HIV patients co-infected with HIV exist thus far. Caution must be observed with concomitant use of Kaletra (400 mg lopiavir/100 mg ritonavir) and bedaquiline, as exposure (AUC) to bedaquiline may be increased. Co-administration of nevirapine, isoniazid, or pyrazinamide with bedaquiline requires no dose adjustment. No major pharmacokinetic changes have been observed when bedaquiline is co-administered with ethambutol, kanamycin, pyrazinamide, ofloxacin, or cycloserine.

Food-Drug Interactions: Not reported

Allergy/Cross Reactive Substances: Not reported

Pregnancy/lactation rating: Category B. No evidence of fetal harm has been observed in reproduction studies in rats and rabbits with a plasma exposure (AUC) corresponding to 2 times that of humans. However, the drug should be used during pregnancy only if clearly need, because no studies have been performed with pregnant women. Whether bedaquiline or its metabolites are excreted in human milk is unknown; however, rat studies show concentration of the drug in breast milk 6- to 12-fold higher than the maximum concentration in maternal plasma with doses 1 to 2 times the clinical dose. These breastfeeding pups showed reduced body weights. Therefore, one should decide whether to discontinue nursing or the drug in breastfeeding women.

HIV/MDR-TB co-infected patients: No clinical data or only limited clinical data exist on the use of bedaquiline in HIV patients taking antiretroviral therapy or not taking antiretroviral therapy (n=22), respectively.

Carcinogenesis/Mutagenesis: The drug was negative on tests for mutagenesis, clastogenesis, fertility, reproduction, and development.

Dose Index (efficacy/toxic): Bedaquiline induces reversible phospholipidosis, mainly in cells of the monocytic phagocytic system, at nearly every dose in animals, resulting in increases in pigment-laden or foamy macrophages, mostly in the lymph nodes, spleen, lungs, liver, stomach, skeletal muscle, pancreas, and uterus. Reversible muscle degeneration was observed in animals; for example, the diaphragm, esophagus, quadriceps, and tongue of rats were affected after 26 weeks of treatment at doses similar to clinical exposures. Degeneration of the stomach fundic mucosa, hepatocellular hypertrophy, and pancreatitis also were observed.

Look-alike / Sound-alike (LA/SA) Error Risk Potential:

NME Drug Name	Lexicomp	Clinical Judgment
LA/SA for bedaquiline	none	none
LA/SA for Sirturo	none	none

ADVERSE REACTIONS[1]

Table 1: Select Adverse Drug Reactions from Study 1 That Occurred More Frequently Than

	Adverse Drug Reactions SIRTURO Treatment Group N = 79 n (%)	Placebo During Treatment with SIRTURO Placebo Treatment Group N = 81 n (%)
Nausea	30 (38.0)	26 (32.1)
Arthralgia	26 (32.9)	18 (22.2)
Headache	22 (27.8)	10 (12.3)
Transaminases Increased*	7 (8.9)	1 (1.2)
Blood Amylase Increased	2 (2.5)	1 (1.2)
Hemoptysis†	14 (17.7)	9 (11.1)
Chest Pain†	9 (11.4)	6 (7.4)
Anorexia†	7 (8.9)	3 (3.7)
Rash†	6 (7.6)	3 (3.7)

** Terms represented by 'transaminases increased' included transaminases increased, AST increased, ALT increased, hepatic enzyme increased, and hepatic function abnormal.*

† Reported Adverse Events with a greater incidence in the SIRTURO treatment group but which were not identified as adverse drug reactions.

Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-945-5220 | **Fax** 503-947-1119

Abbreviated New Drug Evaluation: Simeprevir

Month/Year of Review: January 2014
New Drug: Simeprevir **(**Olysio®)
Dossier Received: Pending

End of literature search: September 2013
Manufacturer: Janssen Therapeutics

FDA Approved Indication: Simeprevir is a hepatitis C virus (HCV) protease inhibitor indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen.[1]

- Simeprevir efficacy has been established in combination with peginterferon alfa and ribavirin in HCV genotype 1 infected subjects with compensated liver disease (including cirrhosis).
- Simeprevir must not be used as monotherapy.
- Alternative therapy should be considered for patients infected with HCV genotype 1a containing he Q80K polymorphism.

Research Questions:

- Is there any evidence that simeprevir is effective for the treatment of CHC in reaching sustained virologic response (SVR) or reducing mortality and the development of long term clinical outcomes such as hepatocellular carcinoma?
- Is there evidence demonstrating the safety of simeprevir in the treatment of CHC?
- Is there any comparative evidence demonstrating superior efficacy or safety of simeprevir compared to other protease inhibitors?
- Are there subpopulations of patients for which simeprevir is more effective or associated with less harm?

Conclusions:

- There is evidence that simeprevir in combination with peginterferon alfa and ribavirin significantly improves SVR rates compared to placebo in patients with genotype 1 CHC, in both treatment- naïve patients (80% vs. 50%) and treatment experienced (79% vs. 36%, respectively). Most of the data remains unpublished and cannot be assessed for quality.
- There is low quality evidence, based on one phase IIb trial, that simeprevir in combination with peginterferon alfa and ribavirin is effective in achieving SVR in partial and null responders.
- Compared to placebo, there is low quality evidence that simeprevir does not significantly improve SVR rates in patients infected with HCV genotype 1a with an NS3 Q80K polymorphism at baseline. Screening patients with HCV genotype 1 for the presence of this polymorphism is strongly recommended and alternative therapy should be considered for patients infected with the Q80K polymorphism.
- There is insufficient evidence evaluating simeprevir in patients who have previously failed therapy with a treatment regimen that includes simeprevir or other HCV protease inhibitors.

- There is insufficient evidence evaluating the use of simeprevir in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C).The combination of simeprevir should not be used in patients with decompensated cirrhosis (moderate to severe hepatic impairment).
- There is low quality evidence of an increased risk of adverse reactions in patients of East Asian ancestry due to higher simeprevir exposure.

Recommendations:

- Implement initial PA criteria (Appendix 1) based on package insert and prescribing information.
- Bring back more detailed review and quality assessment of the evidence for further decision-making.

Reason for Review: Two new drugs indicated for the treatment of CHC have recently been approved. This review will evaluate the evidence for efficacy and safety of simeprevir and determine its place in therapy.

Methods:

A MEDLINE OVID search was conducted using simeprevir for chronic Hepatitis C or Hepatitis C virus and limited to randomized controlled trials (RCTs) and meta-analysis, English language, and conducted in humans. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. From the literature search, two phase 2 studies were identified.[2,3] One open-label pharmacokinetic study was excluded due to study design.[4] No published phase 3 studies were available at the time of this report.

Background:

Chronic HCV is the leading cause of complications from chronic liver disease, including cirrhosis, liver failure, and hepatocellular carcinoma.[5] The goal of treatment for CHC is to prevent these long-term health complications. However, it remains difficult to design long term clinical trials that are large enough to provide direct evidence for these outcomes. The SVR rate is defined as the proportion of patients who experience a decline in HCV-RNA to undetectable levels following completion of antiviral treatment. It is the standard marker of successful treatment in clinical trials and is associated with the long-term absence of viremia. There is some evidence of an association of achieving an SVR and reductions in mortality, liver failure, and cancer.[5] The two major predictors of SVR are viral genotype and the pretreatment viral load. Other factors associated with an increased likelihood of achieving an SVR include female sex, age less than 40 years, non-Black race, lower body weight, absence of insulin resistance, and absence of bridging fibrosis or cirrhosis on liver biopsy.

In the United States, genotype 1 infection is found in around three-quarters of patients and is associated with a lower response to antiviral treatment than infection with genotypes 2 and 3, which are present in about 20% of patients.[5] Current standard of care for Genotype 1 CHC is a protease inhibitor (boceprevir or telaprevir) plus pegylated interferon and ribavirin.[6] This is based on several RCTs showing improved rates of SVR (63-79%) with triple therapy compared to the previous standard of care of pegylated interferon and ribavirin dual therapy (55-60%). There is no direct comparative evidence on the effectiveness of the currently available protease inhibitors. However, these agents come with several safety concerns and still depend on combination therapy with interferon and ribavirin which also include adverse reactions an increased risk of anemia and rash sometimes require premature treatment discontinuation and additional management, adding to the complexity of treatment.[7] There are also important drug interactions seen with these protease inhibitors. For genotypes 2 and 3, the standard of care is still dual therapy with pegylated interferon and ribavirin for 24 weeks, which has shown SVR rates of 71-75% in genotype 2 and 61-66% in genotype 3.[8]

Simeprevir is a recently approved protease inhibitor used in combination with pegylated interferon and ribavirin for the treatment of adult patients with genotype 1 CHC. This includes patients with compensated liver disease, including patients with cirrhosis, who are treatment-naïve or who failed prior interferon therapy with or without ribavirin. There are trials underway evaluating its use in genotype 4 infection and HCV/HIV co-infection. Studies investigating the use of simeprevir as part of interferon-free regimens have also been intiated.[7] Simeprevir structurally binds to a target enzyme which is different than telaprevir and boceprevir (14-membered macrocycle). It is given orally once a day with any type of food for 12-48 weeks depending on whether the patient is treatment-naïve, a prior relapse, or a nonresponder.

Clinical Trials:

Efficacy

Simeprevir has been studied in two fair quality phase 2 trials[2,3] and three Phase 3 trials.[1, 6] None of the phase III trials have been published and therefore cannot be assessed for quality. Two double-blind, placebo-controlled phase 2b studies were provided in support of the proposed indication that were designed to evaluate various doses and durations of therapy, one in treatment-naïve patients and one in treatment-experienced patients. Study C205 (n=388) was a randomized, double-blind, placebo-controlled trial to evaluate simeprevir 75 and 150 mg daily given for either 12 or 24 weeks in treatment-naïve CHC genotype 1 subjects.[2] This was compared to placebo (for 24 weeks) in combination with peginterferon and ribavirin for 48 weeks. The second phase 2b trial (C206) also compared the safety and efficacy of different regimens of simeprevir (100 or 150 mg daily) plus peginterferon and ribavirin in CHC genotype 1 subjects who had failed to respond during or had relapsed following at least 1 course of dual therapy for various durations (12 weeks, 24 weeks, or 48 weeks).[3] The primary endpoint was SVR at weeks 72 and 24. Patients with cirrhosis and co-infected with HIV were excluded from the studies. Most patients were Caucasian males with a median age of 46.5 years. In study C205, SVR at week 72 ranged from 70.7% to 84.8% compared with 64.9% for those on dual therapy ($p<0.05$). The study was designed to evaluate two different doses and two different durations of triple combination therapy. All four treatment arms accomplished similar rates of SVR (75% to 86%) which were statistically significantly higher than placebo in all but one of the 75 mg treatment groups. In study C206, SVR at week 24 was achieved in 60.6%-80% of simeprevir groups compared to 22.7% in placebo ($p<0.001$). SVR was achieved in more patients in the 150 mg group compared to 100 mg group (72.9% vs. 65.5%) and similar results were seen for those receiving 12 weeks, 24 weeks, and 48 weeks of triple therapy (68.2%, 69.2%, and 70.2%, respectively). SVR rates in patients with a prior null response (41.2%-58.8%), partial response (65.2%-86.4%), and relapse (76.9%-88.9%) were also promising. In a pooled analysis, the difference in SVR24 rates between simeprevir groups and placebo in partial responders reached statistical significance ($p<0.0001$) and did not reach statistical significance in null responders (45% vs. 19%, $p=0.11$).

The phase 3 trials were randomized, double-blind, placebo controlled trials in subjects with HCV genotype 1.[7] They evaluated the combination of simeprevir 150 mg daily for 12 weeks plus peginterferon-alpha and ribavirin for 12 weeks followed by peginterferon alpha and ribavirin alone for either 12 or 36 weeks based on virologic response compared to placebo in combination with peginterferon alpha and ribavirin for a fixed 48 week duration. The primary endpoint was SVR 12 weeks after the end of treatment. Two trials enrolled only treatment-naïve subjects and the third enrolled subjects who had received at least 24 weeks of a pegylated interferon-based therapy and had relapsed within 1 year (relapsers). According to the FDA, demographic characteristics were generally well balanced in the phase 3 trials. The majority of subjects were Caucasian (86-96%). Cirrhotic subjects (Metavir Fibrosis score of F4) comprised from 7 to 15% of subjects across study arms.

The pooled results from the two trials in treatment naïve subjects resulted in a 80% SVR in the treatment group compared to 50% in placebo ($p <0.001$ for both trials). In the trial of relapsers, 79% of subjects receiving treatment reached an SVR compared to 36% in placebo ($p<0.001$). SVR rates at weeks 24 and 72

correlated well with the primary SVR12 endpoint. In subgroup analysis, no statistically significant differences in SVR rates were observed in those with the Q80K polymorphism at baseline (58% vs. 55%) between the simeprevir and control arms. The Q80K polymorphism is a common polymorphism found in genotype 1 patients. Given the high frequency in the U.S. population and its significant impact on rates of SVR12, the drug advisory committee recommended that all genotype 1a patients be screened for the Q80K polymorphism and alternative treatment options should be considered for patients found to be infected with this variant. This was also similar in the trial including relapsers (47% vs. 30%). In all other subgroup analyses, SVR rates were significantly higher in the simeprevir group compared to the control group.

A secondary endpoint of the phase 3 studies was the proportion of patients able to shorten total treatment duration to 24 weeks. In the triple therapy groups, 85% and 91% of the treatment-naïve patients, and 93% of the prior relapse patients were eligible for a shortened total treatment duration with peginterferon and ribavirin from 48 to 24 weeks.

Safety:

A total of 1178 subjects who received simeprevir or placebo in clinical trials contribute to the safety data available at this time. The most common adverse events seen in clinical trials were rash (28%), pruritus (22%), nausea (22%), influenza like illness (26%), and myalgia (16%), and photosensitivity. Adverse reactions that occurred with at least 3% higher frequency among subjects receiving simeprevir compared to placebo are included in the table below:

Adverse Reaction	**Simeprevir + Peginterferon alfa+ Ribavirin N=781 % (n)**	**Placebo + Peginterferon alfa+ Ribavirin N=397 % (n)**
Rash (including photosensitivity)	28 (218)	20 (79)
Pruritus	22 (168)	15 (58)
Nausea	22 (173)	18 (70)
Myalgia	16 (126)	13 (53)
Dyspnea	12 (92)	8 (30)

*Adapted from Simeprevir prescribing information[1]

Discontinuations due to adverse reactions occurred in 2% of simeprevir treated subjects and 1% of placebo subjects. Dyspnea occurred in 12% of subjects in the simeprevir group and 8% in the control group. A greater frequency of adverse events associated with increased bilirubin was reported in the simeprevir group. It was known since its early development that hyperbilirubinemia was associated with the use of simeprevir, and occurred in 49% of simeprevir patients compared to 26% in the control group. Elevations occurred early after the initiation of treatment and levels returned to near baseline often by week 4 and there was no observed clinically relevant hepatotoxicity associated with the increase. There were no reported causes of Stevens Johnson syndrome or toxic epidermal necroylsis, however an increase in serious adverse events and increase in rates of discontinuation due to rash/photosensitivity related events occurred. The proportion of patients who discontinued simeprevir treatment early was 6.7% in the treatment group and 66.5% in patients on placebo, mainly due to meeting the treatment stopping rule at week 4. During the first 12 weeks, 1.8% of the simeprevir treated patients and 1.3% of the patients on placebo discontinued due to an adverse event. Rash was the most common event leading to discontinuation of treatment in the simeprevir arm (0.6%).

References:

1. Simeprevir prescribing information. Titusville NJ : Janseen Therapeutics. November 2013.

2. Fried MW, Buti M, Dore GJ, et al. Once-daily simeprevir (TMC435) with pegylated interferon and ribavirin in treatment-naïve genotype 1 hepatitis C: The randomized PILLAR study. *Hepatology*. 2013;58(6):1918–1929. doi:10.1002/hep.26641.

3. Zeuzem S, Berg T, Gane E, et al. Simeprevir Increases Rate of Sustained Virologic Response Among Treatment-Experienced Patients With HCV Genotype-1 Infection: A Phase IIb Trial. *Gastroenterology*. 2013. doi:10.1053/j.gastro.2013.10.058.

4. Hayashi N, Seto C, Kato M, Komada Y, Goto S. Once-daily simeprevir (TMC435) with peginterferon/ribavirin for treatment-naïve hepatitis C genotype 1-infected patients in Japan: the DRAGON study. *J Gastroenterol*. 2013. doi:10.1007/s00535-013-0875-1.

5. Chou R, Hartung D, Rahman B, Wasson N, Cottrell E, Fu R. *Treatment for Hepatitis C Virus Infection in Adults*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012. Available at: http://www.ncbi.nlm.nih.gov/books/NBK115347/. Accessed July 18, 2013.

6. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 2011;54(4):1433–1444. doi:10.1002/hep.24641.

7. Simeprevir (TMC435). FDA Antiviral Drugs Advisory Committee Meeting. October 24th, 2013. Background Packate for NDA 205123. Available at: http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0CC4QFjAA&url=http%3A%2F%2Fwww.fda.gov%2Fdownloads%2FAdvisoryCommittees%2FCommitteesMeetingMaterials%2FDrugs%2FAntiviralDrugsAdvisoryCommittee%2FUCM371623.pdf&ei=8lGvUr-UMsWbygHIr4DoAw&usg=AFQjCNGsHT7v0WZNvYximPhkr9qgFSuhMw&sig2=fKXf_Fo7xTH1FcoXHlmxrQ&bvm=bv.57967247,d.aWc&cad=rja.

8. Chou R, Hartung D, Rahman B, Wasson N, Cottrell EB, Fu R. Comparative effectiveness of antiviral treatment for hepatitis C virus infection in adults: a systematic review. *Ann Intern Med*. 2013;158(2):114–123.

Appendix 1: Current PA Criteria

Hepatitis C Oral Protease Inhibitors/Triple Therapy

Goal(s) :

- Approve treatments of chronic hepatitis C which are supported by the medical literature

Length of Authorization

- Initial trial of ~~6-10~~ 8-12weeks (depending on regimen)
- Continuation of therapy up to 48 weeks of total therapy

Requires PA:

- Telaprevir
- Boceprevir
- Simeprevir

Approval Criteria		
1. Is the request for treatment of Chronic Hepatitis C? Document appropriate ICD9 code:	**Yes:** Go to #2	**No:** Pass to RPh, Deny For Appropriateness
2. Does the patient have documented HCV genotype 1? Record Genotype:	**Yes:** Go to #3	**No:** Pass to RPh, Deny For Appropriateness
3. Is the prescription for simeprevir?	**Yes: Go to #4**	**No: Go to #6**
4. Has the patient been screened for the presence of virus with the NS3 Q80K polymorphism at baseline?	**Yes: Go to #5**	**No:** Pass to RPh, Deny For Appropriateness. Recommend that the screening take place.
5. Does the patient have the genotype 1 Q80K polymorphism virus?	**Yes:** Pass to RPh, Deny for Appropriateness	**No:** Go To #6
~~4.~~6. Is the patient also being prescribed peginterferon alfa-2a or -2b and ribavirin and has been granted prior authorization or meets criteria for pegylated interferon-alfa and ribavirin?	**Yes:** Go to #7~~4~~	**No:** Pass to RPh, Deny For Appropriateness
~~5.~~7. Is the request for continuation of therapy? (Patient has been on triple therapy with an oral antiviral agent in preceding 6 weeks)	**Yes**: Go to "Continuation of Therapy	**No**: Go to #8~~5~~
~~6.~~8. Does the patient have a Child-Pugh score < 7 (compensated liver disease)?	**Yes:** Go to #9~~6~~	**No:** Pass to RPh, Deny For Appropriateness
~~7.~~9. Is the medication being prescribed by or in consultation with a specialist in the field of gastroenterology, infectious disease, or hepatitis C?	**Yes:** Go to #10~~7~~	**No:** Pass to RPh, Deny For Appropriateness

~~8.~~10. If the patient has been treated with peginterferon and ribavirin before, do they have documented compliance/adherence to their previous treatment?	**Yes:** Go to #11~~8~~	**No:** Pass to RPh, Deny For Appropriateness
~~9.~~11. Does the patient have a biopsy to indicate moderate to severe fibrosis (stage 2 or greater) OR radiologic, laboratory, or clinical evidence of cirrhosis? OR has extrahepatic manifestations (vasculitis, glomerulonephritis, cryoglobulins).	**Yes:** Go to #12~~9~~	**No:** Pass to RPh, Deny For Appropriateness
~~10.~~12. Does the patient have a HIV coinfection?	**Yes:** Go to #13~~0~~	**No:** Go to #11
~~11.~~13. Is the patient under the supervision of an HIV specialist?	**Yes:** Go to #14~~1~~	**No:** Pass to RPh; Deny (medical appropriateness)
~~12.~~14. Has the patient previously been treated with boceprevir, telaprevir, or simeprevir?	**Yes**: Pass to RPh, Deny for appropriateness	**No:** Go to #15~~2~~
~~13.~~15. Is the request for telaprevir 750mg (two tabs) TID for 12 weeks?	**Yes:** Approve for 8 weeks to allow for 4 week viral load check to continue for a maximum of 12 weeks	**No:** Go to #16~~3~~ (If dose is different pass to RPh for appropriateness)
~~14.~~16. Is the request for boceprevir 800mg (four tabs) TID and the patient has completed 4 weeks of lead-in treatment with ribavirin and peginterferon?	**Yes:** Approve for 12 weeks to allow for 8 week viral load check to continue for a maximum of 24, 32, or 40 weeks based on response	**No:** Go to #17 (If dose is different pass to RPh for appropriateness)~~Pass to RPh; Deny for appropriateness~~
17. Is the request for simeprevir 150 mg once daily for 12 weeks?	**Yes: Approve for 8 weeks to allow for 4 weeks viral load check to continue for a maximum of 12 weeks**	**No: Pass to RPh; Deny for appropriateness**

Continuation of Therapy- Telaprevir		
1. Is the patient treatment-naïve or a prior relapse patient and has undetectable HCV RNA or measured at 4 and 12 weeks?	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for 12 weeks (total treatment duration of 24 weeks).	**No:** DENY (Medical Appropriateness) Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24.
2. Is the patient treatment-naïve or a prior relapse patient and has detectable (1000 IU/mL or less) at Weeks 4 and/or 12	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for additional 36 weeks (total treatment duration of 48 weeks).	**No:** DENY (Medical Appropriateness) Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24.

3. Is the patient a prior partial or null responder?	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for additional 36 weeks (total treatment duration of 48 weeks).	**No:** DENY (Medical Appropriateness)
4. Is the patient treatment-naïve with documented cirrhosis that has undetectable HCV-RNA at weeks 4 and 12?	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for additional 36 weeks (total treatment duration of 48 weeks).	**No:** DENY (Medical Appropriateness) Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24.
***TREATMENT FUTILITY RULES** Week 4 or Week 12: HCV-RNA greater than 1000 IU/mL: Discontinue INCIVEK and peginterferon alfa and ribavirin (INCIVEK treatment complete at 12 weeks) Week 24: Detectable Discontinue peginterferon and ribavirin. If peginterferon alfa or ribavirin is discontinued for any reason, INCIVEK must also be discontinued		

Continuation of Therapy- Boceprevir		
1. Is the patient treatment-naïve and have undetectable HCV RNA at treatment weeks 8 and 24?	**Yes:** Approve as follows: • Approve additional 14 weeks of boceprevir for total treatment duration of 28 weeks (4 week lead-in, 24 weeks triple therapy)	**No:** DENY (Medical Appropriateness)

2. Is the patient treatment-naïve and have detectable HCV RNA at treatment week 8 and undetectable at week 24?	**Yes:** Approve as follows: • Approve additional 22 weeks of boceprevir followed by continued dual therapy with peginterferon and ribavirin for 16 weeks for total treatment duration of 48 weeks (4 week lead-in, 32 weeks triple therapy, 12 weeks dual therapy)	**No:** DENY (Medical Appropriateness)
3. Is the patient a previous partial responder or relapser and has undetectable HCV RNA at treatment weeks 8 and 24?	**Yes:** Approve as follows: • Approve additional 22 weeks of boceprevir for total treatment duration of 36 weeks (4 week lead-in, 32 weeks triple therapy)	**No:** DENY (Medical Appropriateness)
4. Is the patient a previous partial responder or relapser and has detectable HCV RNA at treatment week 8 and undetectable at week 24?	**Yes:** Approve as follows: • Approve additional 22 weeks of boceprevir followed by continued dual therapy with peginterferon and ribavirin for 16 weeks for total treatment duration of 48 weeks (4 week lead-in, 32 weeks triple therapy, 12 weeks dual therapy)	**No:** DENY (Medical Appropriateness)
5. Does the patient have documented cirrhosis or is documented as a null responder and does not meet the futility rules at treatment weeks 8, 12, and 24?	**Yes:** Approve as follows: • Continue triple therapy with boceprevir for a total treatment duration of 48 weeks (4 week lead-in, 44 weeks triple therapy).	**No:** DENY (Medical Appropriateness)
***TREATMENT FUTILITY RULES** If the patient has HCV-RNA results greater than or equal to 100 IU/mL at TW12, then discontinue three-medicine regimen. If the patient has confirmed, detectable HCV-RNA at TW24, then discontinue three-medicine regimen.		

Continuation of Therapy- Simeprevir: Simeprevir in combination with peginterferon alfa and ribavirin should only be given for 12 weeks. No more simeprevir should be approved. The following are the recommended duration of treatments for dual therapy with peginterferon alfa and ribavirin after the initial 12 weeks of triple therapy

1. Is the patient treatment-naïve or a prior relapse and has undetectable HCV RNA (< 25 IU/ml) at week 4?	**Yes:** Approve as follows: • Approve additional 4 weeks of simeprevir for total treatment duration of 12 weeks of triple therapy, followed by continued dual therapy with peginterferon and ribavarin for 12 weeks (total treatment duration of 24 weeks).	**No:** DENY (Medical Appropriateness) It is unlikely that patients with inadequate on-treatment virologic response will achieve a SVR, therefore discontinuation of treatment is recommended in these patients.
2. Is the patient a prior non-responder (including partial and null responders) and has an undetectable HCV RNA (<25 IU/ml) at week 4?	**Yes:** Approve as follows: • Approve additional 4 weeks of simeprevir for total treatment duration of 12 weeks of triple therapy, followed by continued dual therapy with peginterferon and ribavarin for 36 weeks (total treatment duration of 48 weeks).	**No:** DENY (Medical Appropriateness) It is unlikely that patients with inadequate on-treatment virologic response will achieve a SVR, therefore discontinuation of treatment is recommended in these patients
***TREATMENT FUTILITY RULES** If the patient has HCV-RNA results greater than or equal to 25 IU/mL at TW12, then discontinue three-medicine regimen. If the patient has confirmed, detectable HCV-RNA at TW24, then discontinue two-medicine regimen.		

Appendix 2: Specific Drug Information

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability	Good oral bioavailability
Protein Binding	>99.9%, mainly albumin
Elimination	Predominantly in the feces via biliary excretion
Half-Life	41 hours
Metabolism	CYP3A enzymes

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
150 mg	PO	Q24H	150 mg once daily with food	No adjustment needed	A dose recommendation cannot be made for patients with moderate to severe hepatic impairment. Is contraindicated in patients with decompensated cirrhosis.	No information available..	No differences in safety, efficacy or response have been observed among patients of varying age. Skin changes with advanced age may lead to increased rug exposure.	• A dose recommendation cannot be made for patients of East Asian ancestry. • Should be administered with both peginterferon alfa and ribavirin. The recommended duration of simeprevir is 12 weeks, followed by either 12 or 36 additional weeks of peginterfron alfa and ribavirin depending on prior response status. • For discontinuation, the daily dose should be reduced by 2mg/24 hours with a dose reduction preferably every other day, until complete withdrawal.

The recommended duration of treatment with simeprevir, peginterferon alfa and ribavirin is presented in the following table:

Duration of Treatment with OLYSIO, Peginterferon Alfa and Ribavirin			
	Treatment with simeprevir, Peginterferon alfa and Ribavirin*	**Treatment with Peginterferon alfa and Ribavirin***	**Total Treatment Duration***

Treatment-naïve and prior relapser patients† including those with cirrhosis	First 12 weeks	Additional 12 weeks	24 weeks
Prior non-responder patients‡ (including partial and null responders) including those with cirrhosis	First 12 weeks	Additional 36 weeks	48 weeks
* Recommended duration of treatment if patient does not meet stopping rule (see Table 2). † Prior relapser: undetectable HCV RNA at the end of prior interferon-based therapy and detectable HCV RNA during follow-up ‡ Prior partial responder: prior on-treatment ≥ 2 log10 IU/ml reduction in HCV RNA from baseline at Week 12 and detectable HCV RNA at end of prior interferon-based therapy. Prior null responder: prior on-treatment < 2 log10 reduction in HCV RNA from baseline at Week 12 during prior interferon-based therapy			

Stopping rules for simeprevir are presented here:

Treatment Stopping Rules in Any Patient with Inadequate On-Treatment Virologic Response	
HCV RNA	Action
Treatment Week 4: greater than or equal to 25 IU/mL	Discontinue simeprevir, peginterferon alfa and ribavirin
Treatment Week 12: greater than or equal to 25 IU/mL	Discontinue peginterferon alfa and ribavirin (treatment with OLYSIO is complete at Week 12)
Treatment Week 24: greater than or equal to 25 IU/mL	Discontinue peginterferon alfa and ribavirin

DRUG SAFETY[1]

Contraindications: All contraindications to peginterfron alfa and ribavirin also apply to simeprevir combination treatment and is contraindicated in pregnant women and in men whose female partners are pregnant.

Warnings and Precautions:

- Embryofetal Toxicity (use with ribavirin). Ribavirin may cause defects and fetal death. Avoid pregnancy in female patients and female partners of male patients.
- Photosensitivity: serious photosensitivity reactions have been observed. Use sun protection measures and limit sun exposure. Consider discontinuation if a photosensitivity reaction occurs.
- Rash. Discontinue if severe rash occurs.

Drug Interactions:

- Co-administration with drugs that are moderate or strong inducers or inhibitors of CYP3A may significantly affect the plasma concentrations of simeprevir.

Look-alike/Sound-alike Potential:

Rotigotine may be confused with : *rasagiline, rivastigmine, ropinirole*
Neupro may be confused with: *Neupogen, Neurontin*

Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-945-5220 | **Fax** 503-947-1119

Abbreviated Class Update: Hepatitis C

Month/Year of Review: January 2014
New Drug: Sofosbuvir **(**Sovaldi®)
Dossier Received: Yes

End of literature search: September 2013
Manufacturer: Gilead Sciences

FDA Approved Indication: Sofosbuvir is a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen.[1]

- The efficacy of sofosbuvir has been established in subjects with HCV genotype 1, 2, 3 or 4 infections, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection.

Research Questions:

- Is there any evidence that sofosbuvir is effective for the treatment of CHC in reaching sustained virologic response (SVR) or reducing mortality and the development of long term clinical outcomes such as hepatocellular carcinoma?
- Is there evidence demonstrating the safety of sofosbuvir in the treatment of CHC?
- Is there any comparative evidence demonstrating superior efficacy or safety of sofosbuvir compared to other protease inhibitors?
- Are there subpopulations of patients for which sofosbuvir is more effective or associated with less harm?

Conclusions:

- There is poor quality evidence, based on one open-label trial, that sofosbuvir in combination with ribavirin for 12 weeks is noninferior to pegylated interferon plus ribavirin for 24 weeks in genotype 2 and 3 treatment-naïve CHC in achieving SVR at week 12 (67% for both groups).[2]
- There is moderate quality evidence that sofosbuvir in combination with ribavirin for 12 weeks is superior to placebo in genotype 2 and 3 CHC patients who are intolerant or ineligible for interferon based therapy in achieving SVR at week 12 (78% vs. 0%; p<0.001), as well as in patients who did not have a response to interferon therapy.[3]
- There is evidence that extending the duration of treatment in genotype 3 patients to 24 weeks improves SVR rates compared to 12 weeks of treatment. Across all studies, genotype 2 patients achieved consistently higher SVR rates than genotype 3 patients
- In genotype 1, there low quality evidence that the combination of sofosbuvir plus ribavirin plus peginterferon alfa results in higher rates of SVR at 12 weeks than historical control rates (90% vs. 60%). This is based on a single arm, open-label study. [2]
- Based on limited data, sofosbuvir appears to have no serious adverse event concerns associated with its use and is well-tolerated for 12-16 weeks. The most common adverse events (>20%) of sofosbuvir in combination with ribavirin were fatigue and headache. The most common adverse events in combination with peginterferon alfa and ribavirin were fatigue, headache, nausea, insomnia, and anemia. Overall discontinuations due to adverse events in trials were low (0-2%).

Recommendations:

- Implement initial PA criteria based on package insert and prescribing information (Appendix 1).

Reason for Review: Two new drugs indicated for the treatment of CHC have recently been approved. This review will evaluate the evidence for the effectiveness and safety of sofosbuvir and determine its appropriate place in therapy.

Background:

Chronic HCV is the leading cause of complications from chronic liver disease, including cirrhosis, liver failure, and hepatocellular carcinoma.[4] The goal of treatment for CHC is to prevent these long-term health complications. However, it remains difficult to design long term clinical trials that are large enough to provide direct evidence for these outcomes. The SVR rate is defined as the proportion of patients who experience a decline in HCV-RNA to undetectable levels following completion of antiviral treatment. It is the standard marker of successful treatment in clinical trials and is associated with the long-term absence of viremia. There is some evidence of an association of achieving an SVR and reductions in mortality, liver failure, and cancer. [4] The two major predictors of SVR are viral genotype and the pretreatment viral load. Other factors associated with an increased likelihood of achieving an SVR include female sex, age less than 40 years, non-Black race, lower body weight, absence of insulin resistance, and absence of bridging fibrosis or cirrhosis on liver biopsy. Trials have historically used SVR at week 24 of follow-up (SVR24) as a primary endpoint. The studies evaluating sofosbuvir use SVR at week 12 of follow-up (SVR12) as the primary endpoint, based on evidence that the majority of patients who have an SVR at week 12 maintain it until week 24.[5]

In the United States, genotype 1 infection is found in around three-quarters of patients and is associated with a lower response to antiviral treatment than infection with genotypes 2 and 3, which are present in about 20% of patients. [4] Current standard of care for Genotype 1 CHC is a protease inhibitor (boceprevir or telaprevir) plus pegylated interferon and ribavirin.[6] This is based on several RCTs showing improved rates of SVR (63-79%) with triple therapy compared to the previous standard of care of pegylated interferon and ribavirin dual therapy (55-60%). There is no direct comparative evidence on the effectiveness of the currently available protease inhibitors. However, these agents come with several safety concerns and still depend on combination therapy with interferon and ribavirin which can result in serious adverse reactions. There are also important drug interactions seen with these protease inhibitors. For genotypes 2 and 3, the standard of care is still dual therapy with pegylated interferon and ribavirin for 24 weeks, which has shown SVR rates of 71-75% in genotype 2 and 61-66% in genotype 3.[7]

Sofosbuvir is a nucleotide inhibitor of HSV NS5B RNA-dependent RNA polymerase with broad genotypic activity. Sofosbuvir was given breakthrough therapy designation as the first potential interferon-free CHC therapy from the FDA that allowed an expedited approval program.[5] The criteria for a breakthrough therapy designation from the FDA is that a) it is used for a serious condition, and b) preliminary clinical evidence demonstrates substantial improvement over available therapy on one more clinically significant endpoints. Unlike the other available protease inhibitors, there is no response guided therapy criteria for its use.

Methods:

A MEDLINE OVID search was conducted using sofosbuvir for chronic Hepatitis C or Hepatitis C virus and limited to randomized controlled trials (RCTs) and meta-analysis, English language, and conducted in humans. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality systematic reviews. The FDA website was searched for new drugs,

indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. From the literature search, three phase 2 studies[8–10] and four phase 3 published studies were identified.[2,3] One open-label study was excluded due to study design.[11]

Clinical Trials:

Efficacy

The approval of sofosbuvir was based on five phase 3 trials, four of which have been published.[5] It was studied in multiple populations including interferon ineligible or intolerant. It has not been studied in a population that has failed previous protease inhibitor treatment. Sofosbuvir was studied in combination with ribavirin for genotypes 2 and 3, and in combination with pegylated interferon and ribavirin for genotypes 1, 4, 5, and 6. All sofosbuvir arms used a dose of 400 mg once daily and weight-based ribavirin.

Genotypes 2 and 3:

Four phase III trials evaluated sofosbuvir in the treatment of genotypes 2 and 3 CHC. Three of these are currently published and available for quality appraisal.[2,3] These studies included treatment-experienced patients, treatment-naïve patients, and subjects in which interferon was not a treatment option. The primary endpoint in all trials was SVR at week 12 after discontinuation of active treatment (SVR12). Across all studies, genotype 2 patients achieved consistently higher SVR rates than genotype 3 patients.

The FISSION trial was a phase 3 randomized, open-label, active control trial comparing 12 weeks of sofosbuvir plus ribavirin (n=256) to 24 weeks of peginterferon alfa-2a plus ribavirin (n=243) in genotype 2 and 3 CHC treatment-naive patients.[2] A total of 20% of patients in the sofosbuvir group and 21% in the peginterferon group had cirrhosis. Sofosbuvir plus ribavirin was shown to be noninferior to peginterferon plus ribavirin in SVR rates at week 12 (67% in both groups). Results varied based on cirrhosis or no cirrhosis and which genotype. Lowest response rates were in genotype 3 subjects with cirrhosis (34% and 30%), and highest rates were in genotype 2 patients with no cirrhosis (97% vs. 81%) for sofosbuvir treated patients and peginterferon plus ribavirin patients, respectively. Complete data for SVR24 rates are not available at this time. Relapse accounted for most treatment failures with genotype having a relapse rate of 40% compared with a 5% relapse rate in genotype 2. Subgroup analysis demonstrated that genotype 2 infection (OR 42.49, 95% CI 9.539-189.239) and an absence of cirrhosis (OR 2.935, 95% CI 1.377-6.257) were strongly associated with higher rates of SVR12. The major limitation of this study was the open-label design, increasing the risk of bias and lowering the quality of the study.

POSITRON was a phase 3 randomized, double blind trial in genotype 2 or 3 CHC patients for whom treatment with peginterferon was not an option either due to intolerance, ineligibility, or unwillingness to take interferon.[3] The most common reasons that interferon was not an option were psychiatric disorders (57%) and autoimmune disorders (19%).Patients were randomized to sofosbuvir plus ribavirin (n=207) or matching placebo (n=71) for 12 weeks. Approximately 20% of patients of patients had evidence of cirrhosis. The most common reasons for interferon ineligibility were psychiatric (58%) and autoimmune (19%), and for interferon intolerance were flue-like symptoms (32%), psychiatric (20%), thrombocytopenia (16%), and local/systemic adverse reactions (12%). Overall, 78% of subjects in the sofosbuvir group achieved SVR at week 12 compared to 0% in the placebo group ($p<0.001$). When analyzed by genotype, 93% of genotype 2 subjects and 61% of genotype 3 subjects achieved SVR in the sofosbuvir group. Likewise, 81% of patients without cirrhosis had an SVR as compared with 61% of patients with cirrhosis.

FUSION randomized blinded patients who had not had a response to prior interferon therapy to sofosbuvir plus ribavirin for 12 weeks, followed by 4 weeks of marching placebo (n=103) or 16 weeks of treatment (n=98), including 34% with compensated cirrhosis, a higher percentage than enrolled in the other phase 3

trials.[3] The rates of SVR were superior to the historical control rate of 25%, with rates of 50% in the 12-week group and 73% in the 16-week group (p<0.001 for both). This historical rate was agreed upon by the FDA. Patients receiving 16 weeks of treatment had a significantly higher rate of SVR than patients receiving 12 weeks of treatment (71% vs. 50%, treatment difference of -23%, 95% CI -35 to -11%, p<0.001). Data for SVR24 are not available at this time. Extending the treatment duration by 4 weeks increased the SVR rates in HCV genotype 3 subjects from 30% to 62%. This indicates that 12 weeks of sofosbuvir plus ribavirin is not the optimal regimen for HCV genotype 3 patients.

The VALENCE trial evaluated sofosbuvir in combination with ribavirin in genotype 2 or 3 HCV infection in treatment-naïve subjects or subjects who did not achieve SVR with prior interferon-based treatment. The original trial design was a randomized and blinded trial comparing combination therapy for 12 weeks to placebo. Based on emerging data, this trial was unblended and all genotype 2 subjects continued the original planned treatment and genotype 3 subjects were given an extended regimen of 24 weeks of sofosbuvir and ribavirin.[1] Overall SVR was 93% in genotype 2 subjects and 84% in genotype 3 subjects. This data is unpublished and therefore unable to be assessed for quality and risk of bias.

Genotypes 1,4,5,6:
NEUTRINO was a single-group, open-label poor-quality study evaluating a 12-week regimen of sofosbuvir plus peginterferon alfa-2a and ribavirin in 327 patients with treatment-naive HCV genotype 1,4,5, or 6 (89% had genotype 1, and 9% had genotype 4).[2] A total of 295 (90%) had a SVR 12 weeks after treatment. This was demonstrated to be superior to the historical response rate of 60% (p<0.001). Rates of SVR did not differ greatly according to HCV genotype (89% in genotype 1, 96% in genotype 4, and 100% in genotype 5/6). However, very few patients with genotype 5 or 6 were included in the trial, making it very difficult to make definitive dosing recommendations in this population. In patients without cirrhosis, 92% achieved an SVR, as compared to 80% in patients with cirrhosis. A Multivariate logistic regression showed that cirrhosis (OR 3.924, 95% CI 1.6629.265), IL28B (OR 7.989, 95% CI 1.815-35.168), and ribavirin exposure (OR 1.384, 95% CI 1.153-1.662) were all significantly associated with SVR12. Responses did not vary substantially according to race or ethnic group. The open-label, single-arm design of this trial increases the risk of bias associated with these results and the trial is therefore rated as poor quality.

Specific Populations:
Sofosbuvir has been studied in patients with HCV/HIV co-infection as well as in patients with hepatocellular carcinoma awaiting liver transplantation. Trials are currently ongoing. In patients with hepatocellular carcinoma, preliminary results with sofosbuvir has demonstrated efficacy in a limited number of subjects (pTVR12 of 64%, 23/36). Although this addresses an unmet clinical need, data is still very limited and safety is a concern as higher rates of serious adverse events, grade 3 or 4 adverse events, and deaths were reported in the pre-transplant population compared to the phase 3 trials.[5]

There have been no clinical trials in genotype 1 patients who have failed prior treatment. The FDA analysis looked at whether the high SVR rate in the treatment-naïve population provided evidence to support use of sofosbuvir in combination with peginterferon and ribavirin in patients with genotype 1 infection who are nonresponders to prior course of peginterferon and ribavirin. They predicted high SVR rates in genotype 1 peginterferon plus ribavirin treatment experienced patients. However, this is based on many assumptions.

The safety and efficacy of sofosbuvir was assessed in 223 HCV/HIV-1 co-infected subjects in an open-label clinical trial (PHOTON-1).[1] Subjects with genotype 1, 2, or 3 were included. All genotype 1 subjects were treatment-naïve, while patients with genotype 2 or 3 were either treatment naïve or treatment experienced. Patients were either not on antiretroviral therapy with a CD4+ cell count >500 cells/mm3 or had virologically suppressed HIV-1 with a CD4+ cell count >200 cells/mm3. Subjects received sofosbuvir and ribavirin for 12 or 24 weeks based on genotype and prior treatment history. Overall, rates of SVR were 76%, 88%, and 67% in genotype 1, 2, and 3 subjects, respectively. This data is currently unpublished and cannot be assessed for quality and risk of bias.

Safety:

The safety assessment of sofosbuvir from phase 3 data (both controlled and uncontrolled) includes subjects receiving combination therapy with sofosbuvir plus ribavirin and sofosbuvir plus ribavirin plus peginterferon alfa for time periods of 12 weeks to 24 weeks. The most common adverse events (>20%) of sofosbuvir in combination with ribavirin were fatigue and headache. The most common adverse events in combination with peginterferon alfa and ribavirin were fatigue, headache, nausea, insomnia, and anemia. The following table shows treatment-emergent adverse events reported in at least 15% of subjects in any treatment arm.

	Arm Interferon-free Regimens			**Interferon-containing Regimens**	
	PBO 12 weeks	**SOVALDI + RBV[a] 12 weeks**	**SOVALDI + RBV[a] 24 weeks**	**Peg-IFN alfa + RBV[b] 24 weeks**	**SOVALDI + Peg-IFN alfa + RBV[a] 12 weeks**
	N=71	N=650	N=250	N=243	N=327
Fatigue	24%	38%	30%	55%	59%
Headache	20%	24%	30%	44%	36%
Nausea	18%	22%	13%	29%	34%
Insomnia	4%	15%	16%	29%	25%
Pruritus	8%	11%	27%	17%	17%
Anemia	0%	10%	6%	12%	21%
Asthenia	3%	6%	21%	3%	5%
Rash	8%	8%	9%	18%	18%
Decreased Appetite	10%	6%	6%	18%	18%
Chills	1%	2%	2%	18%	17%
Influenza Like Illness	3%	3%	6%	18%	16%
Pyrexia	0%	4%	4%	14%	18%
Diarrhea	6%	9%	12%	17%	12%
Neutropenia	0%	<1%	<1%	12%	17%
Myalgia	0%	6%	9%	16%	14%
Irritability	1%	10%	10%	16%	13%

Overall, there were no significant serious adverse events. The incidence of serious adverse events was considered related to the study drug was very low (<1%) and the only serious adverse event seen in 3 or more subjects in sofosbuvir plus ribavirin group was malignant hepatic neoplasm. There were no serious or severe cardiac adverse events reported and no obvious safety issue related to cardiac toxicity. Sofosbuvir treatment was better tolerated than pegylated interferon and ribavirin, with no increases in the occurrences of rash, anemia, or neutropenia. There were reported laboratory abnormalities that can be seen in the table below.

	Interferon-free Regimens			**Interferon-containing Regimens**	
Hematological Parameters	**PBO 12 weeks**	**SOVALDI + RBV[a] 12 weeks**	**SOVALDI + RBV[a] 24 weeks**	**Peg-IFN + RBV[b] 24 weeks**	**SOVALDI + Peg-IFN + RBV[a] 12 weeks**

	N=71	N=647	N=250	N=242	N=327
Hemoglobin (g/dL)					
< 10	0	8%	6%	14%	23%
< 8.5	0	1%	<1%	2%	2%
Neutrophils (x10^9/L)					
≥0.5 - < 0.75	1%	<1%	0	12%	15%
< 0.5	0	<1%	0	2%	5%
Platelets (x10^9/L)					
≥25 - < 50	3%	<1%	1%	7%	<1%
< 25	0	0	0	0	0

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) SVR at 24 weeks
2) Discontinuations due to adverse events
3) Mortality
4) Hepatocellular carcinoma
5) Serious Adverse events

Primary Study Endpoint:

1) SVR at 12 weeks after the end of treatment

Ref./Study Design[a]	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns

FISSION[2] Randomized, open-label, active-contro study, non-inferiority	1. sofosbuvir 400mg + ribavirin 12 weeks 2. Peginterferon alfa-2a plus ribavirin x 24 weeks	Treatment Naïve Genotype 2 and 3 20% with cirrhosis 87% Caucasian 3.5 black 72% genotype 3 <u>Exclusion Criteria:</u> Hepatitis B, HIV, other chronic liver disease, decompensated liver disease, psychiatric illness, pulmonary disease, cardiac disease, seizure disorder, poorly controlled diabetes, cancer, QT interval ≥ 450 ms or 500 ms if cirrhotic, major organ transplation, active substance abuse, neutrophil count <1500, Hgb < 11 in females and <12 in males, platelet ≤ 90,000 or 75,000 if cirrhotic, Creatining ≥1.5 ULN, GFR <60, Bilirubin ≥1.5 X ULN, albumin ≤3.2	N=256 N=242	<u>SVR12:</u> 1. 67% (170/253) 2. 67% (162/243) P<0.001 for noninferiority; absolute difference of 0.3% (95% CI -7.5-8) P<0.001 <u>Genotype 2 - SVR12:</u> 1. 97% (68/70) 2. 78% (52/67) *With Cirrhosis* 1. 91% (10/11) 2. 62% (8/13 *Without Cirrhosis* 1. 98% (58/59) 2. 82% (44/54) <u>Genotype 3 - SVR12:</u> 1. 56% (102/183) 2. 63% (110/176) *With Cirrhosis* 1. 34% (13/38) 2. 30% (11/37) *Without Cirrhosis* 1. 61% (89/145) 2. 71% (99/139)	N/A – noninferiorit N/A N/A	<u>Discontinuation due to AE's:</u> 1. 1.2% (3/256) 2. 10.7% (26/242) <u>Serious AE's:</u> 1. 3% (7/256) 2. 1% (3/242)	N/A N/A	**Quality Rating:** Poor-Fair **Internal Validity: RoB** <u>Selection:</u> Randomization through centralized system. No allocation concealment as it was open-label. Patients similar at baseline; more patients in the peginterferon group had HCV RNA > 800,000 IU/ml (65% vs. 57%) <u>Performance:</u> Open-label; no blinding <u>Detection:</u> Open-label; no blinding <u>Attrition:</u> Overall attrition to week 12 post treatment visit SVR12 high at 33%; higher in the peginterferon group (22%) due to AE's and viral failure. **External Validity:** <u>Recruitment:</u> Unclear <u>Patient Characteristics:</u> Extensive exclusion criteria; limited non-Caucasian patients whic limits the generalizability of results (only. However, 20% of patients were cirrhotic. <u>Setting:</u> 97 sites in the US, Australia, New Zealand, Italy, Sweden, and the Netherlands <u>Outcomes:</u> The primary endpoint was SVR 1 with a pre-specified 15% non-inferiority margin.

POSITRON[3] RCT, DB, PC	1. sofosbuvir 400mg + ribavirin 12 weeks 2. Placebo	Genotype 2 and 3 patient who had previously d/c'd interferon therapy due to AE's who could not take interferon therapy due to a medical condition 16% with cirrhosis Mean age 52 92% white 50% genotype 3 <u>Exclusion Criteria:</u> Pregnant, chronic liver disease, HBV, HIV, h/o malignancy, chronic immunosuppressives, drug/alcohol abuse, hepatic decompensation, excessive alcohol use, ALT/AST >10 x ULN, HB <12 for male or <11 for females, albumin <3 g/dl, bilirubin > 1.5 x ULN, CrCl <60 ml/min	N=207 N=71	<u>SVR12:</u> 1. 77.8% (161/207) 2. 0% (0/71) P<0.001 <u>Genotype 2 - SVR12:</u> 1. 92.7% (101/109) 2. 0% (0/34) *With Cirrhosis* 1. 94% (16/17) 2. 0% *Without Cirrhosis* 1. 92% (85/92) 2. 0% <u>Genotype 3 - SVR12:</u> 1. 61.2% (60/98) 2. 0% (0/37) *With Cirrhosis* 1. 21% (3/14) 2. 0% *Without Cirrhosis* 1. 68% (57/84) 2. 0%	N/A N/A N/A	<u>Discontinuation due to AE's:</u> 1. 2% (5/207) 2. 4% (3/71) <u>Serious AE's:</u> 1. 5% (11/207) 2. 3% (2/71)	NS NS	**Quality Rating: Fair** **Internal Validity: RoB** <u>Selection:</u> An interactive web response system was used to manage subject randomization and study drug assignment. Similar baseline characteristics. <u>Performance:</u> Double-dummy design <u>Detection:</u> Results blinded to the investigator and sponsor <u>Attrition:</u> The majority of patients completed assigned treatment (3.3% attrition). 17% of patients did not return for post-treatment wk 12 visit. **External Validity:** <u>Recruitment:</u> Unclear <u>Patient Characteristics:</u> <u>Setting:</u> 63 sites in the US, Canada, Australia, and New Zealand <u>Outcomes:</u> Data for SVR 24 not available.

FUSION[3] RCT, DB, PC, AC	1. sofosbuvir 400mg + ribavirin 12 weeks, followed by 4 weeks of matching placebo 2. Sofosbuvir 400mg + ribavirin for 16 weeks	Genotype 2 and 3in patients who did not have a response to prior treatment with interferon 34% had cirrhosis Mean age 54 86% white 63% genotype 3 30% with non-CC IL28B genotypes Exclusion Criteria: Same as above for POSITRON	N=103 N=98	SVR12: 1. 50% (50/100) 2. 73% (69/95) P<0.001 for both compared to the historical rate (25%) 1 vs. 2: Difference, -23% (95% C -35 to -11); p<0.001 Genotype 2 - SVR12: 1. 86% (31/36) 2. 94% (30/32) *With Cirrhosis* 1. 60% (6/10) 2. 78% (7/9) *Without Cirrhosis* 1. 96% (25/26) 2. 100% (23/23) Genotype 3 - SVR12: 1. 30% (19/64) 2. 62% (39/63) *With Cirrhosis* 1. 19% (5/26) 2. 61% (14/23) *Without Cirrhosis* 1. 37% (14/38) 2. 63% (25/40)	N/A N/A	Discontinuation due to AE's: 1. 1% (1/103) 2. 0 Serious AE's: 1. 5% (5/103) 2. 3% (3/98)	NS NS	**Quality Rating: Fair** **Internal Validity: RoB** Selection: Randomization through centralized system and interactive web response system. Baseline characteristics similar at baseline. Performance: Double-dummy design Detection: Results blinded to the investigator and sponsor Attrition: Low attrition to completion of treatment (1%) but Overall attrition to week 12 post treatment visit SVR12 high at 61.5%; only 50% in the 12week group returned for SVR12 **External Validity:** Recruitment: Unclear Patient Characteristics: Low number of non-white patients. High number of cirrhotic patients as well as patients with high HCV baseline levels. Setting: 67 sites in the US, Canada, New Zealand Outcomes: The primary efficacy endpoint of SVR 12 from each treatment arm were compared with a historical SVR control rate of 25%. Data for SVR 24 not available.

NEUTRINO[2] Single-group, open-label study	1. sofosbuvir plus peginterferon alfa 2a plus ribavirin x 12 weeks	Genotypes 1, 4, 5, or 6 HCV Treatment-naïve Mean age 52 4.3% > 65 years 79% white, 17% black Genotype 1 89% Genotype 4 9% Cirrhosis 17% Exclusion criteria: Prior treatment with interferon or ribavirin, HBV, HIV, chronic liver disease, decompensated liver disease, autoimmune disorders, psychiatric illness, drug or alcohol abuse, pregnancy, ALT/AST >10 x ULN, HB <12 for male or <11 for females, albumin <3 g/dl, bilirubin > 1.5 x ULN, CrCl <60 ml/min, h/o cardiac disease, severe COPD, chronic immunosuppressives, h/o malignancy	N=327	SVR12: 90% (295/327) P<0.001 (compared to historical rate of 60%) SVR12 based on genotype: GT1: 89% GT4: 96% *With cirrhosis:* 80% *Without cirrhosis:* *92%* SVR24: 92.4%	N/A	Discontinuation due to AE: 5 (2%) Serious AE's: 4 (1%)	N/A	**Quality Rating: Poor** **Internal Validity: RoB** Selection: non-randomized, open-label Performance: open-label Detection: open-label, single arm design Attrition: Low attrition to completion of treatment (2%) and low attrition to the week 12 post-treatment assessment (8%) **External Validity:** Recruitment: Unclear Patient Characteristics: Low number of non-white patients. High number of cirrhotic patients as well as patients with high HCV baseline levels. Setting: 56 sites in the US Outcomes: The primary efficacy endpoint of SVR 12 from each treatment arm were compared with a historical SVR control rate of 25%. Data for SVR 24 not available.
DB=double blinded, R=randomized, PC=placebo controlled, AC=active control, HCV=hepatitis C virus, ULN=upper normal limit, SVR=sustained virologic response, RoB=risk of bias, ARR = absolute risk reduction, NNT = number needed to treat, HBV = hepatitis B virus								

References:

1. Sofosbuvir (Sovaldi) prescribing information. Gilead Sciences: Foster City, Ca. December, 2013.

2. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med*. 2013;368(20):1878–1887. doi:10.1056/NEJMoa1214853.

3. Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med*. 2013;368(20):1867–1877. doi:10.1056/NEJMoa1214854.

4. Chou R, Hartung D, Rahman B, Wasson N, Cottrell E, Fu R. *Treatment for Hepatitis C Virus Infection in Adults*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012. Available at: http://www.ncbi.nlm.nih.gov/books/NBK115347/. Accessed July 18, 2013.

5. FDA Antiviral Drugs Advisory Committee Meeting. Sofosbuvir (GS-7977) Background Packate. October 25, 2013. Available at:http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/antiviraldrugsadvisorycommittee/ucm371876.pdf.

6. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 2011;54(4):1433–1444. doi:10.1002/hep.24641.

7. Yee HS, Chang MF, Pocha C, et al. Update on the management and treatment of hepatitis C virus infection: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office. *Am J Gastroenterol*. 2012;107(5):669–689; quiz 690. doi:10.1038/ajg.2012.48.

8. Osinusi A, Meissner EG, Lee Y-J, et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. *JAMA*. 2013;310(8):804–811. doi:10.1001/jama.2013.109309.

9. Lawitz E, Lalezari JP, Hassanein T, et al. Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naive patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. *Lancet Infect Dis*. 2013;13(5):401–408. doi:10.1016/S1473-3099(13)70033-1.

10. Kowdley KV, Lawitz E, Crespo I, et al. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial. *Lancet*. 2013;381(9883):2100–2107. doi:10.1016/S0140-6736(13)60247-0.

11. Gane EJ, Stedman CA, Hyland RH, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N Engl J Med*. 2013;368(1):34–44. doi:10.1056/NEJMoa1208953.

12. Neupro. (rotigotine) prescribing information. Smyrna, GA; UCB, Inc; March 2012.

Appendix 1: Proposed PA Criteria

Sofosbuvir

Goal(s) :

- Approve treatments of chronic hepatitis C which are supported by the medical literature

Length of Authorization

- Initial trial of 12 weeks
- Continuation of therapy up to 24 weeks of total therapy based on therapy regimen and genotype

Requies PA:

- Sofosbuvir

Approval Criteria		
1. Is the request for treatment of Chronic Hepatitis C? Document appropriate ICD9 code:	**Yes:** Go to #2	**No:** Pass to RPh, Deny For Appropriateness
2. Does the patient have documented HCV genotype 1 or 4? Record Genotype:	**Yes:** Go to #3	**No:** Go to #4
3. Is the patient also being prescribed peginterferon alfa-2a or -2b and ribavirin and has been granted prior authorization or meets criteria for pegylated interferon-alfa and ribavirin?	**Yes:** Go to #4	**No:** Pass to RPh, Deny For Appropriateness
4. Does the patient have documented HCV genotype 2 or 3? Record Genotype:	**Yes**: Go to #5	**No**: Pass to RPh, Deny For Appropriateness
5. Is the patient also being prescribed ribavirin?	**Yes:** Go to #6	**No:** Pass to RPh, Deny For Appropriateness
6. Is the medication being prescribed by or in consultation with a specialist in the field of gastroenterology, infectious disease, or hepatitis C?	**Yes:** Go to #7	**No:** Pass to RPh, Deny For Appropriateness
7. If the patient has been treated with peginterferon and ribavirin before, do they have documented compliance/adherence to their previous treatment?	**Yes:** Go to #8	**No:** Pass to RPh, Deny For Appropriateness
8. Does the patient have a biopsy to indicate moderate to severe fibrosis (stage 2 or greater) OR radiologic, laboratory, or clinical evidence of cirrhosis? OR has extrahepatic manifestations (vasculitis, glomerulonephritis, cryoglobulins).	**Yes:** Go to #9	**No:** Pass to RPh, Deny For Appropriateness
9. Does the patient have a HIV coinfection?	**Yes:** Go to #10	**No:** Go to #11
10. Is the patient under the supervision of an HIV specialist?	**Yes:** Go to #11	**No:** Pass to RPh; Deny (medical appropriateness)
11. Has the patient previously been treated with boceprevir, telaprevir, or simeprevir?	**Yes**: Pass to RPh, Deny for appropriateness	**No:** Go to #12

12. Is the request for sofosbuvir 400 mg daily in genotype 3 (without HIV coinfection) chronic Hepatitis C?	**Yes:** Approve for 24 weeks	**No:** Go to #13 (If dose is different pass to RPh for appropriateness)
13. Is the request for sofosbuvir 400 mg daily in genotype 1, 2, or 4 chronic Hepatitis C (or genotype 3 with HIV coinfection)?	**Yes:** Approve for 12 weeks	**No:** Pass to RPh; Deny for appropriateness

P&T Board Action: 1/30/13 (MH)
Revision(s):
Initiated:

Appendix 2: Specific Drug Information

PHARMACOKINETICS[12]

Parameter	Result
Oral Bioavailability	Peak concentration 0.5-2 hours post dose
Protein Binding	61-65%
Elimination	80% eliminated through the kidney
Half-Life	27 hours
Metabolism	Liver

DOSE & AVAILABILITY[12]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
400 mg	PO	Q24H	400 mg daily for 12 weeks	A dose recommendation cannot be made for severe renal impairment (CrCl <30ml/min) or ESRD/ safety and efficacy has not been established in these patients.	No dose adjustment in hepatic impairment. Safety and efficacy have not been established in patients with decompensated cirrhosis.	Safety and effectiveness has not been established	Was administered to 90 subjects aged 65 and older. Response rates were similar to that of younger subjects.	• Should be used in combination with ribavirin or in combination with pegylated interferon and ribavirin

The recommended combination therapy is as follows:

HCV Mono-infected and HCV/HIV-1 Co-infected	Treatment	Duration
Genotype 1 or 4	SOVALDI + peg-interferon alfa + ribavirin	12 weeks
Genotype 2	SOVALDI + ribavirin	12 weeks
Genotype 3	SOVALDI + ribavirin	24 weeks

*24 weeks of treatment with sofosbuvir and ribavirin can be considered for CHC patients with genotype 1 who are interferon ineligible

* Should be used in combination with ribavirin for treatment of CHC in patients with hepatocellular carcinoma awaiting liver transplantion for up to 48 weeks or until liver transplantation

DRUG SAFETY[12]

Contraindications: All contraindications to peginterfron alfa and ribavirin also apply to simeprevir combination treatment and is contraindicated in pregnant women and in men whose female partners are pregnant.

Warnings and Precautions:

- Embryofetal Toxicity (use with ribavirin). Ribavirin may cause defects and fetal death. Avoid pregnancy in female patients and female partners of male patients.

Drug Interactions:

- Drugs that are potent intestinal P-gp inducers (rifampin, St. John's wort) may alter concentrations of sofosbuvir.

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Class Update: Second Generation Antipsychotics

Month/Year of Review: January 2014
PDL Class: Second Generation Antipsychotics

Date of Last Review: March 2012
Source Document: DERP

Current Status of Voluntary PDL Preferred/Non-Preferred Second Generation Antipsychotics

Current Preferred Agents	Current Non-Preferred Agents
Clozapine tablet	Aripiprazole (Abilify®) tablet/solution/Discmelt®/IM
Olanzapine tablet	Iloperidone (Fanapt®) tablet
Quetiapine tablet	Paliperidone (Invega®) tablet
Risperidone tablet/solution	Paliperidone (Invega®) Sustenna®
Ziprasidone capsule	Ziprasidone (Geodon®) for injection
	Lurasidone (Latuda®) tablet
	Risperidone (Risperdal®) Consta®
	Asenapine (Saphris®) SL tablet
	Quetiapine (Seroquel®) XR tablet
	Olanzapine (Zyprexa®) Relprevv®
	Olanzapine (Zyprexa®) Zydis®

Current Status of the Voluntary PDL:
Currently, all antipsychotics are available without prior authorization for non-preferred placement. Oregon law prohibits traditional methods of PDL enforcement on mental health drugs. Second generation antipsychotics have been reviewed for clinical efficacy and safety and specific agents were chosen as clinically preferred; this eliminates a copay. Oregon's Medicaid program currently charges no copayment for preferred PDL drugs. There is current prior authorization criteria for low-dose quetiapine (<150 mg/day) to discourage off-label use for insomnia (see Appendix 2).

Research Questions:

- Is there new comparative evidence of a meaningful difference in efficacy or effectiveness of second generation antipsychotics?
- Is there any new comparative evidence of a meaningful difference in harms of second generation antipsychotics?
- Is there new comparative evidence of a meaningful difference in efficacy or harms of second generation antipsychotics in subgroups?
- Is there evidence that the new formulation of aripiprazole is more efficacious or safer in certain populations?

Conclusions:

- There continues to be no consistent differences in the efficacy between clozapine, olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole or asenapine in shorter-term trials.[1] There is moderate quality evidence for aripiprazole, clozapine, olanzapine, quetiapine and risperidone. The comparative evidence is insufficient or very low for aripiprazole long-acting injection, Iloperidone, olanzapine long-acting injection, olanzapine ODT, extended-release paliperidone and lurasidone.[1]
- There is new moderate quality evidence that the risk of relapse may be lower with olanzapine and risperidone than immediate-release quetiapine and with risperidone long-acting injection than with oral risperidone in patients with first-episode schizophrenia.[1]
- There is new moderate quality evidence of no difference in response or remission rates between extended-release paliperidone and either olanzapine or immediate-release quetiapine for manic and mixed episodes of bipolar disorder.[1]
- There continues to be insufficient comparative evidence of efficacy and effectiveness of second generation antipsychotics in the treatment of Major Depressive Disorder, Bipolar Disorder in children and adolescents, Pervasive Developmental Disorders and Disruptive Behavior Disorders.[1]
- There is moderate quality evidence that the rate of clinically important weight gain (> 7% increase from baseline) in clinical trials was greater with olanzapine than with aripiprazole (RR 2.31), asenapine (RR 2.59), clozapine (RR 1.71), quetiapine (RR 1.82), risperidone (RR 1.81) and particularly ziprasidone (RR 5.76) across 3.7 to 24 months. Single studies of olanzapine and olanzapine long-acting injection, olanzapine ODT, and paliperidone palmitate did not find statistically significant differences in risk of weight gain. Data for other second generation antipsychotics was insufficient to assess the risk of clinically important weight gain compared with olanzapine.[1]
- There is limited comparative effectiveness data available for this class in regards to mortality and serious harms.[1]
- High rates of attrition and small sample sizes in randomized clinical trials make it difficult to draw strong conclusions for this class in systematic review.[2–5]
- There continues to be insufficient comparative evidence of a meaningful difference in efficacy or harms of second generation antipsychotics in any subgroup population.[1]
- There is low quality evidence that aripiprazole long-acting injection improves time to relapse compared to placebo; there are no head-to-head trials comparing aripiprazole long-acting injection to other second generation antipsychotics.[6]
- There is insufficient evidence to determine the long-term safety and comparative efficacy of aripiprazole long-acting injection.[6]

Recommendations:

- Based on the lack of long-term effectiveness and safety data, recommend listing aripiprazole long-acting injection as non-preferred on the voluntary PDL.
- No changes are recommended for the second generation antipsychotic preferred drug class list based on safety and efficacy. Costs should be reviewed in executive session.

Reason for Review:

The Pacific Northwest Evidence-Based Practice Center Drug Effectiveness Review Project (DERP) published an update to the drug class review on second generation antipsychotics in November 2013. This update will summarize findings from the DERP class review regarding the use of second generation antipsychotics and identify any other new relevant comparative effectiveness evidence, high-quality systematic reviews, or evidence-based guidelines. Aripiprazole long-acting injection (LAI) (Abilify Maintena™) was approved for use in February 2013.[6]

Previous Conclusions and Recommendation:
See Appendix 1

Background:

Antipsychotic medications are approved by the U.S. Food and Drug Administration (FDA) for treatment of schizophrenia and bipolar disorder and are divided into conventional, first generation antipsychotics and the second generation (or atypical) antipsychotics. There are currently ten second generation antipsychotics available in the US. They come in a variety of dosage forms (i.e. orally disintegrating tablets or long-acting injectables), have an assortment of FDA-approved indications (ranging from the irritability associated with autistic disorder in children and adolescents to the maintenance treatment of schizophrenia in adults), and are commonly used off-label for various psychiatric conditions. Side effect profiles between agents vary and are often an important factor in treatment selection. These side effects include extrapyramidal symptoms, autonomic effects, increased prolactin levels, metabolic effects, and cardiac risks including risk of ventricular arrhythmias. Commonly used outcomes in clinical trials include the Positive and Negative Syndrome Scale (PANSS) which is a validated 30-item rating scale used to assess the effects of drug treatment in schizophrenia, and the Clinical Global Impression Severity Scale (CGI-S) which measures the subject's current severity of illness. Data from the CATIE trial, a large, multicenter trial for patients with schizophrenia, suggests a minimal clinically important difference in the PANSS Scale is 15 points, but will vary according to a patient's baseline PANSS score.[7]

Long-acting injection (LAI) antipsychotics are widely use, especially for treating patients who show non-adherence or partial adherence to oral therapy. Drug adherence is essential in improving clinical and social outcomes in schizophrenia. First generation antipsychotics LAIs have been available since the late 1960s, and more recently second generation antipsychotic LAI formulations have become available (olanzapine pamoate, paliperidone palmitate, risperidone LAI, and aripiprazole LAI). Data on the safety and efficacy of second generation antipsychotic LAI formulations is lacking, particularly head-to-head data.[8]

Methods:
A Medline literature search was conducted for new meta-analyses and randomized controlled trials (RCT's) comparing Abilify® (aripiprazole), clozapine, risperidone, olanzapine, quetiapine, ziprasidone, paliperidone (Invega®), iloperidone (Fanapt®), asenapine (Saphris®), and lurasidone (Latuda®) since the date of the literature search included in the DERP report. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched

for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. After review of the citations from Medline and the manual searches, four high-quality systematic reviews, one new guideline, and one new drug formulation were reviewed along with the DERP updated drug class review.

DERP[1]

Schizophrenia and Related Psychoses

- Effectiveness
  - Strength of evidence for all effectiveness outcomes[1]:
    - Aripiprazole, clozapine, olanzapine, quetiapine and risperidone: Moderate
    - Asenapine, Paliperidone palmitate, and ziprasidone: Low to moderate
    - Extended-release paliperidone and lurasidone: Very low
    - Aripiprazole long-acting injection, Iloperidone, Olanzapine long-acting injection, and olanzapine ODT : Insufficient
  - Suicide: Clozapine was superior to olanzapine in preventing suicide or suicidality in patients at high risk of suicide (number needed to treat=12). This study also reported significantly greater rates of weight gain with olanzapine compared with clozapine (number needed to harm=4). Evidence on other drugs is insufficient for drawing comparative conclusions. [1]
  - Quality of Life: Good-quality trial evidence did not differentiate asenapine, olanzapine, quetiapine, risperidone or ziprasidone. [1]
  - Relapse: Risk of relapse may be lower with olanzapine and risperidone than immediate-release quetiapine and with risperidone long-acting injection versus oral risperidone (first-episode patients).[1] Results were mixed with risperidone versus olanzapine, and not different between long-acting injection risperidone and aripiprazole, lurasidone and oral risperidone or lurasidone and extended-release quetiapine.[1]
  - Hospitalization. Evidence suggested a lower risk of hospitalization with olanzapine than immediate-release quetiapine, risperidone, and ziprasidone, but was not consistent. Very limited evidence suggested that lurasidone results in lower hospitalization rates than immediate-release quetiapine over 12 months.
  - Functioning: Olanzapine, risperidone, immediate-release quetiapine, or ziprasidone were not different on employment or general function outcomes. Social function was not different between long-acting risperidone and paliperidone palmitate injections. [1] Global functioning was superior with olanzapine vs. ziprasidone in patients with depressive symptoms and with immediate-release quetiapine in patients with prominent negative symptoms, but similar between immediate-release quetiapine and risperidone in patients with a first-episode of schizophrenia.[1]
  - Rate and time to discontinuation of drug: Olanzapine was superior to aripiprazole, asenapine, lurasidone, olanzapine long-acting injection, paliperidone palmitate, quetiapine, risperidone, and ziprasidone, but not different to clozapine. [1] Clozapine was found to have lower discontinuation rates than asenapine, lurasidone, paliperidone palmitate, immediate-release quetiapine, risperidone, and ziprasidone. [1] Risperidone was found superior to asenapine, immediate-release quetiapine and ziprasidone, but inferior to lurasidone. This analysis also finds asenapine inferior to aripiprazole. Olanzapine ODT or extended release paliperidone were not found statistically significantly different to any of the other drugs, possibly due to small numbers of comparisons. In studies > six months, olanzapine was also superior to olanzapine ODT, and extended-release paliperidone, clozapine was superior to olanzapine long-acting injection (OR 0.46 (95% CI 0.25 to .88), and aripiprazole was superior to ziprasidone (OR 0.71 (95% CI 0.49 to 0.99) and lurasidone (OR 0.58, 95% CI 0.36 to 0.98). [1] In contrast, shorter studies found no

statically significant differences between the drugs. Olanzapine had longer time to discontinuation than immediate-release quetiapine, risperidone, and ziprasidone.[1]

- Efficacy: Consistent differences in efficacy were not found between clozapine, olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole or asenapine in shorter-term trials.[1]
    - Strength of evidence[1]:
        - Aripiprazole, clozapine, olanzapine, quetiapine and risperidone: Moderate
        - Asenapine, Paliperidone palmitate, Ziprasidone: Low to moderate
        - Extended-release paliperidone and lurasidone: Very low
        - Aripiprazole long-acting injection, Iloperidone, Olanzapine long-acting injection, and olanzapine ODT : Insufficient
- Tolerability and adverse events
    - Strength of evidence for all tolerability and adverse event outcomes[1]:
        - Aripiprazole, clozapine, olanzapine, quetiapine, risperidone and ziprasidone: Moderate
        - Asenapine and Paliperidone palmitate,: Low to moderate
        - Extended-release paliperidone and lurasidone: Very low
        - Aripiprazole long-acting injection, Iloperidone, Olanzapine long-acting injection, and olanzapine ODT : Insufficient[1]
    - Rate of discontinuation due to adverse events: Mixed-treatment comparisons analysis controlling for within-study dose comparisons and study duration indicated clozapine resulted in discontinuation due to adverse events statistically significantly more often than olanzapine, immediate-release quetiapine, or risperidone. [1] Sensitivity analyses of studies of > and < than 6 months found no statistically significant differences, although the point estimates were in the same direction as the overall analysis. [1] Fewer data were available for the lurasidone, new formulation of olanzapine, asenapine and paliperidone palmitate long-acting injection, and no data for iloperidone. [1]
    - Extrapyramidal symptoms: Rates of patients experiencing extrapyramidal symptoms or increases in measures of severity of symptoms were not found to be different among the drugs in most trials.[1]
    - Weight gain: The rate of clinically important weight gain (> 7% increase from baseline) in clinical trials was greater with olanzapine than with aripiprazole (RR 2.31), asenapine (RR 2.59), clozapine (RR 1.71), quetiapine (RR 1.82), risperidone (RR 1.81) and particularly ziprasidone (RR 5.76) across 3.7 to 24 months.[1] Single studies of olanzapine and olanzapine long-acting injection, olanzapine ODT, and paliperidone palmitate did not find statistically significant differences in risk of weight gain.[1] Data for other second generation antipsychotics was insufficient to assess the risk of clinically important weight gain compared with olanzapine.[1]
    - Sexual dysfunction: Evidence on sexual dysfunction is inconsistent for risperidone vs. immediate-release quetiapine. Individual trials found no differences among olanzapine and long-acting paliperidone, risperidone, or ziprasidone or between long-acting formulations of paliperidone and risperidone. [1] This evidence suffers from inadequate sample sizes or lack of explicit methodology to measure symptoms. [1]
    - Metabolic Syndrome: The risk of metabolic syndrome may be greater with olanzapine compared with paliperidone extended release. [1] Fair-quality randomized trials found no significant differences between other second generation antipsychotics. [1]
- Benefits and harms in subgroups
    - Strength of evidence for all benefit and harm in subgroup outcomes[1]:
        - First episode: Low

        - Others: Insufficient
    - First-episode of schizophrenia: Evidence does not support a difference between the drugs in response and remission between olanzapine, immediate-release quetiapine, risperidone, ziprasidone, aripiprazole, or extended-release paliperidone. [1] Evidence for rate or time to discontinuation is inconsistent, with few studies finding better results with olanzapine. [1]
    - Age: Differences in response, persistence, or quality of life based on age were not found between olanzapine and risperidone. Patients < 40 years old were found to be at a higher risk of new-onset diabetes with olanzapine and risperidone relative to risks in older age groups.[1]
    - Race: Limited evidence suggests that Mexican Americans and African American patients discontinued their prescribed second generation antipsychotic 18-19 days earlier than white patients, but an effect of the specific drug (olanzapine or risperidone) was not found.[1]
    - Illicit drug dose: No difference in discontinuation found among users and non-users. Response rates were similar for olanzapine and risperidone in patients with first episode schizophrenia and a history of cannabis use disorder. [1]
    - Obesity: Paliperidone palmitate injection was non-inferior to long-acting risperidone injection in PANSS total score mean change in normal to overweight patients, but was inferior in obese patients.[1]

<u>Bipolar Disorder in Adults</u>

- Effectiveness
    - Strength of evidence for all effectiveness outcomes[1]:
        - QOL: Moderate
        - Others: Low
    - Quality of life: no significant difference between risperidone and olanzapine or between asenapine and olanzapine was found. [1]
    - Functional capacity: No significant difference between paliperidone extended release and quetiapine on 12-week GAF scores. [1]
    - Hospitalizations: Observational evidence indicated lower risk of hospitalization with quetiapine monotherapy than with risperidone and olanzapine monotherapies and lower risk with adjunctive aripiprazole than with adjunctive ziprasidone, olanzapine, quetiapine, and risperidone.[1]
- Efficacy: No significant differences in response or remission rates between risperidone and olanzapine or asenapine and olanzapine, or between extended-release paliperidone and either olanzapine or immediate-release quetiapine for manic and mixed episodes. [1] Olanzapine may be superior to paliperidone extended release in preventing recurrence. [1]
    - Strength of evidence for all efficacy outcomes[1]**:**
        - Response or remission in manic/mixed episodes: Moderate
        - Recurrence: Low
- Harms
    - Strength of evidence for all harms outcomes[1]:
        - Diabetes: Insufficient
        - Pneumonia: Low
        - Weight, EPS, Discontinuation: Moderate
    - Diabetes: No direct comparative evidence[1]

- Pneumonia: Similar increases in risk for clozapine, olanzapine, immediate-release quetiapine, risperidone[1]
- Weight gain ≥7%: Higher risk for olanzapine compared with asenapine and for quetiapine compared with paliperidone extended release. [1]
- Extrapyramidal symptoms: Occurred more frequently with paliperidone extended release than olanzapine, but similar among other drugs. [1]
- Discontinuations due to adverse events: Higher rates for asenapine compared with olanzapine, but similar among risperidone, olanzapine, quetiapine, and paliperidone extended release. [1]

<u>Bipolar Disorder in Children and Adolescents</u>

- Effectiveness: Evidence of effectiveness in this population was not found. [1]
  - Strength of evidence: Insufficient[1]
- Efficacy
  - Strength of evidence for all efficacy outcomes[1]:
    - Response in preschool children: Low
    - Manic/mixed episodes: Insufficient
    - Depressed episodes: Insufficient
  - Direct evidence: Rate of response was similar for olanzapine compared with risperidone in preschool-aged children[1]
  - Indirect evidence: Time to discontinuation for any reason was significantly longer for aripiprazole compared to placebo over 72 weeks. [1]
  - Manic and mixed episodes - Response: Significantly greater than placebo for aripiprazole, olanzapine, immediate-release quetiapine, and risperidone as monotherapy and for immediate-release quetiapine in combination with divalproex. [1]
    - Remission: Significantly greater than placebo for aripiprazole, olanzapine, immediate-release quetiapine, and risperidone as monotherapy. [1]
    - Depressed episodes: No significant difference between immediate-release quetiapine and placebo groups in proportion of adolescents who met criteria for response or remission. [1] Also no significant difference was found between extended-release quetiapine and placebo in the proportion of children and adolescents who met criteria for response or remission. [1]
- Harms
  - Strength of evidence for all harms outcomes[1]:
    - Weight: Moderate
    - EPS: insufficient
  - Weight gain: No significant difference in weight gain for olanzapine compared with risperidone in preschool-age children. [1] For acute treatment, compared to placebo, mean weight gain was greatest for olanzapine and was successively lower for quetiapine IR, risperidone, and lowest for aripiprazole. [1] For maintenance treatment, evidence on aripiprazole's effects on weight gain compared with placebo was mixed.[1]
  - Extrapyramidal symptoms: Compared with placebo, rates were significantly greater for both aripiprazole and risperidone.

<u>Major Depressive Disorder</u>

- Effectiveness, Efficacy: No direct comparative evidence available. [1]
  - Strength of evidence: Insufficient[1]

- Harms: Observational evidence suggests that the use of SSRIs plus olanzapine is associated with significantly greater weight gain than SSRIs plus either quetiapine or risperidone. [1]
    - Strength of evidence: Moderate[1]

<u>Pervasive Developmental Disorders and Disruptive Behavior Disorders</u>

- Effectiveness and Efficacy
    - Indirect evidence from placebo-controlled trials of individual drugs was insufficient to draw conclusions about comparative effectiveness due to heterogeneity among trials in populations and outcome measures. No effectiveness evidence was found for either population.[1]
    - Pervasive developmental disorders: No head to head trials were found. Risperidone (five trials), aripiprazole (two trials), and olanzapine (one trial) were superior to placebo for improving behavioral symptoms in children with pervasive developmental disorders. Olanzapine was similar in efficacy to haloperidol in one small study.[1] Conclusions about comparative efficacy could not be drawn from this body of evidence because trials varied in their populations, duration of treatment and outcome measures used.[1]
    - Disruptive behavior disorder: Five fair-quality, short-term placebo-controlled trials found risperidone superior to placebo; one of these was conducted in hospitalized adolescents and the rest in outpatients. Quetiapine showed better efficacy than placebo in one study of adolescents with conduct disorder and moderate-to-severe aggressive behaviors.[1] No evidence was found for other second generation antipsychotics.[1]
    - Strength of evidence: Insufficient[1]
- Safety
    - Indirect evidence from placebo-controlled trials of individual drugs was insufficient to draw conclusions about comparative safety of the different drugs in this class. [1]
    - Weight change: increases reported in short-term trials ranged from 2.7 to 5.7 kg. Weight increase was significantly greater than placebo in trials of aripiprazole, olanzapine, and risperidone, and greater with olanzapine than haloperidol in one trial. In a Cochrane meta-analysis of 2 trials of risperidone in children with autism, the mean difference from placebo in weight gain with risperidone was 1.78 kg (95% CI, 1.15 to 2.41).[1] Longer-term evidence included three 6-month placebo-controlled trials and 4 open-label extension studies of short-term efficacy trials of risperidone. Weight gain ranged from 2.1 to 5.6 kg in studies up to 1 year. In a 2-year open-label extension study of 14 children, mean weight gain was 8.09 kg.[1] Other adverse events were infrequent. [1]
    - Extrapyramidal symptoms: The incidence of extrapyramidal symptoms and other adverse events was low in short-term trials. [1]
    - Longer term safety: No comparative evidence was found. Studies were conducted on risperidone only in longer-term evidence, none were conducted for olanzapine. [1]
- Effectiveness and safety in subgroups
    - No conclusions about comparative effectiveness or harms of second generation antipsychotics based on age, gender, or comorbidities could be made from this body of evidence. [1] Risperidone remained superior to placebo in mean decrease from baseline in ABC Irritability Subscale Score in subgroups of children with autism based on age, gender, ethnicity and income. [1] Risperidone was also superior to placebo in improving symptoms of children with disruptive behavior disorders and below-average IQ. [1]
    - Strength of evidence: Insufficient[1]

Serious Harms

- Strength of evidence for all serious harms outcome[1]:
  - Mortality, cardiovascular disease, tardive dyskinesia: Low
  - Diabetes: Moderate
  - Seizures, agranulocytosis, neuroleptic malignant syndrome: Insufficient
- Mixed Populations, primarily adults with schizophrenia
  - Mortality: Limited comparative evidence was available[1]
    - Quetiapine was found to have statistically significantly lower risk of mortality after 6 months of treatment in older patients with bipolar disorders compared with risperidone, hazard ratio 0.45 (95% CI 0.27 to 0.77). [1] Olanzapine and risperidone were not found to have statistically significant difference in risk, hazard ratio of 0.99 (95% CI 0.61 to 1.60. Cardiovascular mortality was found to be similar between clozapine and risperidone after 6 to 10 years of follow-up, 34.8% with clozapine, and 25% with risperidone (relative risk 1.39, 95% CI 0.61 to 2.5).[1] Stratification by age (< 55 or > 55 years at drug initiation) did not alter these findings, although the absolute rates are more divergent in the older group (e.g. 2.7% and 2.8% at 10 years in the younger group and 16.0% and 5.7% in the older group with clozapine and risperidone, respectively). [1]
  - Cardiac and cardiovascular risk: The risk of cardiovascular mortality was not different between clozapine and risperidone after 6-10 years of follow-up. [1] Clozapine was found to be associated with myocarditis or cardiomyopathy, while olanzapine, immediate-release quetiapine and risperidone were not. [1]
  - Diabetes: Olanzapine resulted in an increased risk of new-onset diabetes (OR, 1.16; 95% CI, 1.0 to 1.31 compared with risperidone). [1] Differences were not found with clozapine, immediate-release quetiapine, or risperidone. [1]
  - Tardive dyskinesia: Risperidone resulted in a small increased risk of new-onset tardive dyskinesia (1% to 2% difference). [1]

Systematic Reviews:

AHRQ Treatment of Adults with Post-Traumatic Stress Disorder (PTSD):
There is a low strength of evidence that risperidone may have some benefit for reducing PTSD symptoms, but insufficient evidence of its effects on depression symptoms. [9]

Cochrane Reviews:

One systematic review was identified from the Cochrane Library evaluating aripiprazole versus other atypical antipsychotics for schizophrenia.[2] This review shows that it remains difficult to draw strong conclusions due to the high attrition rates in these groups. Differences in efficacy between aripiprazole and other second generation antipsychotics (olanzapine, risperidone, ziprasidone) showed no advantage in terms of overall global state (defined as MD average change in CGI-S score) or mental state (defined as MD total change in PANNS score) in head-to-head RCTs.[2] When compared with any one of several new generation antipsychotic drugs in one RCT (n=523), the aripiprazole group showed improvement in energy, mood, negative symptom, somnolence, and weight gain.[2] More nausea was seen in patients given aripiprazole (n=2881, 3 RCTs, RR 3.13; 95% CI 2.12 to 4.61). [2] Weight gain in patients on aripiprazole was less common (n=330,

1 RCT, RR 0.35; 95% CI 0.19 to 0.64). Attrition in studies was 30% to 40% (no differences between groups), limiting validity.[2] There is limited data on the safety and efficacy of aripiprazole compared to other second generation antipsychotics and more large, long-term studies are needed before the clinical application of aripiprazole is fully understood.[2]

In a systematic review evaluating atypical antipsychotics for disruptive behavior disorders in children and youths, the use of risperidone and quetiapine were assessed.[3] There is limited evidence of efficacy of risperidone in reducing aggression and conduct problems in children aged 5 to 18 in short term trials. [3] Findings from one study assessing impact in the longer term suggest that the effects are maintained to some extent for up to six months. [3] Evidence was restricted by heterogeneity of the population and methodological issues in some studies, such as use of enriched designs and risk of selection bias. [3] There is currently no evidence to support the use of quetiapine for disruptive behaviors in these populations. [3] There still exists gaps in research with clinically representative youths and long-term follow-up, which will need to be closed before the effects of this class on disruptive behavior disorders is fully understood. [3]

A Cochrane Review evaluated antipsychotics for acute and chronic pain in adults.[4] Data from five included RCT showed beneficial effects of antipsychotics in the treatment of acute and chronic pain, but sample sizes in RCTs were small and results for antipsychotics in the treatment of different painful conditions are mixed. [4] There is a low level of evidence that antipsychotics may be used as add-on therapy in the treatment of painful conditions, but more data is needed to fully understand the benefit. [4] The most commonly reported adverse effects were extrapyramidal and sedating effects.[4] Further, larger studies are needed to determine the true effects of antipsychotics on patient with acute and chronic pain.[4]

A systematic review of atypical antipsychotics for psychosis in adolescents evaluated atypical antipsychotic medication with placebo or another pharmacological intervention or with psychosocial interventions, standard psychiatric treatment or no intervention in this population.[5] There was no convincing evidence that suggest that atypical antipsychotic medications are superior to typical medications for the treatment of adolescents with psychosis. [5] Atypical medications may be more acceptable to young people because fewer symptomatic adverse effects are seen in the short term. [5] Little evidence is available to support the superiority of one atypical antipsychotic medication over another, but side effect profiles are different for different medications. [5] Treatment with olanzapine, risperidone and clozapine is often associated with weight gain.[5] Aripiprazole is not associated with increase prolactin or with dyslipidemia.[5] Adolescents may respond better to standard-dose as opposed to lower-dose risperidone, but for aripiprazole and ziprasidone, lower doses may be equally effective.[5]

New Guidelines:

Scottish Intercollegiate Guidelines Network: Management of Schizophrenia (March 2013)[10]

- Grades of Recommendation[10]
    - Level A evidence: At least one meta-analysis, systematic review or RCT rated as high quality with very low risk of bias and directly applicable to the target population; or a body of evidence consisting principally of well conducted meta-analyses, systematic reviews or RCTs with low risk of bias directly applicable to the target population and demonstrating overall consistency of results
    - Level B evidence: A body of evidence including high quality systematic reviews of case control or cohort studies directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from high quality meta-analyses, systematic reviews or RCTs with low risk of bias

    - Level C evidence: A body of well conducted case control or cohort studies with low risk of confounding or bias and a moderate probability that the relationship is not causal, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from high quality systematic reviews of case control or cohort studies
    - Level D evidence: Non-analytic studies (case reports, case series) or expert opinion; or extrapolated evidence from well conducted case control or cohort studies with a low risk or confounding or bias and a moderate probability that the relationship is causal
- Antipsychotic tolerability
    - Healthcare professionals and patients should work together to find the most appropriate medication and the lowest effective dose. There should be detailed discussion with service users outlining the potential benefits and harms of individual medications. Service user preference should be elicited and taken into account (expert consensus). [10]
    - Local arrangements for physical heath monitoring should be put in place at the time of antipsychotic prescribing (expert consensus).[10]
- Initial treatment in first episode psychosis
    - Following initiation of antipsychotics in the first episode of psychosis, the medicine should be continued for at least two weeks unless there are significant tolerability issues, and an assessment of dose and response should be monitored during this early phase (level D evidence).[10]
    - If there is no response to medication after four weeks, despite dose optimization, a change in antipsychotic should be considered (level D evidence).[10]
    - Where there is a partial response, patients should be reassessed after eight weeks unless there are significant adverse effects (level D evidence).
    - Minimum effective dose of either first- or second-generation antipsychotics should be used in individuals in the first episode of schizophrenia (level D evidence). [10]
    - Following remission of the first episode of schizophrenia, the duration of maintenance treatment with an antipsychotic should be at least 18 months (level D evidence).[10]
- Treating acute exacerbation or recurrence
    - Consider amisulpride, olanzapine or risperidone as the preferred medications with chlorpromazine and other low-potency first-generation antipsychotics providing suitable alternatives.[10] Consideration should be given to previous response to individual antipsychotic medications and adverse effect profiles (level A evidence). [10]
    - The medication should be continued for at least four weeks unless there are significant tolerability issues (level D evidence).[10]
    - Where a partial response is seen after review at four weeks, the medication should be reassessed after eight weeks unless there are significant adverse effects (level D evidence).[10]
- Treatment to prevent relapse during remission
    - Antipsychotics should be used for maintenance treatment in remission (level A evidence).[10]
    - Preferred medications are amisulpride, olanzapine or risperidone; suitable alternatives are chlorpromazine and other low-potency first-generation antipsychotics (level B evidence).[10]
    - Remission should be treated for a minimum of 2 years (level A evidence).[10]
    - Patients who request depot and those with medication adherence difficulties should be offered maintenance treatment with depot antipsychotic medication (level B evidence).[10]
- Treatment-resistant schizophrenia

- Clozapine should be offered to service users who have treatment-resistant schizophrenia (level A evidence).[10]
- Clozapine should be considered for patients whose schizophrenia has not responded to two antipsychotics including a second-generation antipsychotic medication (level B evidence).[10]
- A trial of clozapine augmentation with a second SGA should be considered for patients whose symptoms have not responded adequately to clozapine alone, despite dose optimization.[10] Treatment should be continued for a minimum of 10 weeks (level C evidence).[10]
- A trial of clozapine augmentation with lamotrigine may be considered for patients whose symptoms have had an insufficient response to clozapine alone (level B evidence).[10]
- Prescribing high dose antipsychotics should only be considered after adequate trials of antipsychotic monotherapy and augmentation, including a trial of clozapine, has failed (level D evidence).[10]

- Management of adverse effects[10]

Concern and/or risk	Strength of evidence	Consider
Extrapyramidal Side Effects	B	SGAs or low-potency FGAs
Tardive Dyskinesia	B	SGA
Sedation	B	Haloperidol or aripiprazole
Weight Gain	A	Haloperidol, aripiprazole, or amisulpride (not available in the US)
Weight gain on antipsychotic medications	A	Lifestyle interventions
	B	Metformin

- Comorbidities
  - Second-generation antipsychotics should be considered for individuals with schizophrenia which is in remission who have comorbid depressive symptoms (level B evidence).[10]

Horizon Scan

A recent AHRQ Horizon Scan report identified two antipsychotics in Phase III trials for the treatment of schizophrenia.[11] These agents target different receptors than currently approved agents, including a glycine transporter and a nicotine receptor, and will be used to treat negative symptoms and cognitive symptoms of schizophrenia.

New Formulations:

Aripiprazole long-acting injection (LAI) (Abilify Maintena™) was approved for use in February 2013. [6] The initial and usual maintenance dose of aripiprazole LAI is 400 mg once a month.[6] The dose can be reduced to 300 mg or 200 mg monthly based on drug interactions or tolerability. Patients should have established tolerability to aripiprazole before receipt of the LAI formulation.[6] Oral aripiprazole, 10-30 mg/day, or another oral antipsychotic must be continued for 2-weeks after the initial dose, and then discontinued. [6]

Aripiprazole LAI's efficacy and safety are based on experience with the oral formulation as well as pharmacokinetic trials and one 52-week randomized, double-blind, placebo-controlled trial.[12] The primary outcome was time to impending relapse in subjects who were stabilized on treatment with aripiprazole-IM depot for at least 12 weeks and then randomly assigned to either aripiprazole-IM-depot or placebo. [12] The randomized trial was terminated early because the difference in time to relapse met a predetermined statistically significant threshold (p=0.001) favoring aripiprazole LAI. [12] The rate of impending relapse was 10% with aripiprazole LAI and nearly 40% in the placebo group in the final analysis (HR 5.03; 95% CI 3.15-8.02. [12] The duration of exposure was limited due to the study's premature termination.[12]

Insomnia, headache and tremor were the most common adverse events reported with aripiprazole LAI relative to placebo. [6] Extra pyramidal symptoms were more common in the aripiprazole LAI group with the difference accounted for by Parkinson's symptoms.[6] Aripiprazole LAI shares the same contraindications, warnings and precautions as the oral form. Concurrent use of CYP 2D6 and 3A4 inhibitors requires a reduction in the monthly dose of aripiprazole. [6] Aripiprazole LAI should be avoided in patients taking a CYP3A4 inducer.[6]

Possible disadvantages of this new formulation include the requirement that patient continue oral aripiprazole for the 2 weeks following their first LAI dose as this could mistakenly lead to continuation of oral antipsychotics.[6] Unlike risperidone long-acting injection, aripiprazole LAI does not have a label indication for bipolar disorder and no trials have been published to support such off-label use.[6]

References:

1. McDonagh, M., Peterson, K., Fu, R. & Thakurta, S. Drug class review: Second Generation Antipsychotic Drugs. Update 4. (2013).
2. Khanna, P. *et al.* Aripiprazole versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev* **2,** CD006569 (2013).
3. Loy, J. H., Merry, S. N., Hetrick, S. E. & Stasiak, K. Atypical antipsychotics for disruptive behaviour disorders in children and youths. *Cochrane Database Syst Rev* **9,** CD008559 (2012).
4. Seidel, S. *et al.* Antipsychotics for acute and chronic pain in adults. Cochrane Database of Systematic Reviews 2013, Issue 8. Art. No.: CD004844. DOI: 10.1002/14651858.CD004844.pub3.
5. Kumar, A., Datta, S. S., Wright, S. D., Furtado, V. A. & Russell, P. S. Atypical antipsychotics for psychosis in adolescents. Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD009582. DOI: 10.1002/14651858.CD009582.pub2.
6. Aripiprazole Long-acting IM Drug Monograph. *US Department of Veterans Affairs* (2013). at <http://www.pbm.va.gov/>
7. Hermes, E. D. A., Sokoloff, D. M., Stroup, T. S. & Rosenheck, R. A. Minimum Clinically Important Difference In The Positive And Negative Syndrome Scale Using Data From The CATIE Schizophrenia Trial. *J Clin Psychiatry* **73,** 526–532 (2012).
8. Gentile, S. Adverse Effects Associated with Second-Generation Antipsychotic Long-Acting Injection Treatment: A Comprehensive Systematic Review. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy* **33,** 1087–1106 (2013).
9. Psychological and Pharmacological Treatments for Adults With Posttraumatic Stress Disorder (PTSD) - Research Review - Final | AHRQ Effective Health Care Program. at <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1435>
10. Management of Schizophrenia: A National Clinical Guideline. Scottish Intercollegiate Guidelines Network. March 2013. Available. at <http://www.sign.ac.uk/pdf/sign131.pdf>
11. ECRI Institute. AHRQ Healthcare Hroizon Scanning System Status Update. (Prepared by ECRI Institute under Contract No. HHSA290201000006C). Rockville, MD: Agency for Healthcare Research and Quality. September 2013. at <http://www.effectivehealthcare.ahrq.gov/reports/final.cfm>
12. Kane, J. M. *et al.* Aripiprazole intramuscular depot as maintenance treatment in patients with schizophrenia: a 52-week, multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* **73,** 617–624 (2012).
13. McDonagh, M., Peterson, K., Carson, S., Fu, R. & Thakurta, S. Drug class review: Atypical antipsychotic drugs. Update 3.
14. Health Resources Commission. Atypical Antipsychotic Drugs. (2010). at <http://www.oregon.gov/OHA/pharmacy/therapeutics/ebr.shtml>

Appendix 1:

Previous Conclusions by DERP[13,14]:

Schizophrenia:

1. No consistent differences in efficacy were found between clozapine, olanzapine, quetiapine, risperidone, ziprasidone, Iloperidone, asenapine or aripiprazole in shorter-term trials of inpatients or outpatients.
2. There is insufficient evidence to draw conclusions regarding the impact of medications in this class on suicide death.
3. There is no evidence of a clinically meaningful difference in rates of re-hospitalization for the included drugs.
4. Good quality evidence shows olanzapine is superior to quetiapine for reduction in relapse rate. Evidence for olanzapine vs. risperdone was mixed for relapse rate. No evidence was found for the other included drugs
5. There was no evidence to differentiate between drugs in this class for quality of life. Olanzapine, quetiapine, risperdone, ziprasidone and clozapine were the only drugs compared.
6. In a single 12 month study (n=108) no difference was seen between clozapine and risperdone for social functioning. There is insufficient evidence to draw conclusions about differences between quetiapine, risperidone, clozapine, and extended release palinperidone for social functioning.
7. There is insufficient evidence to draw conclusions regarding the impact of this class of drugs on:
    - Employment, Global assessment of functioning, Violent behavior, Rates of discontinuation or time to discontinuation, Inpatient outcome, Aggressive behavior, Length of stay, Time to onset of efficacy, Nursing burden in inpatient setting, Comparative differences in extrapyramidal symptoms, Metabolic syndrome, Subgroups of race, age, and gender
8. There was consistent evidence that showed no difference for medications in this class for response rates. Asenapine and iloperidone had no published studies.
9. One good quality study of first episode schizophrenia (n=400) found no statistically significant differences in overall discontinuation rates (primary outcome) or symptom response for olanzipine, immediate release quetiapine, and risperidone.
10. Weight gain was 6 to 13 pounds greater with olanzapine than the other atypical antipsychotics over periods of 1.5 to 18 months of treatment.
11. There was no evidence of clinically meaningful differences in rates of sexual dysfunction for the included drugs.
12. Evidence indicates that clozapine is more sedating than risperidone and olanzapine.

Bipolar Disorder

1. There is insufficient evidence to determine a clinically meaningful difference between drugs in this class for bipolar disorder.
2. The strength of evidence for efficacy and comparative difference between drugs in this category is low.

Major Depressive Disorder

1. No atypical antipsychotic had evidence of providing a significant long-term benefit when used as an adjunctive treatment for augmentation of antidepressant therapy in adults with treatment resistant depression.

Dementia

1. There was no consistent evidence that any atypical antipsychotic was superior to haloperidol for treating behavioral and psychological symptoms of dementia.
2. There were no significant differences between drugs or between drug and placebo on a variety of evaluation scales.

3. The incidence of Parkinsonism is higher with olanzapine and risperidone compared to immediate release quetiapine and placebo in patients with dementia.

Children with Pervasive Developmental Disorder or Disruptive Behavior Disorder

1. There is insufficient evidence to draw conclusions regarding the impact of medications in this class on patients with pervasive developmental disorder or disruptive behavior disorder.
2. The conclusions that could be drawn from these reviews were limited by the small numbers of available trials and lack of long-term follow-up data.

Serious Harms

1. While clozapine has been shown to be associated with an increased risk of seizures (2.9% and 4.2% in two separate studies) and agranulocytosis (13 studies reported incidence of 0-2.4%), differences among the drugs in other serious harms have not been clearly shown

Off-Label Uses

- There is moderate to high level of evidence available to support the following off-label use of the listed atypical antipsychotics.
    - Generalized anxiety disorder: quetiapine
    - Dementia (overall): aripiprazole, risperidone
    - Dementia (psychosis): risperidone
    - Dementia (agitation): olanzapine, risperidone
    - Depression (selective serotonin reuptake inhibitor (SSRI)/ selective serotonin-norepinephrine reuptake inhibitor (SNRI) augmentation): aripiprazole, quetiapine, risperidone
    - Depression (monotherapy): quetiapine
    - Obsessive Compulsive Disorder (SSRI augmentation): risperidone
    - Post-Traumatic Stress Disorder (PTSD): risperidone
- Based upon findings from the AHRQ report on off-label antipsychotics, it is recommended to maintain the current dose limit for quetiapine (limits doses <150mg for >3 months) to prevent off-label use.
- Due to the need for voluntary compliance with the PDL for this drug class, it is recommended that educational outreach interventions be considered in the management strategy.
    - As one example, academic detailing can be used to promote appropriate utilization and minimize inappropriate off-label use.

Appendix 2: Low dose quetiapine PA criteria

Low-Dose quetiapine (Seroquel® and Seroquel XR®)

Goal(s):

- To promote and ensure use of quetiapine that is supported by the medical literature.
- To discourage off-label use for insomnia.
- Promote the use of non-pharmacologic alternatives for chronic insomnia

Initiative: Require Prior Authorization for quetiapine doses <150 mg/day for greater than 90 days.
HSN = 14015

Length of Authorization: Up to 12 months (criteria specific)

Covered alternatives for insomnia:

- Covered alternatives listed at www.orpdl.org
- zolpidem
- benzodiazepine sedatives are available for short-term (15 doses/30days) without PA.
- mirtazapine (Off-label use)

Table.1 Adult (>18 years old) FDA-Approved Indications for quetiapine

Bipolar Disorder	296.0, 296.4, 296.6-296.8,296.89	
Major Depressive Disorder	296.2, 296.24, 296.3, 296.23, 296.33, 296.34, 296.5, 296.53, 296.54	For Seroquel XR® only, Adjunctive therapy with antidepressants for Major Depressive Disorder
Schizophrenia	295, 295.4, 295.44, 295.45, 295.6,295.62, 295.64, 295.85, 295.95, 295.80-295.82,295.40-295.42, 295.90-295.92	
Bipolar Mania	296.1, 296.3, 296.4, 296.43, 296.44	
Bipolar Depression	296.5	

Table.2. Pediatric FDA-Approved Indications

Schizophrenia	Adolescents (13-17 years)	
Bipolar Mania	Children and Adolescents (10 to 17 years),	Monotherapy

Approval Criteria		
1. What is the diagnosis?	Record the ICD9 code. Do not proceed and deny if diagnosis is not listed in Table. 1 or Table 2 above. (Medically Appropriate)	
2. Is the prescription for quetiapine less than 150 mg/day? (Verify that day's supply entry is accurate)	**Yes:** Go to #3.	**No:** Trouble-shoot claim processing with the pharmacy.
3. Is planned duration of therapy greater than 90 days?	**Yes:** Go to #4.	**No:** Approve for titration up to maintenance dose (60days).
4. Is reason for dose <150 mg/day due to any of the following: • low dose needed due to debilitation from a medical condition or age; • unable to tolerate higher doses; • stable on current dose; or • impaired drug clearance?	**Yes:** Approve for up to 1 year.	**No:** Deny, (Medically Appropriate). • Provide tapering schedule if needed. See below. • Approve up to 6 months to allow taper.

Suggested tapering strategies for quetiapine:

According to the manufacturer, downward dosage adjustments may be made dependent upon the clinical response and tolerance of the patient. Several other references which include the Journal of Family Practice, the Texas Medication Algorithm Project Procedural Manual on Bipolar Disorder Algorithms, and the State of Connecticut Department of Developmental Services Neuroleptic Taper Protocol recommend reducing the antipsychotic dose by 10 to 25 % of the current regimen every 1 to 2 weeks, with the exception of the State of Connecticut Protocol recommendation of additional decreases every 3 to 6 months as tolerated.

References:

1. Prescribing information for Seroquel®. AstraZeneca Pharmaceuticals LP. Wilmington, DE 19850. November 2009.
2. Prescribing information for Seroquel XR®. AstraZeneca Pharmaceuticals LP. Wilmington, DE 19850. November 2009.
3. Ramaswamy S, Malik S, Dewan V. Tips to manage and prevent discontinuation syndromes. J Fam Pract 2005; 4(9): 1-7.
4. Texas Department of State Health Services. Texas Medication Algorithm Project Procedural Manual: Bipolar disorder algorithms. http://www.dshs.state.tx.us/mhprograms/pdf/TIMABDman2007.pdf. (Accessed 2010 June 4).
5. State of Connecticut Department of Developmental Services Neuroleptic Taper Protocol. http://www.ct.gov/dds/cwp/view.asp?a=2042&q=391462. (Accessed 2010 June 4).

Appendix 3: Abstracts of potentially relevant systematic reviews

Khanna, P. *et al.* Aripiprazole versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev* **2,** CD006569 (2013).

BACKGROUND: In most western industrialised countries, second generation (atypical) antipsychotics are recommended as first line drug treatments for people with schizophrenia. In this review we specifically examine how the efficacy and tolerability of one such agent - aripiprazole - differs from that of other comparable second generation antipsychotics.

OBJECTIVES: To evaluate the effects of aripiprazole compared with other atypical antipsychotics for people with schizophrenia and schizophrenia-like psychoses.

SEARCH METHODS: We searched the Cochrane Schizophrenia Group Trials Register (November 2011), inspected references of all identified studies for further trials, and contacted relevant pharmaceutical companies, drug approval agencies and authors of trials for additional information.

SELECTION CRITERIA: We included all randomised clinical trials (RCTs) comparing aripiprazole (oral) with oral and parenteral forms of amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole, ziprasidone or zotepine for people with schizophrenia or schizophrenia-like psychoses. Data collection and analysis.

DATA COLLECTION AND ANALYSIS: We extracted data independently. For dichotomous data we calculated risk ratios (RR) and their 95% confidence intervals (CI) on an intention-to-treat basis based on a random-effects model. Where possible, we calculated illustrative comparative risks for primary outcomes. For continuous data, we calculated mean differences (MD), again based on a random-effects model. We assessed risk of bias for each included study.

MAIN RESULTS: We included 12 trials involving 6389 patients. Aripiprazole was compared to olanzapine, risperidone and ziprasidone. All trials were sponsored by an interested drug manufacturer. The overall number of participants leaving studies early was 30% to 40%, limiting validity (no differences between groups). When compared with olanzapine no differences were apparent for global state (no clinically important change: n = 703, 1 RCT, RR short-term 1.00 95% CI 0.81 to 1.22; n = 317, 1 RCT, RR medium-term 1.08 95% CI 0.95 to 1.22) but mental state tended to favour olanzapine (n = 1360, 3 RCTs, MD total Positive and Negative Syndrome Scale (PANSS) 4.68 95% CI 2.21 to 7.16). There was no significant difference in extrapyramidal symptoms (n = 529, 2 RCTs, RR 0.99 95% CI 0.62 to 1.59) but fewer in the aripiprazole group had increased cholesterol levels (n = 223, 1 RCT, RR 0.32 95% CI 0.19 to 0.54) or weight gain of 7% or more of total body weight (n = 1095, 3 RCTs, RR 0.39 95% CI 0.28 to 0.54). When compared with risperidone, aripiprazole showed no advantage in terms of global state (n = 384, 2 RCTs, RR no important improvement 1.14 95% CI 0.81 to 1.60) or mental state (n = 372, 2 RCTs, MD total PANSS 1.50 95% CI -2.96 to 5.96). One study compared aripiprazole with ziprasidone (n = 247) and both the groups reported similar change in the global state (n = 247, 1 RCT, MD average change in Clinical Global Impression-Severity (CGI-S) score -0.03 95% CI -0.28 to 0.22) and mental state (n = 247, 1 RCT, MD change PANSS -3.00 95% CI -7.29 to 1.29). When compared with any one of several new generation antipsychotic drugs the aripiprazole group showed improvement in global state in energy (n = 523, 1 RCT, RR 0.69 95% CI 0.56 to 0.84), mood (n = 523, 1 RCT, RR 0.77 95% CI 0.65 to 0.92), negative symptoms (n = 523, 1 RCT, RR 0.82 95% CI 0.68 to 0.99), somnolence (n = 523, 1 RCT, RR 0.80 95% CI 0.69 to 0.93) and weight gain (n = 523, 1 RCT, RR 0.84 95% CI 0.76 to 0.94). Significantly more people given aripiprazole reported symptoms of nausea (n = 2881, 3 RCTs, RR 3.13 95% CI 2.12 to 4.61) but weight gain (7% or more of total body weight) was less common in people allocated aripiprazole (n = 330, 1 RCT, RR 0.35 95% CI 0.19 to 0.64). Aripiprazole may have value in aggression but data are limited. This will be the focus of another review.

AUTHORS' CONCLUSIONS: Information on all comparisons are of limited quality, are incomplete and problematic to apply clinically. Aripiprazole is an antipsychotic drug with a variant but not absent adverse effect profile. Long-term data are sparse and there is considerable scope for another update of this review as new data emerges from the many Chinese studies as well as from ongoing larger, independent pragmatic trials.

Loy, J. H., Merry, S. N., Hetrick, S. E. & Stasiak, K. Atypical antipsychotics for disruptive behaviour disorders in children and youths. *Cochrane Database Syst Rev* **9,** CD008559 (2012).

BACKGROUND: Disruptive behaviour disorders include conduct disorder, oppositional defiant disorder and disruptive behaviour not otherwise specified. Attention deficit hyperactivity disorder (ADHD) is frequently associated with disruptive behaviour disorders. The difficulties associated with disruptive behaviour disorders are demonstrated through aggression and severe behavioural problems. These often result in presentation to psychiatric services and may be treated with medications such as atypical antipsychotics. There is increasing evidence of a significant rise in the use of atypical antipsychotics for treating disruptive behaviour disorders in child and adolescent populations.

OBJECTIVES: To evaluate the effect and safety of atypical antipsychotics, compared to placebo, for treating disruptive behaviour disorders in children and youths.

SEARCH METHODS: We searched the following databases in August 2011: CENTRAL (2011, Issue 3), MEDLINE (1948 to August Week 1), EMBASE (1980 to 2011 Week 32), PsycINFO (1806 to August Week 2 2011), CINAHL (1937 to current), ClinicalTrials.gov (searched 15 August 2011), Australian New Zealand Clinical Trials Registry (ANZCTR) (searched 15 August 2011), CenterWatch (searched 15 August 2011) and ICTRP (searched 15 August 2011).

SELECTION CRITERIA: We included randomised controlled trials with children and youths up to and including the age of 18, in any setting, with a diagnosis of a disruptive behaviour disorder. We included trials where participants had a comorbid diagnosis of attention deficit hyperactivity disorder, major depression or an anxiety disorder.

DATA COLLECTION AND ANALYSIS: Two review authors independently selected the studies and disagreements were resolved by discussion. Two review authors extracted data independently. One review author entered data into Review Manager software and another checked it. We contacted trial authors for information about adverse effects and to provide missing data.

MAIN RESULTS: We included eight randomised controlled trials, spanning 2000 to 2008. Seven assessed risperidone and one assessed quetiapine. Three of the studies were multicentre. Seven trials assessed acute efficacy and one assessed time to symptom recurrence over a six-month maintenance period. We performed meta-analyses for the primary outcomes of aggression, conduct problems and weight changes but these were limited by the available data as different trials reported either mean change scores (average difference) or final/post-intervention raw scores and used different outcome measures. We also evaluated each individual trial's treatment effect size where possible, using Hedges' g.For aggression, we conducted two meta-analyses. The first included three trials (combined n = 238) using mean difference (MD) on the Aberrant Behaviour Checklist (ABC) Irritability subscale. Results yielded a final mean score with treatment that was 6.49 points lower than the post-intervention mean score with placebo (95% confidence interval (CI) -8.79 to -4.19). The second meta-analysis on aggression included two trials (combined n = 57) that employed two different outcome measures (Overt Aggression Scale (modified) (OAS-M) and OAS, respectively) and thus we used a standardised mean difference. Results yielded an effect estimate of -0.18 (95% CI -0.70 to 0.34), which was statistically non-significant. We also performed two meta-analyses for conduct problems. The first included two trials (combined n = 225), both of which employed the Nisonger Child Behaviour Rating Form - Conduct Problem subscale (NCBRF-CP). The results yielded a final mean score with treatment that was 8.61 points lower than that with placebo (95% CI -11.49 to -5.74). The second meta-analysis on conduct problems included two trials (combined n = 36), which used the Conners' Parent Rating Scale - Conduct Problem subscale (CPRS-CP). Results yielded a mean score with treatment of 12.67 lower than with placebo (95% CI -37.45 to 12.11), which was a statistically non-significant result. With respect to the side effect of weight gain, a meta-analysis of two studies (combined n = 138) showed that participants on risperidone gained on average 2.37 kilograms more than those in the placebo group over the treatment period (MD 2.37; 95% CI 0.26 to 4.49).For individual trials, there was a range of effect sizes (ranging from small to large) for risperidone reducing aggression and conduct problems. The precision of the estimate of the effect size varied between trials.

AUTHORS' CONCLUSIONS: There is some limited evidence of efficacy of risperidone reducing aggression and conduct problems in children aged 5 to 18 with disruptive behaviour disorders in the short term. For aggression, the difference in scores of 6.49 points on the ABC Irritability subscale (range 0 to 45) may be clinically significant. For conduct problems, the difference in scores of 8.61 points on the NCBRF-CP (range 0 to 48) is likely to be clinically significant. Caution is required due to the limitations of the evidence and the small number of relevant high-quality studies. The findings from the one study assessing impact in the longer term suggest that the effects are maintained to some extent (small effect size) for up to six months. Inadequately powered studies produced non-significant results. The evidence is restricted by heterogeneity of the population (including below average and borderline IQ), and methodological issues in some studies, such as use of enriched designs and risk of selection bias. No study addressed the issue of pre-existing/concurrent psychosocial interventions, and comorbid stimulant medication and its dosage was only partially addressed. There is currently no evidence to support the use of quetiapine for disruptive behaviour disorders in children and adolescents. It is uncertain to what degree the efficacy found in clinical trials will translate into real life clinical practice. Participants in the studies were recruited from clinical services but those who agree to take part in the clinical trials are a subset of the overall population presenting for care. There are no research data for children under five years of age. Further high-quality research is required with large samples of clinically representative youths and long-term follow-up to replicate current findings.

Seidel, S. *et al.* Antipsychotics for acute and chronic pain in adults. Cochrane Database of Systematic Reviews 2013, Issue 8. Art. No.: CD004844. DOI: 10.1002/14651858.CD004844.pub3.

BACKGROUND: This is an updated version of the original Cochrane review published in Issue 4, 2008. The role of antipsychotics as adjuvant analgesics is a subject of longstanding controversy. Neuroleptanalgesia (that is a state of quiescence, altered awareness, and analgesia produced by a combination of taking an opioid analgesic and an antipsychotic), an established term for the management of acute pain, was shown to negatively influence disease course and total mortality in unstable angina patients. Nevertheless, antipsychotics are used to treat chronic pain (for example chronic headache, fibromyalgia and diabetic neuropathia). With atypical antipsychotics, a new class of antipsychotics, both fewer extrapyramidal side effects and additional benefits may be available.

OBJECTIVES: To assess the analgesic efficacy and adverse effects of antipsychotics in acute or chronic pain in adults.

SEARCH METHODS: The following databases were searched: CENTRAL, on The Cochrane Library, (Issue 12 of 12, 2012); MEDLINE (1966 to 11/1/2013); EMBASE (1980 to 2013 week 03) and PsycINFO 1806 to Jan week 3 2013. Searches were run originally in 2007 and then again in 2011 and 2013.

SELECTION CRITERIA: Randomised controlled trials (RCTs) of adults prescribed any dose of an oral antipsychotic for acute or chronic pain, where subjective pain assessment was described as either the primary or a secondary outcome, were included in this review.

DATA COLLECTION AND ANALYSIS: Data were extracted by two independent review authors, and results were compared for differences. Discrepancies were resolved by discussion. All trials were quality scored according to the methods set out in section six of the Cochrane Handbook for Systematic Reviews of Interventions.

MAIN RESULTS: A total of 770 participants were involved in the 11 included studies. Data from five included randomised double-blind studies showed beneficial effects of antipsychotics in the treatment of acute and chronic pain. Quantitative analysis of these studies showed a significant reduction of mean pain intensity after administration of the antipsychotic compared to placebo or another active compound, weighted mean difference (WMD) -1.78 (95% CI -2.71 to -0.85) for the continuous data; and relative risk (RR) 0.43 (95% CI 0.25 to 0.73), number needed to treat to benefit (NNT) 2.6 for the dichotomous data. Nevertheless, the test for heterogeneity was significant for both the continuous data (P = 0.0007) and the dichotomous data (P = 0.04). Obviously this makes the calculated NNT less reliable and caution is warranted when interpreting these results. The most frequently reported adverse effects were extrapyramidal (that is involuntary movements, parkinsonism and akathisia) and sedating effects.

AUTHORS' CONCLUSIONS: The recent search found five new studies which were all excluded, so the review remains the same as previously. Antipsychotics might be used as an add-on therapy in the treatment of painful conditions. Nevertheless, extrapyramidal and sedating side effects have to be considered before using antipsychotics for treating painful conditions. Results for antipsychotics in the treatment of different painful conditions are mixed and most sample sizes in the reviewed RCTs are small. Further studies on atypical antipsychotics in larger double-blind placebo-controlled studies that include standardised pain assessment and documentation are warranted.

Kumar, A., Datta, S. S., Wright, S. D., Furtado, V. A. & Russell, P. S. Atypical antipsychotics for psychosis in adolescents. Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD009582. DOI: 10.1002/14651858.CD009582.pub2.

BACKGROUND: Schizophrenia often presents in adolescence, but current treatment guidelines are based largely on studies of adults with psychosis. Over the past decade, the number of studies on treatment of adolescent-onset psychosis has increased. The current systematic review collates and critiques evidence obtained on the use of various atypical antipsychotic medications for adolescents with psychosis.

OBJECTIVES: To investigate the effects of atypical antipsychotic medications in adolescents with psychosis. We reviewed in separate analyses various comparisons of atypical antipsychotic medications with placebo or a typical antipsychotic medication or another atypical antipsychotic medication or the same atypical antipsychotic medication but at a lower dose.

SEARCH METHODS: We searched the Cochrane Schizophrenia Group Register (October 2011), which is based on regular searches of BIOSIS, CENTRAL, CINAHL, EMBASE, MEDLINE and PsycINFO. We inspected references of all identified studies and contacted study authors and relevant pharmaceutical companies to ask for more information.

SELECTION CRITERIA: We included all relevant randomised controlled trials (RCTs) that compared atypical antipsychotic medication with placebo or another pharmacological intervention or with psychosocial interventions, standard psychiatric treatment or no intervention in children and young people aged 13 to 18 years with a diagnosis of schizophrenia, schizoaffective disorder, acute and transient psychoses or unspecified psychosis. We included studies published in English and in other languages that were available in standardised databases.

DATA COLLECTION AND ANALYSIS: Review authors AK and SSD selected the studies, rated the quality of the studies and performed data extraction. For dichotomous data, we estimated risk ratios (RRs) with 95% confidence intervals (CIs) using a fixed-effect model. When possible, for binary data presented in the 'Summary of findings' table, we calculated illustrative comparative risks. We summated continuous data using the mean difference (MD). Risk of bias was assessed for included studies.

MAIN RESULTS: We included 13 RCTs, with a total of 1112 participants. We found no data on service utilisation, economic outcomes, behaviour or cognitive response. Trials were classified into the following groups. 1. Atypical antipsychotics versus placebo. Only two studies compared one atypical antipsychotic medication with placebo. In one study, the number of non-responders treated with olanzapine was not different from the number treated with placebo (1 RCT, n = 107, RR 0.84, 95% CI 0.65 to 1.10); however, significantly more (57% vs 32%) people left the study early (1 RCT, n = 107, RR 0.56, 95% CI 0.36 to 0.87) from the placebo group compared with the olanzapine group. With regard to adverse effects, young people treated with aripiprazole had significantly lower serum cholesterol compared with those given placebo (1 RCT, n = 302, RR 3.77, 95% CI 1.88 to 7.58). 2. Atypical antipsychotics versus typical antipsychotics When the findings of all five trials comparing atypical antipsychotic medications with a typical antipsychotic medication were collated, no difference in the mean end point Brief Psychiatric Rating Scale (BPRS) score was noted between the two arms (5 RCTs, n = 236, MD -1.08, 95% CI -3.08 to 0.93). With regard to adverse effects, the mean end point serum prolactin concentration was much higher than the reference range for treatment with risperidone, olanzapine and molindone in one of the studies. However, fewer adolescents who were receiving atypical antipsychotic medications left the study because of adverse effects (3 RCTs, n = 187, RR 0.65, 95% CI 0.36 to 1.15) or for any reason (3 RCTs, n = 187, RR 0.62, 95% CI 0.39 to 0.97). 3. One atypical antipsychotic versus another atypical antipsychotic. The mean end point BPRS score was not significantly different for people who received risperidone compared with those who received olanzapine; however, the above data were highly skewed. Overall no difference was noted in the number of people leaving the studies early because of any adverse effects between each study arm in the three studies comparing olanzapine and risperidone (3 RCTs, n = 130, RR 1.15, 95% CI 0.44 to 3.04). Specific adverse events were not reported uniformly across the six different studies included in this section of the review; therefore it was difficult to do a head-to-head comparison of adverse events for different atypical antipsychotic medications. 4. Lower-dose atypical antipsychotic versus standard/higher-dose atypical antipsychotic. Three studies reported comparisons of lower doses of the atypical antipsychotic medication with standard/higher doses of the same medication. One study reported better symptom reduction with a standard dose of risperidone as compared with a low dose (1 RCT, n = 257, RR -8.00, 95% CI -13.75 to -2.25). In another study, no difference was reported in the number of participants not achieving remission between the group receiving 10 mg/d and those who received 30 mg/d of aripiprazole (1 RCT, n = 196, RR 0.84, 95% CI 0.48 to 1.48). Similarly in the other study, authors reported no statistically significant difference in clinical response between the two groups receiving lower-dose (80 mg/d) and higher-dose (160 mg/d) ziprasidone, as reflected by the mean end point BPRS score (1 RCT, n = 17, MD -4.40, 95% CI -19.20 to 10.40).

AUTHORS' CONCLUSIONS: No convincing evidence suggests that atypical antipsychotic medications are superior to typical medications for the treatment of adolescents with psychosis. However, atypical antipsychotic medications may be more acceptable to young people because fewer symptomatic adverse effects are seen in the short term. Little evidence is available to support the superiority of one atypical antipsychotic medication over another, but side effect profiles are different for different medications. Treatment with olanzapine, risperidone and clozapine is often associated with weight gain. Aripiprazole is not associated with increased prolactin or with dyslipidaemia. Adolescents may respond better to standard-dose as opposed to lower-dose risperidone, but for aripiprazole and ziprasidone, lower doses may be equally effective. Future trials should ensure uniform ways of reporting.

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Class Update: Analgesics for Gout

Month/Year of Review: January 2014
PDL Classes: Analgesics for Gout

Date of Last Review: February 2012
Source Document: OSU College of Pharmacy

Current Status of PDL Class:
- Preferred Agents: ALLOPURINOL, COLCHICINE/PROBENECID
- Non-Preferred Agents: COLCHICINE (COLCRYRS®), FEBUXOSTAT (ULORIC®), PROBENECID, PEGLOTICASE (KRYSTEXXA)

Research Questions:
- Is there any new evidence about the comparative effectiveness of analgesics for the treatment of gout in reduction of gout flares or progression of disease?
- Is there any new evidence on the comparative harms of analgesics for the treatment of gout?

Previous Conclusions and Recommendation:
- There is moderate quality evidence of no difference in efficacy/effectiveness or safety between agents.
- Colchicine is the only agent for gout and Familial Mediterranean Fever
- Febuxostat reduces serum urate below 6mg/dl in a significantly greater proportion of patients with gout and hyperuricemic compared to patients receiving allopurinol but there was no difference in gout flares
- Recommend inclusion of each chemical entity
- Block pharmacy claims for pegloticase

Conclusions and Recommendations:
- Therapy with xanthine oxidase inhibitors remains first-line therapy for chronic gout/hyperuricemia.[1]
- There is insufficient evidence of any significant difference between allopurinol and feboxostat in clinical outcomes such as gout flares.[2] The American College of Rheumatology guidelines give no preference to either agent and both are recommended as first line treatment. [1]
- There is insufficient evidence for the treatment of intra-articular corticosteroids for the treatment of acute gout.[3]

Recommendations:
No further review or research needed. Evaluate comparative costs in executive session.

Background:
Gout is a disease caused by high uric acid levels (>6.8 mg/dl) in the blood leading to crystal formation in the joints. People with gout can have flares of red and swollen joints, usually occurring in the big toe, ankle, or knee.[3] Over the past few years, the prevalence of gout has increased both in the U.S. as well as other countries.[4] There are many possible factors for this rise, including dietary habits, increased prevalence of obesity and an increase in comorbidities that promote hyperuricemia (hypertension, chronic kidney disease, diabetes). Although there is no cure for gout, treatment can prevent recurrent attacks and improve its chronic form. Acute attacks can be caused by trauma, certain medications, hospitalization, alcohol use, and surgery. Due to declining mortality, frequent comorbidities that promote hyperuricemia, and widespread use of diuretics, elderly individuals with gout can be difficult to manage.

Treatment approaches to gout include treating acute attacks, preventing risk factors for hyperuricemia, and treating the underlying hyperuricemia. Non-steroidal anti-inflammatory drugs (NSAIDs) are the first line treatment for acute attacks. Other options include colchicine, intra-articular steroids, corticosteroids, narcotic analgesics, and interleukin-1 receptor antagonists. The goals of urate lowering therapy are to prevent future attacks, prevent joint destruction, and reduce the risk of kidney disease, hypertension, and cardiovascular events. However, clinical trials often use the surrogate outcome of uric acid levels to evaluate for efficacy. Reducing gout flares is a more relevant clinical outcome. Xanthine oxidase inhibitors (allopurinol/febuxostat) are used to treat hyperuricemia, and ultimately prevent recurrent attacks. Allopurinol has been used for more than 40 years, and febuxostat was approved in 2009 as an alternative for first-line treatment of hyperuricemia. In 2010, pegloticase was FDA approved for gout in adults who have failed therapy with maximum doses of xanthine oxidase inhibitors. Pegloticase is a uric acid-specific enzyme that leads to a decrease in uric acid concentrations. However, pegloticase has only been evaluated in clinical trials with surrogate outcomes and there are no data to indicate whether gout flares were reduced. The goals of treatment are to prevent acute gout flares

Methods:
A Medline OVID search was conducted with the following search terms: allopurinol, colchicine, probenecid, febuxostat, gout suppressants, uricosuric agents, xanthine oxidase inhibitor, gout, gouty arthritis, uric acid, urate oxidase, hyperuricemia, renal calculi, and Familial Mediterranean fever. The search was limited to English language articles of controlled trials conducted on humans published from 2010 to September week three 2013.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Systematic Reviews:
Ye et al conducted a systematic review to examine the efficacy of febuxostat compared with placebo or allopurinol to lower uric acid levels in hyperuricemic adults. [5] Ten trials were included; study duration varied from four to 28 weeks. Febuxostat doses varied from 20 to 240 mg per day. Allopurinol doses varied from 100 to 300 mg per day. The primary outcome was achieving a serum uric acid (sUA) level of $\leq$ 6.0 mg/dL. Four trials (n= 1225) were included in the analyses comparing placebo and febuxostat. Febuxostat subjects were much more likely to have a sUA of $\leq$ 6.0 mg/dL after the final visit than their placebo counterparts (76.5% vs. 0.8%; OR 253.73; 95% CI 75.39 to 737.08). For comparison of allopurinol, seven studies were included (n=5690) in the analysis. Febuxostat subjects more frequently achieved a sUA of $\leq$ 6 mg/dL than the allopurinol patients (68.8% vs. 43.3%; OR 3.14; 95% CI 1.82 to 5.44) at their final study visit. A subanalysis of four trials compared subjects on 40 mg febuxostat with subjects on 100 to 300 mg of allopurinol. Again, the febuxostat patients

more often achieved a sUA of ≤ 6 mg/dL than the allopurinol cohort (50.9% vs. 45.6%; OR 1.25; 95% CI 1.05 to 1.49). Individual study quality was assessed for randomization, blinding, allocation concealment, incomplete outcome data, selective outcome reporting, and other sources of bias. Trials were then stratified to the following levels: A (plausible bias was unlikely to obviously alter the results); B (plausible bias raised some doubt about the results); or C (plausible bias seriously weakened confidence in the results). Of the included studies, eight were classified as level A, and two as level B. [5]

Tayar et al also examined the efficacy of febuxostat compared with placebo or allopurinol in a systematic review from the Cochrane Collaboration. [2] Six trials were included with 3978 participants: four randomized control trials and two open label trials. Subjects were at least 18 years old and met the preliminary criteria of the American College of Rheumatologists (ACR) for acute gout arthritis and had serum uric acid levels (sUA) of 8.0 mg/dL. Febuxostat doses ranged from 40 to 240 mg and allopurinol from 100 to 300 mg, both per day. Individual study duration lasted from two to 28 weeks. All trials reported the amount of participants with sUA levels of < 6.0 mg/dL as a primary endpoint. Compared with patients receiving placebo, subjects on febuxostat were significantly more likely to achieve a goal sUA level by the final study visit. This was true for all febuxostat doses studied: 40 mg (RR 40.1; 95% CI 2.5 to 639.1), 80 mg (RR 68.9; 95% CI 13.8 to 343.9), 120 mg (RR 80.7; 95% CI 16.0 to 405.5), and 240 mg (RR 93.4; 95% CI 13.2 to 654.5). Incidence of gout flares was measured as an additional primary outcome for this review. Subjects taking febuxostat 120 mg and 240 mg experienced more flares than placebo patients at 4 to 28 weeks (RR 1.7; 95% CI 1.3 to 2.3, and RR 2.6; 95% CI 1.8 to 3.7 respectively). No significant differences were seen with the 40 mg and 80 mg doses. Compared with allopurinol subjects, patients receiving febuxostat 80 mg or greater were significantly more likely to achieve a sUA < 6 mg/dL by the final study measurement: 80 mg (RR 1.8; 95% CI 1.6 to 2.1), 120 mg (RR 2.2; 95% CI 1.9 to 2.45), and 240 mg (RR 2.3; 95% CI 1.7 to 3.0). Comparing febuxostat 40 mg and allopurinol, there was no statistical difference in subjects achieving the sUA goal. For incidence of gout flares, only the 240 mg febuxostat dose had a significantly higher number of flares when compared with allopurinol (RR 2.3; 95% CI 1.7 to 3.0). In safety and tolerance outcomes, total adverse events were lower for 80 mg (RR 0.93; 95% CI 0.87 to 0.99) and 120 mg febuxostat (RR 0.90; 95% CI 0.84 to 0.96) than the allopurinol groups. Withdrawals for any reason were significantly higher for all of the febuxostat dose groups except the 40 mg cohort: 80 mg (RR 1.3; 95% CI 1.1 to 1.5), 120 mg (RR 1.4; 95% CI 1.1 to 1.7), and 240 mg (RR 1.7; 95% CI 1.2 to 2.2). Individual trial quality was assessed for bias by looking closely at the methodology used for randomization, allocation concealment, and blinding, and for the completeness of outcome reporting. The quality of evidence put forth by the trials was judged by the authors to range from low to high. Selective or incomplete outcome reporting, allocation concealment, and blinding procedures were all singled out for contributing to quality issues.[2]

Another Cochrane Collaboration Systematic Review evaluated the safety and efficacy of intra-articular glucocorticoids in the treatment of acute gout.[3] After a full MEDLINE search, no trials were identified that evaluated the efficacy and safety of intra-articular glucocorticoids for acute gout. Although evidence suggests that intra-articular glucocorticoids may be a safe and effective treatment in osteoarthritis and rheumatoid arthritis, there is no evidence from RCTs to support their use in the treatment of acute gout. The results from studies in these other patient populations may be generalizable to people with acute gout, particularly in people who cannot use non-steroidal anti-inflammatory drugs or colchicine.

Guidelines:

The American College of Rheumatology updated their guidelines for treatment of hyperuricemia in adults in 2012. [1] Guideline recommendations were graded according to the quality of evidence supporting each recommendation. The following recommendations were made on drug therapy:

- Patients with a diagnosis of gouty arthritis and evidence of tophus or tophi are indicated for uric acid lowering treatment. Grade A recommendation
- Patients with a diagnosis of gouty arthritis and frequent gout flares are indicated for uric acid lowering treatment. Grade A recommendation

- Patients with a diagnosis of gouty arthritis and evidence of chronic kidney disease stage 2 or greater are indicated for uric acid lowering treatment. Grade C recommendation
- Patients with a diagnosis of gouty arthritis and evidence of past urolithiasis are indicated for uric acid lowering treatment. Grade C recommendation
- Allopurinol or febuxostat are both recommended as first line agents for uric acid lowering. Grade A recommendation
- Starting allopurinol dosage should be no greater than 100 mg/day for any patient, and start at 50 mg/day in stage 4 or worse CKD. Grade B recommendation
- Gradually titrate allopurinol maintenance doses upward every 2–5 weeks to appropriate maximum dose in order to treat to chosen SUA target. Grade C recommendation
- Dose can be raised above 300 mg allopurinol daily, even with renal impairment, as long as it is accompanied by adequate patient education and monitoring for drug toxicity. Grade B recommendation
- Prior to allopurinol initiation, consider HLA–B*5801 in selected patients, specifically in subpopulations at higher risk for severe allopurinol hypersensitivity reaction (e.g., Koreans with stage 3 or worse CKD, and Han Chinese and Thai irrespective of renal function). Grade A recommendation
- Febuxostat can be substituted for allopurinol or vice versa in the event of drug intolerance and adverse events, and such a substitution should be considered after initial failure of upward dose titration of either. Grade C recommendation
- Effective therapeutic options include addition of a uricosuric agent (e.g., probenecid, fenofibrate, or losartan) to a xanthine oxidase inhibitor. Grade B recommendation
- Probenecid is recommended as an alternative if at least one xanthine oxidase inhibitor is contraindicated. Grade B recommendation
- Probenecid is the first choice among uricosuric agents for uric acid lowering monotherapy. Grade B recommendation
- In gout patients with a creatinine clearance $\leq$50 ml/minute, probenecid is not recommended as first-line monotherapy. Grade C recommendation
- Use of agents other than probenecid with clinically significant uricosuric effects, such as fenofibrate and losartan, can be therapeutically useful as components of a comprehensive uric acid lowering strategy. Grade B recommendation
- History of urolithiasis contraindicates probenecid monotherapy. Grade C recommendation
- Treatment can be started during an acute flare as long as anti-inflammatory management had begun. Grade C recommendation
- Pegloticase is appropriate for patients with severe gout disease burden and refractoriness to, or intolerance of, conventional and appropriately dosed uric acid lowering treatment. Grade A recommendation
- The use of low-dose NSAIDs or low-dose colchicine can be used to prevent against acute flares during initiation of chronic therapy. Level A recommendation

New drugs:
None

New Formulations/Indications:
None

New FDA safety alerts:

None

New Trials (Appendix 1):
A total of 22 citations resulted from the initial Medline search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, two relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 1 for the full abstracts.

A secondary analysis of the CONFIRMS trial by Wells et al examined the efficacy of febuxostat within the subpopulation of African Americans. Subjects (n=228) were randomized to receive 40 mg febuxostat, 80 mg febuxostat or 200-300 mg allopurinol for six months. The primary endpoint was the proportion of subjects in each group with a serum uric acid (sUA) level of < 6.0 mg/dL at the final visit. Subjects in the febuxostat 80 mg group (66.7%) were significantly more likely to meet the endpoint than those in both the febuxostat 40 mg group (34.9%; p <0.001) and the allopurinol group (41.8%; p=0.004). No statistical difference was seen between febuxostat 40 mg and allopurinol. Significantly more subjects with mild or moderate renal impairment achieved a sUA < 6.0 mg/dL in the febuxostat 80 group than in either the febuxostat 40 mg or allopurinol group ($p < 0.05$).[6]

Jackson et al also performed a secondary Ad-Hoc analysis of the CONFIRMS trial. Their evaluation examined the results for a subset of the trial population over 65 years old. Patients (n=374) were randomized to receive 40 mg febuxostat, 80 mg febuxostat or 200-300 mg allopurinol for six months. The primary endpoint was the proportion of subjects in each group with a serum uric acid (sUA) level of < 6.0 mg/dL at the final visit. Both doses of febuxostat were more likely to produce a sUA level at goal by the last study visit than was allopurinol (for febuxostat 80 mg: $p<0.001$, 40 mg: $p= 0.029$); 82% of patients in the febuxostat 80 mg group, 61.7% of the febuxostat 40 mg group, and 47.3% of the allopurinol group achieved a sUA of 6 mg/dL. Febuxostat 80 mg was also significantly more effective at achieving sUA goal than the 40 mg dose ($p<0.001$). This trend continued for patients with mild-to-moderate renal disease; more patients on febuxostat 40 mg (61.6%; $p = 0.028$) and febuxostat 80 mg (82.5%; $p < 0.001$) achieved an sUA of < 6 mg/dL compared to those on allopurinol 200 or 300 mg (46.9%).[7]

References:

1. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care & Research*. 2012;64(10):1431–1446. doi:10.1002/acr.21772.

2. Tayar JH, Lopez-Olivo MA, Suarez-Almazor ME. Febuxostat for treating chronic gout. In: The Cochrane Collaboration, Lopez-Olivo MA, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2012. Available at: http://doi.wiley.com/10.1002/14651858.CD008653.pub2. Accessed October 1, 2013.

3. Wechalekar MD, Vinik O, Schlesinger N, Buchbinder R. Intra-articular glucocorticoids for acute gout. *Cochrane Database Syst Rev*. 2013;4:CD009920. doi:10.1002/14651858.CD009920.pub2.

4. Terkeltaub R. Update on gout: new therapeutic strategies and options. *Nat Rev Rheumatol*. 2010;6(1):30–38. doi:10.1038/nrrheum.2009.236.

5. Ye P, Yang S, Zhang W, et al. Efficacy and Tolerability of Febuxostat in Hyperuricemic Patients With or Without Gout: A Systematic Review and Meta-Analysis. *Clinical Therapeutics*. 2013;35(2):180–189. doi:10.1016/j.clinthera.2012.12.011.

6. Wells AF, MacDonald PA, Chefo S, Jackson RL. African American patients with gout: efficacy and safety of febuxostat vs allopurinol. *BMC Musculoskeletal Disorders*. 2012;13(1):15. doi:10.1186/1471-2474-13-15.

7. Jackson RL, Hunt B, MacDonald PA. The efficacy and safety of febuxostat for urate lowering in gout patients ≥65 years of age. *BMC Geriatrics*. 2012;12(1):11. doi:10.1186/1471-2318-12-11.

Appendix 1: Abstracts of Randomized Control Trials

Wells AF, MacDonald PA, Chefo S, Jackson RL. African American patients with gout: efficacy and safety of febuxostat vs allopurinol. *BMC Musculoskeletal Disorders*. 2012;13(1):15. doi:10.1186/1471-2474-13-15.

Background: African Americans are twice as likely as Caucasians to develop gout, but they are less likely to be treated with urate-lowering therapy (ULT). Furthermore, African Americans typically present with more comorbidities associated with gout, such as hypertension, obesity, and renal impairment. We determined the efficacy and safety of ULT with febuxostat or allopurinol in African American subjects with gout and associated
comorbidities and in comparison to Caucasian gout subjects.
Methods: This is a secondary analysis of the 6-month Phase 3 CONFIRMS trial. Eligible gouty subjects with baseline serum urate (sUA) ≥ 8.0 mg/dL were randomized 1:1:1 to receive febuxostat 40 mg, febuxostat 80 mg, or allopurinol (300 mg or 200 mg depending on renal function) daily. All subjects received gout flare prophylaxis. Primary efficacy endpoint was the proportion of subjects in each treatment group with sUA < 6.0 mg/dL at the final visit. Additional endpoints included the proportion of subjects with mild or with moderate renal impairment who achieved a target sUA < 6.0 mg/dL at final visit. Adverse events (AEs) were recorded throughout the study.
Results: Of the 2,269 subjects enrolled, 10.0% were African American and 82.1% were Caucasian. African American subjects were mostly male (89.5%), obese (BMI ≥ 30 kg/m2; 67.1%), with mean baseline sUA of 9.8 mg/dL and mean duration of gout of 10.4 years. The proportions of African American subjects with a baseline history of diabetes, renal impairment, or cardiovascular disease were significantly higher compared to Caucasians ($p < 0.001$). ULT with febuxostat 80 mg was superior to both febuxostat 40 mg ($p < 0.001$) and allopurinol ($p = 0.004$). Febuxostat 40 mg was comparable in efficacy to allopurinol. Significantly more African American subjects with mild or moderate renal impairment achieved sUA < 6.0 mg/dL in the febuxostat 80 group than in either the febuxostat 40 mg or allopurinol group ($p < 0.05$). Efficacy rates in all treatment groups regardless of renal function were comparable between African American and Caucasian subjects, as were AE rates.
Conclusions: In African American subjects with significant comorbidities, febuxostat 80 mg is significantly more efficacious than either febuxostat 40 mg or allopurinol 200/300 mg. Febuxostat was well tolerated in this African American population.

Jackson RL, Hunt B, MacDonald PA. The efficacy and safety of febuxostat for urate lowering in gout patients ≥65 years of age. *BMC Geriatrics*. 2012;12(1):11. doi:10.1186/1471-2318-12-11.

Background: The incidence of gout rises with increasing age. Management of elderly (≥65 years) gout patients can be challenging due to high rates of comorbidities, such as renal impairment and cardiovascular disease, and concomitant medication use. However, there is little data specifically addressing the efficacy and safety of available urate-lowering therapies (ULT) in the elderly. The objective of this post hoc analysis was to examine the efficacy and safety of ULT with febuxostat or allopurinol in a subset of elderly subjects enrolled in the CONFIRMS trial.
Methods: Hyperuricemic (serum urate [sUA] levels ≥ 8.0 mg/dL) gout subjects were enrolled in the 6-month, double-blind, randomized, comparative CONFIRMS trial and randomized, 1:1:1, to receive febuxostat, 40 mg or 80 mg, or allopurinol (200 mg or 300 mg based on renal function) once daily. Flare prophylaxis was provided throughout the study duration. Study endpoints were the percent of elderly subjects with sUA <6.0 mg/dL at the final visit, overall and by renal function status, percent change in sUA from baseline to final visit, flare rates, and rates of adverse events (AEs).
Results: Of 2,269 subjects enrolled, 374 were elderly. Febuxostat 80 mg was significantly more efficacious (82.0%) than febuxostat 40 mg (61.7%; $p < 0.001$) or allopurinol (47.3%; $p < 0.001$) for achieving the primary efficacy endpoint. Febuxostat 40 mg was also superior to allopurinol in this population ($p = 0.029$). In subjects with mild to- moderate renal impairment, significantly greater ULT efficacy was observed with febuxostat 40 mg (61.6%; $p = 0.028$) and febuxostat 80 mg (82.5%; $p < 0.001$) compared to allopurinol 200/300 mg (46.9%). Compared to allopurinol 200/300 mg, the mean percent change in sUA from baseline was significantly greater for both febuxostat 80 mg ($p < 0.001$) and febuxostat 40 mg ($p = 0.011$) groups. Flare rates declined steadily in all treatment groups. Rates of AEs were low and comparable across treatments.
Conclusions: These data suggest that either dose of febuxostat is superior to commonly prescribed fixed doses of allopurinol (200/300 mg) in subjects ≥65 years of age with high rates of renal dysfunction. In addition, in this high risk population, ULT with either drug was well tolerated.

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Month/Year of Review: November 2013 **Date of Last Review:** January 2012
PDL Classes: Oral Antivirals HSV **Source Document:** OSU College of Pharmacy

Current Status of PDL Class:
- Preferred Agents: ACYCLOVIR TABLET, SUSPENSION, & CAPSULE
- Non-Preferred Agents: VALACYCLOIR, FAMCICLOVIR, ACYCLOVIR CREAM & OINTMENT (ZOVIRAX®), PENCICLOVIR TOPICAL (DENAVIR®), DOCOSANOL TOPICAL (ABREVA®)

Previous Conclusions and Recommendation:
- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harms/adverse events
- Recommend including one or more agents from this category

PA Criteria: Prior authorization criteria are currently in place for non-preferred herpes simplex oral and topical antivirals to cover only for covered diagnoses and for medically appropriate conditions (Appendix 1). Patient must have an ICD9 diagnosis for uncomplicated herpes simplex AND documentation of a disease state or medication that causes immunosuppression.

Conclusions and Recommendations:
- No further review or research needed at this time

Methods:
A Medline OVID search was conducted with the following search terms: acute retinal necrosis, Bell's palsy, cytomegalovirus disease, herpes simplex, varicella, herpes genitalis, herpes labialis, herpes zoster, herpes ocular, HSV, antiviral, acyclovir, Zovirax, famciclovir, ganciclovir, valacyclovir, valganciclovir, penciclovir, docosanol. The search was limited to English language articles of controlled trials conducted on humans published from 2012 to September week two 2013.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Systematic Reviews:

The Cochrane Collaboration performed a 2013 systematic review and meta-analysis to compare HSV antivirals efficacy in the treatment of cytomegalovirus (CMV). Trials (N=37) were included if they examined the efficacy of treatment of, or prophylaxis for, CMV with antivirals in subjects who had undergone a solid organ transplant. The primary endpoints were incidence of CMV and all-cause mortality. All studied antivirals significantly reduced the risk for CMV disease compared with placebo or no treatment: acyclovir (6 studies, n= 421) RR 0.45, 95% CI 0.29 to 0.69; ganciclovir (11 studies, n=917) RR 0.44, 95% CI 0.34 to 0.58; and valacyclovir (2 studies, n=643) RR 0.30, 95% CI 0.19 to 0.49. In head-to-head studies, ganciclovir was more effective than acyclovir in preventing CMV disease in all recipients (7 studies, n=1113): RR 0.37, 95% CI 0.23 to 0.60. There were no significant differences between the two in the risk of death due to CMV disease or all-cause mortality. Valacyclovir was compared with ganciclovir or valganciclovir in three studies (n=171) but no significant difference was seen in incidence of CMV or all-cause mortality. Individual trial quality was assessed for

selection bias (allocation concealment and randomization), performance bias and detection bias (blinding), attrition bias (incomplete outcomes) and reporting bias (selective reporting). Overall quality of the included trials was rated as low to moderate with poor ratings in performance, detection and selective bias.[1]

Guidelines:

In 2012, the American Academy of Family Physicians also updated their guidelines for the treatment of sexually transmitted genital herpes in adults.[2]

- Oral acyclovir (Zovirax), valacyclovir (Valtrex), and famciclovir (Famvir) are effective treatments for initial or recurrent episodes of genital HSV by decreasing symptom duration and viral shedding. Grade A recommendation
- In patients with symptomatic HSV outbreaks, daily acyclovir or valacyclovir should be considered to reduce transmission to seronegative partners. Famciclovir is less effective for reducing viral shedding and HSV transmission. Grade B recommendation

The American Academy of Neurology updated it's guidelines for the treatment of Bell's palsy in 2012. Recommendations were stratified by the level of evidence and strength of recommendation. Evidence was classified as the following: level I evidence generated from prospective, blinded, randomized, controlled clinical trials; level II evidence from prospective matched group cohort studies or a lesser quality RCT; level III evidence is derived from all other controlled trials; and lastly, level IV evidence is from uncontrolled studies, case series, case reports, or expert opinion. Strength of recommendation grading is built upon the level of evidence used and classified as either grade A, B, C, or U. Grade A recommendations are established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population, and requires at least two consistent Class I studies. Grade B recommendations are considered as probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population and requires at least one Class I study or two consistent Class II studies. Grade C recommendations are considered possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population and requires at least one Class II study or two consistent Class III studies. Lastly, grade U recommendations are derived from data established to be either inadequate or conflicting and that, given current knowledge, the treatment is unproven.[3]

- For patients with new-onset Bell's palsy, oral steroids should be offered to increase the probability of recovery of facial nerve function. Level A recommendation
- For patients with new-onset Bell palsy, antivirals (in addition to steroids) might be offered to increase the probability of recovery of facial function. Patients offered antivirals should be counseled that a benefit from antivirals has not been established, and, if there is a benefit, it is likely that it is modest at best. Level C recommendation

New drugs:
None

New Formulations/Indications:
None

New FDA safety alerts:
None

New Trials (Appendix 2):
A total of 207 citations resulted from the initial Medline search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, two relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 2 for the full abstracts.

Perti et al compared effectiveness of valacyclovir and acyclovir in patients coinfected with genital herpes and HIV in an open label crossover trial. Patients with HIV (n=28) but not yet started on antiretroviral therapy were randomized to receive either valacyclovir 1000 mg twice daily or acyclovir 400 mg twice daily for twelve weeks. After twelve weeks patients had a two weeks wash-out period with no medication. They were then started on the alternative regimen for an additional twelve weeks. Primary outcomes were difference in HSV-2 shedding rate and decease in plasma HIV RNA. There was no statistical difference between valacyclovir and acyclovir in rate of HSV-2 viral shedding (7.8% vs. 8.2%; RR 0.95; 95% CI 0.66 to 1.37). Valacyclovir patients had a significantly lower amount of plasma HIV-1 RNA (0.27 $\log^{10}$ copies/mL difference) after treatment than acyclovir patients (95% CI: 20.41 to 20.14 $\log^{10}$ copies/mL). This was poor quality trial with many opportunities for bias due to the study design (open label, cross-over). In addition, the doses given to the patients were not equivalent: valacyclovir subjects were given a high dose regimen, while acyclovir members were given a normal suppressive dose regimen.[4]

Johnston et al conducted a series of three open label crossover trials to determine the effectiveness of different regimens in suppressing genital herpes outbreaks. Subjects with HSV-2 were randomized to receive either standard dose acyclovir (400 mg twice daily) or placebo in the first study (n=32) for four weeks on each medication. Subjects (n=31) were placed on standard dose valacyclovir (500 mg daily) or high dose acyclovir (800 mg three times daily) in the second study for seven weeks each. In the final study (n=50), subjects were randomized to five weeks on either standard dose valacyclovir or high dose valacyclovir (1000 mg twice daily). All three crossover studies had a two week washout period between regimens. The primary outcome was absence of genital HSV viral shedding. Both doses of acyclovir reduced the detection of HSV compared with the no medication cohort (both: $p \leq 0.003$). Subjects on high dose acyclovir had a lower incidence of HSV shedding than those on standard dose valacyclovir (4.2% vs 4.5%; incidence risk ratio [IRR] 0.79; 95% CI 0.63 to 1.00). High dose valacyclovir subjects also had less viral shedding than those on standard dose valacyclovir (3.3% vs. 5.8%; IRR 0.54; 95% CI 0.44 to 0.66). This was a poor quality study with many serious flaws. All three studies were open label; randomization procedures were not described. Subjects were responsible for collecting the swabs used for the primary outcome, and there was up to 3 days lag time before the swabs were delivered to the study administrators. Finally, although the participants were different individuals and the trial lengths each varied, the data from all three studies was pooled, compared and presented in one paper.[5]

References:
1. Hodson EM, Ladhani M, Webster AC, Strippoli GF, Craig JC. Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients. In: The Cochrane Collaboration, Hodson EM, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2013. Available at: http://doi.wiley.com/10.1002/14651858.CD003774.pub4. Accessed September 30, 2013.

2. Roett MA, Mayor MT, Uduhiri KA. Diagnosis and management of genital ulcers. *Am Fam Physician*. 2012;85(3):254–262.

3. Gronseth GS, Paduga R. Evidence-based guideline update: Steroids and antivirals for Bell palsy: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2012;79(22):2209–2213. doi:10.1212/WNL.0b013e318275978c.

4. Perti T, Saracino M, Baeten JM, et al. High-Dose Valacyclovir Decreases Plasma HIV-1 RNA More Than Standard-Dose Acyclovir in Persons Coinfected with HIV-1 and HSV-2: A Randomized Crossover Trial. *JAIDS Journal of Acquired Immune Deficiency Syndromes*. 2013;63(2):201–208. doi:10.1097/QAI.0b013e3182928eea.

5. Johnston C, Saracino M, Kuntz S, et al. Standard-dose and high-dose daily antiviral therapy for short episodes of genital HSV-2 reactivation: three randomised, open-label, cross-over trials. *The Lancet*. 2012;379(9816):641–647. doi:10.1016/S0140-6736(11)61750-9.

Appendix 1: Current PA Criteria

Antivirals, Oral and Topical – HSV

Goal(s): Cover oral and/or topical anti-virals only for covered diagnoses. HSV infections are covered only when complicated by an immunocompromised host.

Antivirals **Length of Authorization: Criteria Specific – up to 1 year**

Preferred Alternatives: **Oral** acyclovir DOES NOT require PA. See PDL list at: http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml.

Requires PA: HIC3 = Q5V

GENERIC	BRAND	ROUTE
Famciclovir	Famvir	Oral
Valacyclovir	Valtrex	Oral
Acyclovir	Zovirax	Topical
Penciclovir	Denavir	Topical
Docosanol	Abreva	Topical

Approval Criteria		
1. What is the diagnosis being treated?	Record ICD9 code	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Health Resource Commission (HRC). Reports are available at: http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml.	**Yes:** Inform provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml.	**No**: Go to #3
3. Is the diagnosis uncomplicated herpes simplex ICD9: 054.2, 054.6, 054.73, 054.9?	**Yes:** Go to #4	**No:** Pass to RPh; Go to #7
4. Is the patient immune compromised? Document ICD9 code. • Current (not history of) diagnosis of cancer AND is currently undergoing Chemotherapy or Radiation? Document therapy and length of treatment • Diagnosis of HIV/AIDS?	**Yes:** Approve for the shorter of expected therapy duration or90 days (applies to both topical and oral antivirals) (Immunocompromised Client)	**No:** Go to #5

<table>
<tr>
<td>5. Is client currently taking an immunosuppressive drug? Document drug:

(If drug not in list below, Pass to RPh for evaluation)

Immunosuppressive drugs include, but are not limited to:
<table>
<tr><th>Generic Names</th><th>Brand Names</th></tr>
<tr><td>Azathioprine
Basiliximab
Cyclosporine

Sirolimus
Tacrolimus
Methotrexate
Hydroxychloroquine
Etanercept
Leflunomide</td><td>Imuran
Simulect
Sandimmune,
Neoral
Rapamune
Prograf
Rheumatrex
Plaquenil
Enbrel
Arava</td></tr>
</table>
</td>
<td>Yes: Approve for the shorter of expected therapy duration or: 90 days (applies to topical or oral antivirals ; Immunocompromised Client).</td>
<td>No: If Diabetes or Sickle-Cell disease-go to #6. All others go to #7.</td>
</tr>
<tr>
<td>6. Does client have Diabetes or Sickle-Cell disease?

Note: Diabetes and Sickle-Cell is not considered as immunocompromisng for antivirals as it is for antifungal</td>
<td>Yes: Pass to RPH; Deny, (Not Covered by the OHP).</td>
<td>No: Pass to RPH to evaluate for immunosuppression.

➢ If not immunocompromised, Deny (Not Covered by the OHP).

➢ If immunocompromised, approve for 1 year.</td>
</tr>
<tr>
<td>7. RPH only
All other indications need to be evaluated as to whether they are above the line or below the line diagnosis.

• <u>If above,</u> viral diagnoses can be approved for treatment course with “prn” renewals. If length of therapy is unknown, please approve for 3 months intervals only (This is an exception to above guidelines and should be discussed with Lead Pharmacist)

• <u>If below,</u> Deny, (Not Covered by the OHP).

• <u>Deny Non-viral diagnoses</u> (Medical Appropriateness).

• <u>Deny Viral ICD-9 codes</u> that do not appear on the OHP list pending a more specific diagnosis code. (Not Covered by the OHP)</td>
<td>If above the line and clinic provides supporting literature: approve for length of treatment.</td>
<td>If below the line: Deny, (Not Covered by the OHP).</td>
</tr>
</table>

Appendix 2: Abstracts of Randomized Control Trials

Perti T, Saracino M, Baeten JM, et al. High-Dose Valacyclovir Decreases Plasma HIV-1 RNA More Than Standard-Dose Acyclovir in Persons Coinfected with HIV-1 and HSV-2: A Randomized Crossover Trial. *JAIDS Journal of Acquired Immune Deficiency Syndromes*. 2013;63(2):201–208. doi:10.1097/QAI.0b013e3182928eea.

Background: Standard doses of herpes simplex virus (HSV) suppressive therapy reduce plasma HIV-1 RNA levels (0.25–0.53 log10 copies per milliliter) among HIV-1/HSV-2 coinfected persons. Postulated mechanisms for this effect include direct inhibition of HIV-1 by acyclovir or indirect reduction by decreasing HSV-associated inflammation. We hypothesized that high-dose valacyclovir would further reduce plasma HIV-1 RNA and that the effect would be mediated by greater suppression of HSV shedding.

Methods: Thirty-four participants with HIV-1 and HSV-2 not on antiretroviral therapy were enrolled into a randomized, open-label crossover trial of valacyclovir 1000 mg twice daily or acyclovir 400 mg twice daily for 12 weeks, followed by a 2-week washout, and then the alternate treatment arm for 12 weeks. HSV DNA was measured from daily self-collected genital swabs for the initial 4 weeks of each arm, and HIV-1 RNA was quantified from weekly plasma samples.

Results: Twenty-eight participants provided plasma samples and genital swabs on both acyclovir and valacyclovir. The genital HSV-2 shedding rate was the same on valacyclovir and acyclovir [7.8% vs. 8.2% of days; relative risk: 0.95; 95% confidence interval (CI): 0.66 to 1.37; P = 0.78]. Plasma HIV-1 RNA was 0.27 log10 copies per milliliter lower on valacyclovir compared with acyclovir (95% CI: 20.41 to 20.14 log10 copies per milliliter; P , 0.001); this was unchanged after adjustment for genital HSV-2 shedding.

Conclusions: High-dose valacyclovir reduces plasma HIV-1 RNA levels more than standard-dose acyclovir in HIV-1/HSV-2–seropositive persons not receiving antiretroviral therapy. The incremental reduction in plasma HIV-1 RNA achieved is not mediated by greater genital HSV-2 suppression.

Johnston C, Saracino M, Kuntz S, et al. Standard-dose and high-dose daily antiviral therapy for short episodes of genital HSV-2 reactivation: three randomised, open-label, cross-over trials. *The Lancet*. 2012;379(9816):641–647. doi:10.1016/S0140-6736(11)61750-9.

Background—Recent studies indicate that short subclinical episodes of herpes simplex virus type 2 (HSV-2) are the predominant form of skin and mucosal viral shedding. We evaluated whether standard or high-dose antiviral therapy reduced the frequency of such shedding.

Methods—To determine whether short episodes of genital HSV shedding are suppressed on standard dose (SD) and high-dose (HD) antiviral therapy, HSV-2 seropositive, HIV seronegative persons in Seattle, WA were enrolled into three separate but complementary randomized, open label, cross-over studies comparing 1) no medication to aciclovir 400 mg twice daily (SD-ACV), 2) valaciclovir 500 mg daily (SD-VAL) to aciclovir 800 mg three times daily (TID) (HD-ACV), and 3) SD-VAL to HD-VAL (1 gm TID). Study arms lasted 4–7 weeks, separated by one week wash-out. Participants obtained genital swabs four times daily for quantitative HSV DNA PCR. The primary endpoint was within-person comparison of shedding rate on each study arm.

Results—Of 113 participants randomized, 90 were eligible for analysis of the primary endpoint. Participants collected 23,605 swabs; of these 1272 (5・4%) had HSV detected. HSV shedding was significantly higher during the no medication arm (18・1% of swabs) compared with SD-ACV (1.2% of swabs, IRR=0・05, 95% CI=0・03–0・08). Breakthrough reactivations occurred on all doses (SD-ACV 1・2%, SD-VAL 5・2%, HD-ACV 4・2%, and HD-VAL 3・3% of swabs). HD-VAL was associated with less shedding compared with SD-VAL (IRR=0・54, 95% CI=0・44–0・66), likely due to more rapid clearance of mucosal HSV (4・7 logs/6 hours on HD-VAL vs. 4・4 logs/6 hours on SD-VAL, (p=0・02)). However, the annualized breakthrough episodes was similar on SD-VAL (22・6) and HD-ACV (20・2, p=0・54) and SD-VAL (14.9) and HD-VAL (16・5, p=0・34). Regardless of dose, breakthrough episodes were short (median 7–10 hours) and 80% were subclinical. Studies were not designed to make inter-trial comparisons between antiviral doses. Except for increased incidence of headaches on HD-VAL, all regimens were well-tolerated.

Conclusions—Short bursts of subclinical genital HSV reactivation are frequent, even during high-dose antiherpes therapy, and likely account for continued transmission of HSV-2 during suppressive antiviral therapy. More potent antiviral therapy is needed to abolish HSV-2 transmission

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Month/Year of Review: January 2014
PDL Classes: Hormone Replacement Therapy

Date of Last Review: November 2012
Source Document: OSU College of Pharmacy

Current Status of PDL Class:

Current Preferred Agents	Current Non-Preferred Agents
Oral HRT - Estrogen	
Estradiol	Conjugated Estrogens, Synthetic B (Enjuvia®)
Conjugated Estrogens, Synthetic A	Esterified Estrogens/methyltestosterone
Estropipate	Esterified estrogens (Menest®)
	Estradiol/norethindrone (Activella®)
	Drospirenone/estradiol (Angeliq®)
	Norethindrone acetate/ethinyl estradiol (Jinteli®)
	Estradiol/norethindrone acetate (Mimvey®)
	Estradiol/norgestimate (Prefest®)
	Conjugated estrogens/Medroxyprogesterone (Prempro®, Premphase®)
	Norethindrone acetate/Ethinyl Estradiol (FEMHRT)
Topical HRT - Estrogen	
Estradiol patch (Climara)	Estradiol gel packet (Divigel®)
	Estradiol gel pump (Elestrin®)
	Estradiol patch (Estraderm®)
	Estradiol patch (Estrasorb®)
	Estradiol gel pump (EstroGel®)
	Estradiol spray (Evamist®)
	Estradiol patch (Vivelle-dot®)
	Estradiol/norethindrone acetate patch (Combipatch®)
	Estradiol/levonorgestrel patch (Climara Pro®)
Vaginal HRT - Estrogen	
Estradiol tablet	Estradiol vaginal cream (Estrace®)
Conjugated Estrogen cream	Estradiol vaginal ring (femring®)

Previous Conclusions and Recommendation:

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harms/adverse events
- Recommend including one or more agents from this category
- Estrogen plus progestin and estrogen alone decreased risk for fractures but increased risk for stroke, thromboembolic events, gallbladder disease, and urinary incontinence.
- Estrogen plus progestin increased risk for breast cancer and probable dementia, whereas estrogen alone decreased risk for breast cancer.
- There are insufficient data to assess the risk of long term hormone therapy use in perimenopausal women or postmenopausal women younger than 50 years of age.
- Hormone therapy for postmenopausal women with an intact uterus should comprise both estrogen and progestin to reduce the risk of endometrial hyperplasia.
- There were no consistent differences by age and comorbidities in subgroup analyses.

- Despite of lacking randomized clinical trials evidence for potential favorable thromboembolic risks using transdermal formulation of hormone therapy, several national guidelines recommended transdermal route of administration over oral route.

Research Questions:

- Is there any new comparative evidence in reducing symptoms of menopause, preventing low bone density, or preventing fractures?
- Is there any new comparative safety evidence of the different preparations?
- Are there subpopulations of patients for which one medication or preparation is more effective or associated with fewer adverse effects?

Methods:

The DERP scan was used to identify any new comparative research that has emerged since the last P&T review.[1]

Conclusions and Recommendations:

- There is no new significant comparative evidence on the efficacy or safety of hormone replacement therapy medications; no further review or research needed.
- Evaluate comparative costs in executive session.

References:

1. Selph S. Drug Effectiveness Review Project: Drug Class Review on Hormone Therapy for Postmenopausal Women or Women in the Menopausal Transition Stage. Preliminary Scan Report #4. Septmember 2013.

Drug Class Review
on
Hormone Therapy for Postmenopausal Women or Women in the Menopausal Transition Stage

Preliminary Scan Report #4

September 2013

Last Report Update #3 (October 2007)

The Agency for Healthcare Research and Quality has not yet seen or approved this report

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Pacific Northwest Evidence-based Practice Center
Roger Chou, MD, Director
Marian McDonagh, PharmD, Associate Director

Oregon Health & Science University

Scan prepared by Shelley S. Selph, MD

OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA since the last report. Other important studies could exist.

Date of Last Update Report:

Update #3 was completed in October 2007, with searches through March 2007.

Date of Previous Update Scans:

Scan #1: May 2009
Scan #2: June 2010
Scan #3: November 2011

Scope and Key Questions

The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative effectiveness of different hormone therapy preparations when used by postmenopausal women or women in the menopausal transition stage for reducing symptoms of menopause: hot flashes/flushes, sleep disturbances/night sweats, mood changes (depression), urogenital atrophy, sexual function, and quality-of-life measures?

2. What is the comparative effectiveness of different hormone therapy preparations when used by postmenopausal women or women in the menopausal transition stage for preventing low bone density and fractures?

3. What is the comparative safety of different hormone therapy preparations for short-term use (<5 years)?

4. What is the comparative safety of different hormone therapy preparations for long-term use (5 or more years)?

5. Are there subgroups of patients based on demographics, other medications, co-morbidities, length of use, or initiation of use relative to onset of menopause, for which one medication or preparation is more effective or associated with fewer adverse effects?

Inclusion Criteria

Populations

- Study participants include women recruited from any health care setting or a population-based sample experiencing menopause. When possible, data are considered separately for women with natural versus surgical menopause (oophorectomy) and for postmenopausal women versus women in the menopausal transition stage.
- Women in the menopausal transition stage are those transitioning through natural menopause who have had irregular menstrual periods within the last 12 months.
- Postmenopausal women are those with surgical or natural menopause and amenorrhea for more than 12 months.

Interventions

Interventions include oral and transdermal estrogen monotherapy or estrogen plus progestin/progesterone preparations listed below for all symptoms, bone density and fracture outcomes, and vaginal tablet or cream for urogenital atrophy, administered as sequential or continuous regimens. Included products are shown in Table 1.

Table 1. Included estrogen products

Included Estrogen Products			
Drug	**Trade names**	**Available strengths**	**FDA-approved indications**
Oral estrogens			
17b Estradiol	Gynodiol (generic) Estradiol (generic) Estrace	0.5, 1, 1.5, 2 mg 0.5, 1, 2 mg 0.5, 1, 2 mg	1. Treatment of moderate to severe vasomotor symptoms associated with menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar or vaginal atrophy, topical vaginal products should be considered. 3. Treatment of Hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. 4. Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease. 5. Treatment of advanced androgen dependant carcinoma of the prostrate (for palliation only). 6. Prevention of osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate.
Estradiol acetate	Femtrace	0.45, 0.9, 1.8 mg	Treatment of moderate to severe vasomotor symptoms associated with the menopause.
Esterified estrogens	Menest Neo-Estrone	0.3, 0.625, 1.25, 2.5 mg 0.3, 0.625, 1.25 mg	1. Treatment of moderate to severe vasomotor symptoms associated with menopause. 2. Atrophic vaginitis. 3. Kraurosis Vulvae. 4. Female hypogonadism. 5. Female castration. 6. Primary ovarian failure. 7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease. 8. Prostatic carcinoma-palliative therapy of advanced disease.
Estropipate	Estropipate (generic) Ogen Ortho-est	0.75, 1.5, 3 mg 0.75, 1.5, 3 mg 0.75, 1.5 mg	1. Signs and symptoms of naturally occurring or surgically induced estrogen deficiency states associated with menopausal and post-menopausal symptoms, e.g., hot flashes, sleep disturbances and urogenital atrophy. 2. Osteoporosis induced by estrogen deficiency states in conjunction with other pertinent measures.

Included Estrogen Products			
Drug	**Trade names**	**Available strengths**	**FDA-approved indications**
Conjugated equine estrogens (CEE)	Premarin	0.3, 0.45, 0.625, 0.9, 1.25 mg	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. 4. Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease. 5. Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only). 6. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate.
Synthetic conjugated estrogens	Cenestin Enjuvia C.E.S Congest PMS-Conjugated	0.3, 0.45, 0.625, 0.9, 1.25 mg 0.625, 1.25 mg 0.3, 0.625, 0.9, 1.25 0.3, 0.625, 0.9, 1.25, 2.5 mg 0.3, 0.625, 0.9, 1.25 mg	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause: 0.45mg, 0.625mg, 0.9mg, 1.25mg 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 0.3 mg
Estrogen-progestin combinations			
CEE, medroxyprogesterone	Prempro Premplus Premphase	0.3 mg CEE/1.5 mg medroxyprogesterone, 0.45/1.5 mg, 0.625/2.5 mg, 0.625/5 mg 2.5/0.625 mg, 5/0.625 mg 0.625 mg CEE, 5.0 mg progesterone	1. Treatment of moderate to severe symptoms associated with menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate.

Included Estrogen Products			
Drug	**Trade names**	**Available strengths**	**FDA-approved indications**
17b-estradiol, norgestimate	Ortho-Prefest	1 mg estradiol/0.9 mg norgestimate	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribed solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.
17-b estradiol, norethindrone acetate	Activella	1 mg estradiol/0.5 mg norethindrone acetate	1.0 mg/0.5mg and 0.5mg/0.1mg 1. Treatment of moderate to severe vasomotor symptoms associated with menopause. 2. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered. 1.0mg/0.5mg 3. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. When used solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
17b-estradiol, drospirenone	Angeliq	1.0 mg estradiol, 0.5 mg drospirenone	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
Ethinyl estradiol, norethindrone acetate	FemHRT	5 mcg ethinyl estradiol/1 mg norethindrone acetate	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis. Non-estrogen medications should be carefully considered.

Included Estrogen Products			
Drug	**Trade names**	**Available strengths**	**FDA-approved indications**
Transdermal estrogens			
17b-estradiol matrix patch	Alora Climara Esclim Vivelle Vivelle-Dot Menostar Estradot Oesclim 17-b estradiol (generic)	0.025, 0.05, 0.075, 0.1 mg/d 0.025, 0.05, 0.06, 0.075, 0.1 mg/d 0.025, 0.0375, 0.05, 0.075, 0.1 mg/d 0.05, 0.1 mg/d 0.025, 0.0375, 0.05, 0.075, 0.1 mg/d 14 mcg/d 25, 37.5, 50, 75, 100 µg/d 25, 50 µg/day 25, 50, 100 µg/d 0.1, 0.05 mg/d	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. 4. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.
17b-estradiol reservoir patch	Estraderm	0.025, 0.0375, 0.05, 0.075, 0.1 mg/d	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. 4. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risks of osteoporosis and non-estrogen medications should be carefully considered.
17b-estradiol, norethindrone acetate patch	Combi-Patch Estalis Estalis Sequi Estracomb	0.05 mg estradiol/0.14 mg norethindrone, 0.05/0.25 mg 140 µg norethindrone acetate/50 µg estradiol-17β per day, 250/50 µg/day 0.05 mg estrogen twice/week (Vivelle 50 patch) for 2 weeks, then 9 or 16 cm^2 Estalis patch twice/week for 2 weeks 0.05 mg estrogen twice/week for 2 weeks, then 0.05 mg estrogen +	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.

Included Estrogen Products			
Drug	**Trade names**	**Available strengths**	**FDA-approved indications**
		0.25 mg progesterone for 2 weeks	
17b-estradiol, levonorgestrel patch	Climara Pro	0.045 mg estradiol/0.015 mg levonorgestrel	Treatment of moderate to severe vasomotor symptoms associated with menopause
17b-estradiol transdermal gel	EstroGel Elestrin Divigel	1.25 g (0.75 mg estradiol) 0.87 g (0.52 mg estradiol) 0.25, 0.5, 1.0 g (0.25, 0.5, 1.0 mg estradiol)	1. Treatment of moderate to severe vasomotor symptoms associated with menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
Estradiol hemihydrate topical emulsion	Estrasorb	1.74 g (0.5 mg estradiol)	Estrasorb is indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause**.**
Topical products			
17b-estradiol vaginal cream	Estrace vaginal cream	0.1 mg estrogen/g	Treatment of vulvar and vaginal atrophy.
CEE cream	Premarin vaginal cream	0.625 mg estrogen/g	Treatment of atrophic vaginitis and kraurosis vulvae.
Esterified estrogen cream	Neo-Estrone vaginal cream	1 mg estrogen/g	1. Treatment of menopausal and post menopausal symptoms. 2. Should be prescribed with an appropriate dosage of a progestin for women with intact uteri to prevent endometrial hyperplasia/carcinoma.
17-b estradiol intravaginal ring	Femring Estring	0.05 mg estradiol, 0.1 mg/d 2 mg (7.5 µg estradiol/day)	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
Estradiol hemihydrate vaginal tablet	Vagifem	25 µg	Treatment of atrophic vaginitis.

Effectiveness Outcomes

- Hot flashes or flushes defined as any otherwise unexplained sensation of flushing/sweating experienced by the woman being studied. Studies will be included if they measured frequency, severity, presence versus absence, or a combination measure of frequency and severity as either primary or secondary outcomes at baseline, 3 months, and/or the end of the study.
- Symptoms such as sleep disturbances/night sweats, mood changes (depression), sexual function, urogenital atrophy, and quality-of-life measures.
- Prevention of osteoporosis measured by improvement in bone density and fracture outcomes after at least 1 year of use.

Harms Outcomes

- Withdrawals
- Withdrawals due to adverse effects
- Withdrawals due to specific adverse effects

For short-term use

- Atypical bleeding; endometrial hypertrophy
- Nausea and vomiting
- Breast tenderness
- Headaches
- Weight changes
- Dizziness
- Thrombosis (including relationship to estradiol levels)
- Cardiovascular events
- Rash and pruritus
- Cholecystitis
- Effects on the liver

For long-term use

- Cardiovascular events
- Breast cancer
- Thrombosis
- Cholecystitis
- Ovarian cancer
- Endometrial cancer

Study Designs

1. Symptoms: Double-blind, randomized controlled trials of at least 3 months duration of one hormone therapy preparation versus another hormone therapy preparation or versus placebo.
2. Prevention of osteoporosis: Double-blind or open, randomized controlled trials of postmenopausal women who are treated for at least 1 year versus another hormone therapy preparation or versus placebo.
3. Good quality systematic reviews and meta-analyses.

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations from 2010 through August 14, 2013 using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. To identify recent comparative effectiveness reviews, we searched the websites of the US Agency for Healthcare Research and Quality (www.ahrq.gov) and the Canadian Agency for Drugs and Technologies in Health (www.CADTH.ca). We also searched FDA (http://www.fda.gov/medwatch/safety.htm) website for identification of new drugs, indications, and safety alerts.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

No new drugs were identified.

New Indications

No new indications for included drugs were identified.

New Safety Alerts

Premarin: 10/28/2011 (oral); 02/14/2012 (topical); 04/11/2012 (injectable)
Prempro, Premphase: 02/02/2012 (oral)

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA

Estrogen-Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding. (See **WARNINGS, Malignant Neoplasms, Endometrial cancer**.)

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders** and **Probable Dementia**.)

The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders**.)

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL STUDIES** and **WARNINGS, Probable Dementia** and **PRECAUTIONS, Geriatric Use**.)

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders** and **Probable Dementia**.)

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders**.)

The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL STUDIES** and **WARNINGS, Probable Dementia** and **PRECAUTIONS, Geriatric Use**.)

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer. (See **CLINICAL STUDIES** and **WARNINGS, Malignant Neoplasms, Breast cancer**.)

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Comparative Effectiveness Reviews

No new comparative effectiveness reviews were identified through searches of the AHRQ and CADTH websites. An AHRQ comparative effectiveness review of therapies for menopausal symptoms is currently in progress with amendments made to the protocol in May 2013. The Key Questions for this review are available at: http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=1022&pageaction=displayproduct#5120

Randomized Controlled Trials

Medline searches resulted in 57 citations. Of those, there are 11 potentially relevant new trials. Table 1 summarizes the studies (see Appendix A for abstracts of new studies, Appendix B for abstracts of previously identified studies). There were no new head-to-head studies, four active-controlled studies, and seven placebo or no treatment-controlled studies.

Table 1. Potentially relevant trials of hormone therapy

Study Year	Comparison	N Duration	Focus
Alhola 2010	Estrogen + progestin Placebo	32 6 months	Cognitive function
Bachmann 2008a	Vaginal estradiol (E2) vs. placebo	230 12 weeks	Atrophic vaginitis
Bachmann 2008b	Transdermal 17-beta-estradiol/levonorgestrel vs. placebo	425 12 weeks	Moderate-severe vasomotor symptoms
Bachmann 2009a	Conjugated estrogens vaginal cream vs placebo	423 12 weeks	Atrophic vaginitis
Bachmann 2009b	Transdermal 17-beta estradiol (low dose or micro-dose) vs placebo	121 12 weeks	Vulvovaginal symptoms
Baksu 2009	Oral conjugated estrogen vs intranasal estradiol hemihidrate vs no treatment	100 1 year	Climacteric symptoms, anxiety and depression
Buster 2008	Transdermal estradiol spray vs. placebo	454 12 weeks	Moderate-severe vasomotor symptoms
Cameron 2006	Continuous transdermal estradiol/levonorgestrel vs. interrupted estradiol patch x 4 days followed by estradiol/levonorgestrel patch	59 6 months	Incidence of amenorrhea and relief of vasomotor symptoms
Carmignani 2010	Estradiol 1 mg/0.5 mg norethisterone vs	60 16 weeks	Psychological, somatic, and urogenital menopausal

Study Year	Comparison	N Duration	Focus
	Soy isoflavone 90 mg vs Placebo		symptoms
Chlebowski, 2010 WHI	CEE 0.625 mg + medroxyprogesterone acetate 2.5 mg Placebo	16,608 Intervention 5.6 years Followup 7.9 years	Breast cancer incidence and breast cancer mortality
Cieraad 2006	17-beta estradiol/dydrogesterone vs. conjugated equine estrogen/norgestrel	169 6 months	Lipids, vasomotor symptoms, bleeding, tolerability
De Franciscis 2007	17-beta estradiol/dydrogesterone vs. dydrogesterone	120 4 weeks	Vasomotor symptoms, bleeding
Endrikat 2007	Estradiol valerate/dienogest vs. placebo	324 12 weeks	Moderate-severe vasomotor symptoms
Fahlen 2011	Estradiol+Progestogen No treatment control	75 1 year	Quality of life in breast cancer survivors
Fonseca 2007	17-beta estradiol/norethisterone vs. placebo	40 cross over at 6 months	Sexual function and vasomotor symptoms
Freedman 2009	Synthetic conjugated estrogens vaginal cream vs placebo	305 12 weeks	Vulvovaginal atrophy
Gambacciani, 2011	17-estradiol 1 mg + drospirenone 2 mg Calcium	70 3 months	Quality of life
Gast 2009	Oral low-dose conjugated estrogens plus conjugated estrogens vaginal cream vs placebo cream and placebo tablet	285 6 weeks	Sexual function and quality of life
Genazzani, 2011a	DHEA 10 mg Estradiol 1 mg + dihydrogesterone 5 mg Tibolone 2.5 mg	48 12 months	Sexual function
Hachul 2008	Estrogen/progesterone vs. placebo	24 12 weeks	Sleep and cognition
Haines 2009	Micro-dose transdermal estradiol vs placebo	165 12 weeks	Asian women, hot flashes
Hassa 2010	Conjugated equine estrogen 0.625 mg vs Transdermal 17 beta-estradiol patch 3.9 mg every other week vs Placebo	N not reported in abstract 6 months	Vasomotor symptoms
Hayashi 2011	All initially taking Estriol + medroxyprogesterone then randomized to same or to raloxifene 60 mg	32 52 weeks	Bone-mineral density

Study Year	Comparison	N Duration	Focus
Hedrick 2009	Various doses of estradiol gel 0.1% vs. placebo	488 12 weeks	Vasomotor symptoms, vaginal atrophy
Heiss 2008	Conjugated equine estrogen/medroxyprogesterone vs Calcium	16,608 Mean 2.4 years of follow-up	To report health outcomes at 3yrs after intervention was stopped (WHI)
Honjo 2009	Low-dose oral estradiol vs placebo	211 8 weeks	Japanese women, hot flashes
Huang 2007	Transdermal estradiol vs. placebo	382 12 months	Bone turnover and BMD (appears to be post-hoc analysis from ULTRA trial)
Huang 2009	CEE vs placebo	2763 1 year	Secondary analysis from HERS study data, risk of coronary heart disease
Kalleinen 2008	Cyclic estrogen-progestin vs. placebo	25 6 months (before-after)	Sleep
Lee 2007	Estradiol/drospirenone vs. placebo	90 4 months	Vasomotor symptoms
Lin 2011	Drospirenone 2 mg + 17-estradiol Placebo	244 4-28 day cycles	Hot flushes in Chinese women
Limpaphayom 2006	Various doses of conjugated estrogen/medroxyprogesterone	1028 24 weeks	Quality of life in 9 ethnic groups of Asian women
Long 2006	Oral vs. vaginal conjugated equine estrogen	57 3 months	Sexual function
Maki 2007	Conjugated equine estrogen/medroxyprogesterone vs. placebo	180 4 months	Cognition, sexual function, quality of life, sleep
Maki 2009	CEE vs black cohosh vs red clover vs placebo	66 1 year	Cognition
Marinho 2008	17-beta estradiol vs. placebo	74 NR	Cognitive function, depression
Mattsson 2007	Various doses of oral estradiol valerate/medroxyprogesterone (continuous HRT)	459 12 months	Moderate-severe vasomotor symptoms
Merz 2010	Norethindrone 1 mg + ethinyl estradiol 10 mcg Placebo	35 12 weeks	Chest pain
Michael 2010	CEE vs placebo	1458 6 years	Secondary analysis of WHI data, physical function in women ages 65 to 79 years at enrollment
Mizunuma 2010	Oral estradiol 0.5 mg or 1.0 mg, with or without levonorgestrel 40 mcg vs	152 52 weeks	Bone mineral density

Study Year	Comparison	N Duration	Focus
	Placebo		
Moriyama 2008	Estradiol valerate vs. exercise	44 6 months	Health-related quality of life, vasomotor symptoms
Panay 2007	Various doses of low dose 17-beta estradiol/norethisterone vs. placebo	577 6 months	Vasomotor symptoms
Pefanco 2007	Micronized 17-beta estradiol vs. placebo	57 3 years	Cognitive function including depression
Pitkin 2007	Various doses of continuous combined HRT consisting of estradiol valerate/medroxyprogesterone	NR 12 months	Health related quality of life
Prior 2007	Conjugated equine estrogen vs. medroxyprogesterone	41 12 months	Vasomotor symptoms
Resnick 2009	CEE vs placebo	886 3 years	Secondary analysis of WHI data, cognition in women age 65 years and older
Samsioe 2007	Transdermal vs. oral estradiol/norethisterone	677 1 year	Harms (safety), tolerability
Schierbeck 2012	Intact uterus: triphasic estradiol and norethisterone acetate No uterus: 2 mg estradiol vs No treatment controls	1006 Intervention stopped after 11 years but followed for up to 16 years	Long term effect of HRT on cardiovascular outcomes
Simon 2007	Transdermal estradiol gel vs. placebo	484 12 weeks	Vasomotor symptoms, vaginal atrophy
Simon 2006	Topical micellar nanoparticle estradiol emulsion vs. placebo	200 12 weeks	Moderate-severe vasomotor symptoms
Simon 2008	Synthetic conjugated estrogen vs. placebo	42 12 weeks	Vulvovaginal atrophy
Stevenson 2010	17 beta-estradiol 0.5 mg/dydrogesterone 2.5 mg vs 17 beta-estradiol 1 mg/dydrogesterone 5 mg vs Placebo	313 52 weeks	Vasomotor symptoms
Valen-Sendstad 2010	Estradiol 1 mg + norethisterone 0.5 mg Placebo	65 12 month	Depressive symptoms and cognitive function in women with Alzheimer disease
Veerus 2008	Continuous combined HRT vs. no treatment, or hormone therapy vs. placebo	1823 mean follow-up 3.6 yrs	Vasomotor symptoms, quality of life
Welton 2008	Conjugated equine estrogen/medroxyprogesterone vs.	3721 12 months	Health related quality of life, emotional and physical

Study Year	Comparison	N Duration	Focus
	placebo		symptoms using scales
Yang 2007	Various doses of transdermal 17-beta estradiol gel vs. estriol	120 12 months	Bone mass
Zaborowska 2007	Transdermal placebo vs. estrogen, or estrogen, acupuncture, or placebo	102 12 weeks	Vasomotor symptoms
Ziaei 2010	CEE 0.625 mg + medroxyprogesterone + Ca+D Tibolone 2.5 mg + Ca+ D Ca+D	140 6 months	Climacteric symptoms and sexual function

Along with the 47 trials identified in previous update scans, there are now 58 potentially relevant new trials for this drug class with 8 previously identified head-to-head trial, nine total active-controlled trials, 37 placebo-controlled or no treatment-controlled trials, and four studies of various doses of the same included drug.

Appendix A. Abstracts of potentially relevant new trials of estrogens (N=11)

Active-controlled (N=4)

Gambacciani, M., G. Rosano, et al. (2011). "Clinical and metabolic effects of drospirenone-estradiol in menopausal women: a prospective study." Climacteric 14(1): 18-24.

OBJECTIVES: To describe the effects of low-dose hormonal replacement therapy (HRT) on quality of life, metabolic parameters and blood pressure in postmenopausal women.
METHODS: Postmenopausal women untreated with HRT or sex steroids in the previous 12 months were randomized to treatment with 17-estradiol (1mg/day) plus drospirenone (2mg/day) (E2+DRSP) or to calcium (controls). Quality of life was evaluated by the Women's Health Questionnaire (WHQ) at baseline and after 6 and 12 weeks of treatment. Anthropometric, metabolic and blood pressure measurements were performed before and after 3 months of treatment.
RESULTS: WHQ domain scores for vasomotor and somatic symptoms, anxiety/fears, depressed mood, sexual behavior and sleep problems decreased significantly in the E2+DRSP group relative to both baseline and control values ($p<0.05$). Body mass index was unchanged, while waist circumference decreased significantly ($p<0.001$) after E2+DRSP treatment. Significant decreases were also observed after E2+DRSP treatment for blood insulin values, insulin resistance (estimated by homeostasis model assessment) and systolic blood pressure ($p<0.001$, all). In subjects with systolic blood pressure<130mmHg at baseline, no changes in systolic values were registered, while women with baseline high-normal systolic blood pressure (130-139mmHg) showed significant decreases ($p<0.0069$). E2+DRSP did not modify diastolic blood pressure values. In the calcium-treatment group, there were no significant changes in WHQ scores or in anthropometric, metabolic or blood pressure measurements.
CONCLUSION: In postmenopausal women, E2+DRSP administration improves vasomotor symptoms and general aspects of quality of life and may positively influence cardiovascular risk factors.

Genazzani, A. R., M. Stomati, et al. (2011). "Effect of 1-year, low-dose DHEA therapy on climacteric symptoms and female sexuality." Climacteric 14(6): 661-668.

BACKGROUND: Sexual desire is affected by endocrine and psychosocial factors. Menopausal hormonal changes are relevant to the causes of sexual dysfunction during reproductive aging.
AIM: To evaluate the effects of different types of hormonal replacement therapy (HRT) on sexual function, frequency of sexual intercourse, and quality of relationship in early postmenopausal women. We recruited 48 healthy postmenopausal women aged 50-60 years (mean age 54.5 +/- 3.3 years). Women with climacteric symptoms were uniformly randomized into three groups receiving either dehydroepiandrosterone (DHEA 10 mg) daily, or daily oral estradiol (1 mg) plus dihydrogesterone (5 mg), or daily oral tibolone (2.5 mg) for 12 months. Women who refused hormonal therapy were treated with oral vitamin D (400 IU). Efficacy was evaluated using the McCoy Female Sexuality Questionnaire before treatment and after 12 months. We evaluated the hormonal profile before treatment and after 3, 6 and 12 months.

RESULTS: The groups receiving DHEA or HRT reported a significant improvement in sexual function compared to baseline ($p < 0.001$ and $p < 0.01$, respectively) using the McCoy total score. The quality of relationship was similar at baseline and after 3, 6 and 12 months of treatment. There were significant increases in the numbers of episodes of sexual intercourse in the previous 4 weeks in women treated with DHEA, HRT and tibolone in comparison with the baseline value ($p < 0.01$, $p < 0.05$, $p < 0.01$, respectively). No changes in the McCoy score occurred in women receiving vitamin D.
CONCLUSIONS: Daily oral DHEA therapy at the dose of 10 mg, HRT and tibolone all provided a significant improvement in comparison with vitamin D in sexual function and in frequency of sexual intercourse in early postmenopausal women.

Hayashi T, Ina K, Maeda M, Nomura H. (2011). "The effects of selective estrogen receptor modulator treatment following hormone replacement therapy on elderly postmenopausal women with osteoporosis. " Nitric oxide. 24(4):199-203, 2011 May.

OBJECTIVES: A comparison between the atheroprotective and osteoprotective effects of the selective estrogen receptor modulator (SERM) raloxifene and those of hormone replacement therapy (HRT) has not been made in elderly women., METHODS: A randomized prospective controlled trial was performed in a cohort of 32 elderly Japanese women with osteoporosis receiving HRT (estriol plus medroxyprogesterone) for more than 1 year. In 16 randomly selected subjects, HRT was changed to raloxifene therapy (60mg/day, 71.4+/-3.4 years, SERM group). The other 16 patients were continued on HRT (71.8+/-2.9 years, HRT group). As a control group, 14 subjects were enrolled, did not take any medications and were age-matched to experimental patients (72.5+/-3.3 years, control group). Plasma lipids, TNF[alpha], adiponectin, NO metabolites (NOx:NO2(-) and NO3(-)), cyclicGMP and bone-mineral density (BMD) were evaluated at baseline and at 26 and 52 weeks after enrollment., RESULTS: SERM (Raloxifene) increased high-density-lipoprotein cholesterol levels and tended to decrease low-density-lipoprotein cholesterol levels (P=0.058) compared with baseline. Adiponectin, NOx and cGMP levels were significantly increased after 6 months compared with baseline or the HRT group. TNF[alpha] was decreased by raloxifene. In control subjects, no significant changes were observed in any of these markers. Bone-mineral density was higher at baseline in the raloxifene and HRT groups than in the control group, and BMD increased 12 months after baseline in the HRT and control group.
CONCLUSION: SERM improved BMD and endothelial function in elderly postmenopausal women with osteoporosis who had received HRT, and these effects were comparable to or slightly stronger than those of HRT. Changes in adiponectin and TNF[alpha] may underlie the improvements in endothelial function, such as NO signaling.

Ziaei, S., M. Moghasemi, et al. (2010). "Comparative effects of conventional hormone replacement therapy and tibolone on climacteric symptoms and sexual dysfunction in postmenopausal women." Climacteric 13(2): 147-156.

OBJECTIVE: To compare the effects of tibolone with those of conventional hormone replacement therapy on climacteric symptoms and sexual function in postmenopausal women.
MATERIALS AND METHODS: In a randomized, controlled trial, 140 postmenopausal women were allocated into three groups. Of the subjects included, 47 women received 2.5 mg tibolone + one Cal+D tablet (500 mg calcium and 200 IU vitamin D) daily; 46 women received 0.625 mg conjugated equine estrogen + 2.5 mg medroxyprogesterone (CEE/MPA) + one Cal+D tablet daily; and 47 women received only one Cal+D tablet as the control group. The Greene Climacteric Scale (GCS) questionnaire was used to detect the efficacy of

treatment on climacteric symptoms. Rosen's Female Sexual Function Index (FSFI) was used for sexual function evaluation. Sex hormone binding globulin (SHBG), free estradiol index (FEI) and free testosterone index (FTI) were measured before and after treatment. The women were followed up for 6 months
RESULTS: After treatment, all subscores in the GCS improved in the tibolone and CEE/MPA groups ($p < 0.01$), except the sexual subscore in the CEE/MPA group, compared with baseline. There were significant differences in the FSFI in the tibolone and CEE/MPA groups in comparison to the control group after treatment. Tibolone, in comparison to CEE/MPA, significantly lowered SHBG levels and increased the FTI and FEI and improved the desire, arousal and orgasm sexual domains of the FSFI ($p < 0.001$).
CONCLUSION: Tibolone may be an alternative to conventional hormone replacement therapy in the treatment of climacteric symptoms and sexual dysfunction in postmenopausal women.

Placebo- controlled or no treatment-controlled (N=7)

Alhola, P., H. Tuomisto, et al. (2010). "Estrogen + progestin therapy and cognition: a randomized placebo-controlled double-blind study." Journal of Obstetrics & Gynaecology Research 36(4): 796-802.

AIMS: The use of hormone therapy (HT) is a relevant and topical issue in the treatment of menopausal symptoms in women. Information regarding the effects of combination treatment with estrogen and progesterone as well as treatment timing on cognitive function is lacking and was evaluated in healthy pre- and postmenopausal women.
METHODS: Sixteen premenopausal (45-51 years) and 16 postmenopausal (58-70 years) women were randomly assigned to receive either estrogen + progestin therapy (HT) or placebo (PL) for six months. The study was double-blind. Cognitive performance was measured at baseline and follow up with tests of verbal and visuomotor functions, verbal and visual memory, and attention.
RESULTS: In premenopausal women, cognitive attention, when compared to baseline, improved with HT but declined slightly with PL in the two-choice reaction time task ($P = .049$), while PL was associated with better performance in tests of shared attention ($P = 0.024$) and auditory attention ($P < 0.05$). In postmenopausal women, HT was associated with improved performance in verbal episodic memory ($P = 0.024$) and a minor decline in auditory attention ($P = 0.025$).
CONCLUSIONS: HT, with estradiol valerate and norethisterone, in healthy women showed only minor effects on attention around the menopausal transition and on memory in postmenopause.

Chlebowski, R. T., G. L. Anderson, et al. (2010). "Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women." JAMA 304(15): 1684-1692.

CONTEXT: In the Women's Health Initiative randomized, placebo-controlled trial of estrogen plus progestin, after a mean intervention time of 5.6 (SD, 1.3) years (range, 3.7-8.6 years) and a mean follow-up of 7.9 (SD, 1.4) years, breast cancer incidence was increased among women who received combined hormone therapy. Breast cancer mortality among participants in the trial has not been previously reported.
OBJECTIVE: To determine the effects of therapy with estrogen plus progestin on cumulative breast cancer incidence and mortality after a total mean follow-up of 11.0 (SD, 2.7) years, through August 14, 2009.

DESIGN, SETTING, AND PARTICIPANTS: A total of 16,608 postmenopausal women aged 50 to 79 years with no prior hysterectomy from 40 US clinical centers were randomly assigned to receive combined conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, or placebo pill. After the original trial completion date (March 31, 2005), reconsent was required for continued follow-up for breast cancer incidence and was obtained from 12,788 (83%) of the surviving participants.
MAIN OUTCOME MEASURES: Invasive breast cancer incidence and breast cancer mortality.
RESULTS: In intention-to-treat analyses including all randomized participants and censoring those not consenting to additional follow-up on March 31, 2005, estrogen plus progestin was associated with more invasive breast cancers compared with placebo (385 cases [0.42% per year] vs 293 cases [0.34% per year]; hazard ratio [HR], 1.25; 95% confidence interval [CI], 1.07-1.46; P = .004). Breast cancers in the estrogen-plus-progestin group were similar in histology and grade to breast cancers in the placebo group but were more likely to be node-positive (81 [23.7%] vs 43 [16.2%], respectively; HR, 1.78; 95% CI, 1.23-2.58; P = .03). There were more deaths directly attributed to breast cancer (25 deaths [0.03% per year] vs 12 deaths [0.01% per year]; HR, 1.96; 95% CI, 1.00-4.04; P = .049) as well as more deaths from all causes occurring after a breast cancer diagnosis (51 deaths [0.05% per year] vs 31 deaths [0.03% per year]; HR, 1.57; 95% CI, 1.01-2.48; P = .045) among women who received estrogen plus progestin compared with women in the placebo group.
CONCLUSIONS: Estrogen plus progestin was associated with greater breast cancer incidence, and the cancers are more commonly node-positive. Breast cancer mortality also appears to be increased with combined use of estrogen plus progestin.

Fahlen, M., B. Wallberg, et al. (2011). "Health-related quality of life during hormone therapy after breast cancer: a randomized trial." Climacteric 14(1): 164-170.

AIM: To study the effects of menopausal hormone therapy (HT) on health-related quality of life in women after breast cancer.
PATIENTS AND METHODS: In the Stockholm trial, breast cancer survivors were randomized to HT (estradiol and progestogen) or to a control group (no treatment). A subgroup of 75 women was studied (38 with HT, 37 controls). Fifty patients were on concomitant tamoxifen. Patients completed three questionnaires (EORTC QLQ C-30, EORTC QLQ-BR 23 and the Hospital Anxiety and Depression Scale (HADS)) during 1 year of treatment.
RESULTS: A significant group-by-time interaction was found for improvement of insomnia in the HT group ($p<0.001$). Within the HT group, but not in the control group, there was significant improvement for HADS anxiety, HADS depression, emotional, cognitive, and social functions and global quality of life. When HT was added to tamoxifen, the increase in global quality of life was significant ($p<0.01$).
CONCLUSION: The effects of HT on quality of life in breast cancer survivors have not previously been reported. The present data suggest that this controversial treatment may improve quality of life after breast cancer.

Lin, S. Q., L. Z. Sun, et al. (2011). "Estradiol 1 mg and drospirenone 2 mg as hormone replacement therapy in postmenopausal Chinese women." Climacteric 14(4): 472-481.

OBJECTIVES: Drospirenone is a novel progestogen that, combined with 17-estradiol, reduces the frequency and severity of menopausal vasomotor symptoms (VMS) in different populations. This double-blind, multicenter study compared the efficacy, safety and

tolerability of 2 mg drospirenone/1 mg estradiol (DRSP/E2) vs. placebo in Chinese postmenopausal women with moderate to severe VMS.
METHODS: Women, aged 45-65 years, were randomized to DRSP/E2 (n=183) or placebo (n=61) once daily for four 28-day cycles. Changes in the frequency and severity of hot flushes were analyzed as primary variables, together with other climacteric and urogenital symptoms, clinical global improvement, adverse events and physical/gynecological parameters.
RESULTS: Relative changes in numbers of hot flushes/week were -80.4% for DRSP/E2 vs. -51.9% for placebo (treatment difference -28.5%, p<0.0001). There were trends toward a greater reduction in severity of hot flushes with DRSP/E2 treatment. Patients treated with DRSP/E2 were more often free from sweating episodes (p<0.0001) and vaginal dryness (p=0.0008). Other climacteric symptoms, including nervousness and pollakisuria, followed a trend of greater response with DRSP/E2. Similar to other combination HRT regimens, DRSP/E2 increased occurrences of bleeding, but these decreased over time. Adverse events in patients treated with DRSP/E2 were mostly mild to moderate and withdrawal rates were low.
CONCLUSIONS: Daily treatment of postmenopausal Chinese women with DRSP/E2 for 16 weeks significantly reduced the incidence of hot flushes and demonstrated advantages vs. placebo for other climacteric symptoms. These results indicate that DRSP/E2 is effective, safe and well tolerated in postmenopausal Chinese women.

Merz, C. N. B., M. B. Olson, et al. (2010). "A randomized controlled trial of low-dose hormone therapy on myocardial ischemia in postmenopausal women with no obstructive coronary artery disease: results from the National Institutes of Health/National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE)." American Heart Journal 159(6): 987.e981-987.

BACKGROUND: Compared with men, women have more evidence of myocardial ischemia with no obstructive coronary artery disease. Although low endogenous estrogen levels are associated with endothelial dysfunction, the role of low-dose hormone therapy has not been fully evaluated. We postulate that a 12-week duration of low-dose hormone replacement therapy is associated with myocardial ischemia and endothelial dysfunction.
METHODS AND RESULTS: Using a multicenter, randomized, placebo-controlled design, subjects were randomized to receive either 1 mg norethindrone/10 microg ethinyl estradiol or placebo for 12 weeks. Chest pain and menopausal symptoms, cardiac magnetic resonance spectroscopy, brachial artery reactivity, exercise stress testing, and psychosocial questionnaires were evaluated at baseline and exit. Recruitment was closed prematurely because of failure to recruit after publication of the Women's Health Initiative hormone trial. Of the 35 women who completed the study, there was less frequent chest pain in the treatment group compared with the placebo group (P = .02) at exit. Women taking 1 mg norethindrone/10 microg ethinyl estradiol also had significantly fewer hot flashes/night sweats (P = .003), less avoidance of intimacy (P = .05), and borderline differences in sexual desire and vaginal dryness (P = .06). There were no differences in magnetic resonance spectroscopy, brachial artery reactivity, compliance, or reported adverse events between the groups.
CONCLUSIONS: These data suggest that low-dose hormone therapy improved chest pain symptoms, menopausal symptoms, and quality of life, but did not improve ischemia or endothelial dysfunction. Given that it was not possible to enroll the prespecified sample size, these results should not be considered definitive.

Schierbeck, L. L., L. Rejnmark, et al. (2012). "Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial." BMJ 345: e6409.

OBJECTIVE: To investigate the long term effect of hormone replacement therapy on cardiovascular outcomes in recently postmenopausal women.
DESIGN: Open label, randomised controlled trial.
SETTING: Denmark, 1990-93.
PARTICIPANTS: 1006 healthy women aged 45-58 who were recently postmenopausal or had perimenopausal symptoms in combination with recorded postmenopausal serum follicle stimulating hormone values. 502 women were randomly allocated to receive hormone replacement therapy and 504 to receive no treatment (control). Women who had undergone hysterectomy were included if they were aged 45-52 and had recorded values for postmenopausal serum follicle stimulating hormone.
INTERVENTIONS: In the treatment group, women with an intact uterus were treated with triphasic estradiol and norethisterone acetate and women who had undergone hysterectomy received 2 mg estradiol a day. Intervention was stopped after about 11 years owing to adverse reports from other trials, but participants were followed for death, cardiovascular disease, and cancer for up to 16 years. Sensitivity analyses were carried out on women who took more than 80% of the prescribed treatment for five years.
MAIN OUTCOME MEASURE: The primary endpoint was a composite of death, admission to hospital for heart failure, and myocardial infarction.
RESULTS: At inclusion the women on average were aged 50 and had been postmenopausal for seven months. After 10 years of intervention, 16 women in the treatment group experienced the primary composite endpoint compared with 33 in the control group (hazard ratio 0.48, 95% confidence interval 0.26 to 0.87; P=0.015) and 15 died compared with 26 (0.57, 0.30 to 1.08; P=0.084). The reduction in cardiovascular events was not associated with an increase in any cancer (36 in treated group v 39 in control group, 0.92, 0.58 to 1.45; P=0.71) or in breast cancer (10 in treated group v 17 in control group, 0.58, 0.27 to 1.27; P=0.17). The hazard ratio for deep vein thrombosis (2 in treated group v 1 in control group) was 2.01 (0.18 to 22.16) and for stroke (11 in treated group v 14 in control group) was 0.77 (0.35 to 1.70). After 16 years the reduction in the primary composite outcome was still present and not associated with an increase in any cancer.
CONCLUSIONS: After 10 years of randomised treatment, women receiving hormone replacement therapy early after menopause had a significantly reduced risk of mortality, heart failure, or myocardial infarction, without any apparent increase in risk of cancer, venous thromboembolism, or stroke.

Valen-Sendstad, A., K. Engedal, et al. (2010). "Effects of hormone therapy on depressive symptoms and cognitive functions in women with Alzheimer disease: a 12 month randomized, double-blind, placebo-controlled study of low-dose estradiol and norethisterone." American Journal of Geriatric Psychiatry 18(1): 11-20.

OBJECTIVE: To elucidate the effects of low-dose 17beta-estradiol and norethisterone (hormone therapy [HT]) versus placebo in women with Alzheimer Disease (AD) on cognition, depressivesymptoms, and activities of daily living.
DESIGN: A 12-month randomized, double-blind, placebo-controlled study, stratified by apolipoprotein E (ApoE) genotype (with versus without the epsilon4 allele), duration of education (< or =9 versus >9 years), and age (< or =75 versus >75 years) performed during 2000-2004.
SETTING: Ambulatory memory clinic in a general hospital.

PARTICIPANTS: Sixty-five female outpatients aged 65-89 years who met criteria for probable AD according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition and International Classification of Diseases, tenth edition. Ten patients were excluded, resulting in 55 participants who had at least one posttreatment efficacy evaluation.
INTERVENTION: Randomly assigned to receive either 1-mg estradiol and 0.5-mg norethisterone or placebo once daily.
MEASUREMENTS: Cognitive variables were the Dementia Rating Scale, tests from Consortium toEstablish a Registry for AD, Global Deterioration Scale (GDS) and Barthel Index.
RESULTS: When only treatment effects were compared by analysis of variance, there were nonsignificant differences between treatment groups for all efficacy variables. A linear model analysis, including stratifying factors in addition to treatment in the model, revealed a significant main effect on mood. The depressive symptoms were lower in the HT group than in the placebo group. Those treated with HT without the ApoE epsilon4 allele had better mood, Word Learning Memory score, and GDS score. Those in the HT group with a higher level of education obtained a better GDS score. Adverse events did not differ between the groups.
CONCLUSION: HT interacts with ApoE genotype in women with AD. Women without an ApoE epsilon4 allele may get better mood and cognition with HT. HT may reduce depressive mood a nd give less cognitive decline.

Appendix B. Abstracts of potentially relevant trials of estrogens previously identified (N=47)

Head-to-head (N=8)

Cameron, S. T., A. F. Glasier, et al. (2006). "Comparison of a transdermal continuous combined and an interrupted progestogen HRT." Maturitas **53**(1): 19-26.

OBJECTIVES: Pilot study to compare the effects of a continuous combined hormone replacement therapy (HRT) regimen with an interrupted progestogen regimen administered transdermally, upon the endometrium of postmenopausal women, the incidence of amenorrhoea and relief of menopausal symptoms. METHODS: Fifty-nine postmenopausal women aged 50-63 years were randomised to either (i) continuous combined regimen: combined oestrogen/progestogen skin patches (releasing continuous 50 microg estradiol and 20 microg levonorgestrel/day) or (ii) interrupted regimen: oestrogen-only patches (releasing 80 microg estradiol/day) for 4 days followed by combined oestrogen/progestogen patches (releasing continuous 50 microg estradiol and 20 microg levonorgestrel/day) for 3 days, for 6 months. An endometrial biopsy was performed at end of treatment for histological analysis. RESULTS: Thirty-three women (56%) completed the study. Significantly higher rates of amenorrhoea were observed with the interrupted than continuous combined regimen (P<0.0001; 25% versus 7% at 6 months). The interrupted regimen was also associated with fewer days of bleeding overall (total 20 versus 44 days during months 4-6; P=0.001). Both regimens improved vasomotor symptoms. No endometrial hyperplasia or atypical changes were observed in endometrial biopsies. CONCLUSIONS: Although significantly less bleeding was observed with the interrupted regimen, it did not have a sufficiently high incidence of amenorrhoea to render it clinically useful.

Cieraad, D., C. Conradt, et al. (2006). "Clinical study comparing the effects of sequential hormone replacement therapy with oestradiol/dydrogesterone and conjugated equine oestrogen/norgestrel on lipids and symptoms." Archives of Gynecology & Obstetrics **274**(2): 74-80.

A clinical study comparing the effects of sequential hormone replacement therapy with oestradiol/dydrogesterone and conjugated equine oestrogen/norgestrel on lipids and symptoms. OBJECTIVE: The objective of the study was to compare the effects of sequential 17beta-oestradiol/dydrogesterone and conjugated equine oestrogens (CEE)/norgestrel on lipid parameters, climacteric symptoms, bleeding patterns and tolerability. STUDY DESIGN: This double-blind study was conducted in 193 peri- and post-menopausal women randomised to receive six, 28-day cycles of oral sequential oestradiol 1 mg/dydrogesterone 10 mg or CEE 0.625 mg/norgestrel 0.15 mg. The change from baseline in serum lipids and hot flushes was analysed using a two-way analysis of variance. RESULTS: After 24 weeks there was a statistically significant increase in high-density lipoprotein (HDL) cholesterol in the oestradiol/dydrogesterone group and a significant reduction in the CEE/norgestrel group. The difference between the groups was significant (P=0.001). The number of hot flushes was reduced by 86% in both groups; this improvement was supported by the Greene Climacteric Symptom Scale score, the patients' opinion and quality of life assessments. The percentage of women experiencing cyclic bleeding was greater with CEE/norgestrel, as was the mean duration and severity of bleeding. Both treatments were well tolerated. CONCLUSION: Oestradiol/dydrogesterone and CEE/norgestrel were equally effective in treating climacteric symptoms, but oestradiol/dydrogesterone showed some advantages in terms of lipid profile and incidence of bleeding.

De Franciscis, P., L. Cobellis, et al. (2007). "Low-dose hormone therapy in the perimenopause." International Journal of Gynaecology & Obstetrics **98**(2): 138-42.

OBJECTIVE: To evaluate the effects of low-dose hormone therapy (LD-HT) on bleeding pattern and vasomotor symptoms in perimenopausal women. METHODS: In a prospective, open-label study at an University clinic, 120 perimenopausal women suffering from irregular menstrual cycles and hot flushes were randomized to micronized 17beta-estradiol 1 mg plus dydrogesterone 10 mg sequential added (LD-HT; group A: 60 subjects) or dydrogesterone 10 mg from day 15 to 28 (group B: 60 subjects). Number and severity of hot flushes and bleeding pattern were assessed throughout the study. RESULTS: Women in group A experienced a significant reduction in number of hot flushes while no significant variation was observed in group B. The incidence of cyclic bleeding was 86% in group A and 76% in group B, the mean duration was significantly lower in group A than in group B. CONCLUSIONS: LD-HT may control both irregular bleeding and hot flushes in perimenopausal women.

Hassa, H., H. M. Tanir, et al. (2010). "Is placebo as effective as estrogen regimens on vasomotor symptoms in women with surgical menopause?" Clinical & Experimental Obstetrics & Gynecology **37**(2): 135-137.

OBJECTIVE: To evaluate the short-term effects of two hormone therapy (HT) regimens and placebo on the Greene Climacteric Scale (GCS) of women with surgical menopause following six months of treatment. METHODS: This 6-month, prospective, randomized, parallel-group, masked evaluator study compared the efficacy of once daily administration of 0.625 mg conjugated equine estrogen (group I), 3.9 mg transdermal 17beta-estradiol patch applied every week (group II) and placebo (group III). Mean GCS before and after six months of treatment in each group was compared. RESULTS: In groups I and II, vasomotor symptoms ($p < 0.005$, $p < 0.05$), somatic symptoms ($p < 0.05$, $p < 0.05$) and total score ($p < 0.005$, $p < 0.01$) significantly reduced from baseline values respectively, while the other subscores revealed no statistically important differences following six months of HT. In group III, vasomotor ($p < 0.05$), subscore and total score ($p < 0.05$) decreased significantly while other subscore reductions were not significant. CONCLUSIONS: Estrogen regimens and placebo seem to be effective in alleviating vasomotor symptoms. Additional larger prospective randomized studies need to be conducted in an aim to look at not only short-term but also long-term effects on climacteric symptoms, in comparison to both placebo arms and different dose and mode of HT use.

Long, C.-Y., C.-M. Liu, et al. (2006). "A randomized comparative study of the effects of oral and topical estrogen therapy on the vaginal vascularization and sexual function in hysterectomized postmenopausal women.[see comment]." Menopause **13**(5): 737-43.

OBJECTIVE: To compare the effects of oral and vaginal estrogen therapy (ET) on the vaginal blood flow and sexual function in postmenopausal women with previous hysterectomy. DESIGN: Fifty-seven women were randomized to receive either oral (0.625 mg of conjugated equine estrogens per tablet; n = 27) or topical (0.625 mg conjugated equine estrogens per 1 g vaginal cream; n = 30) estrogen administered once daily. All women underwent estradiol measurements, urinalysis, pelvic examination, introital color Doppler ultrasonographies, and personal interviews for sexual symptoms using a validated questionnaire before and 3 months after ET. RESULTS: A higher serum level of estradiol was noted in the oral group compared with the topical group after 3 months of ET. There were significant increases in the number of vaginal vessels and the minimum diastole ($P < 0.01$), and marked decreases of pulsatility index values ($P < 0.01$) in both groups after ET. Regarding the systolic peak, we found a significant decrease only in the topical group ($P <$

0.05). Although the post-ET prevalence of anorgasmia decreased significantly in both groups ($P < 0.05$), changes in other domains, including the rates of low libido and coital frequency, were not statistically significant ($P > 0.05$). In the topical group, ET improved sexual function on the vaginal dryness and dyspareunia domains in a statistically significant manner ($P < 0.05$), but this was not the case in the oral group ($P > 0.05$). However, the efficacy of oral ET for vaginal dryness and dyspareunia reached 80% and 70.6%, respectively. The corresponding figures of the topical ET were 79.2% and 75%. CONCLUSIONS: The results of our study suggest that ET alone in hysterectomized postmenopausal women increases the vaginal blood flow and improves some domains of sexual function, but it may not have an impact on diminished sexual desire or activity. Compared with systemic therapy, topical vaginal preparations are found to correlate with better symptom relief despite the lower serum level of estradiol.

Mizunuma, H., Y. Taketani, et al. (2010). "Dose effects of oral estradiol on bone mineral density in Japanese women with osteoporosis." Climacteric **13**(1): 72-83.

OBJECTIVES: This 2-year study compared 0.5 and 1.0 mg oral estradiol (E(2)), with or without levonorgestrel (LNG), for the treatment of postmenopausal osteoporosis in Japanese women. METHODS: Japanese women with osteoporosis after natural menopause or bilateral oophorectomy were randomized to receive E(2) 0.5 or 1.0 mg/day with LNG 40 microg as required, or placebo, for 52 weeks. Women treated with E(2) in the first year continued therapy at the same doses in the second year. Efficacy, safety and pharmacokinetics were assessed. RESULTS: There were 73 women randomized to E(2) 0.5 mg, 157 to E(2) 1.0 mg and 79 to placebo. Lumbar bone mineral density at 52 weeks increased significantly more with E(2) 1.0 mg ($p < 0.001$) and 0.5 mg ($p < 0.001$) than with placebo (no change). After 2 years, a 10% increase in bone mineral density with E(2) 1.0 mg was significantly greater than with E(2) 0.5 mg (8%; $p = 0.008$). E(2) was associated with an acceptable safety and tolerability profile, with slightly more adverse events with E(2) 1.0 than 0.5 mg. Serum E(2) concentration increased in a dose-dependent manner. CONCLUSION: This study showed that E(2), at both 1.0 mg and 0.5 mg doses, was effective in increasing bone mineral density with an acceptable safety and tolerability profile in Japanese postmenopausal women with osteoporosis but that the bone mineral density response was higher with the 1.0 mg dose.

Prior, J. C., J. D. Nielsen, et al. (2007). "Medroxyprogesterone and conjugated oestrogen are equivalent for hot flushes: a 1-year randomized double-blind trial following premenopausal ovariectomy." Clinical Science **112**(10): 517-25.

Oestrogen therapy is the gold standard treatment for hot flushes/night sweats, but it and oestrogen/progestin are not suitable for all women. MPA (medroxyprogesterone acetate) reduces hot flushes, but its effectiveness compared with oestrogen is unknown. In the present study, oral oestrogen [CEE (conjugated equine oestrogen)] and MPA were compared for their effects on hot flushes in a planned analysis of a secondary outcome for a 1-year randomized double-blind parallel group controlled trial in an urban academic medical centre. Participants were healthy menstruating women prior to hysterectomy/ovariectomy for benign disease. A total of 41 women {age, 45 (5) years [value is mean (S.D.)]} were enrolled; 38 women were included in this analysis of daily identical capsules containing CEE (0.6 mg/day) or MPA (10 mg/day). Demographic variables did not differ at baseline. Daily data provided the number of night and day flushes compared by group. The vasomotor symptom day-to-day intensity change was assessed by therapy assignment. Hot flushes/night sweats were well controlled in both groups, one occurred on average every third day and every fourth night. Mean/day daytime occurrences were 0.363 and 0.187 with CEE and MPA respectively, but were not significantly different (P=0.156). Night sweats also did not differ significantly (P=0.766).

Therapies were statistically equivalent (within one event/24 h) in the control of vasomotor symptoms. Day-to-day hot flush intensity decreased with MPA and tended to remain stable with CEE (P<0.001). In conclusion, this analysis demonstrates that MPA and CEE are equivalent and effective in the control of the number of hot flushes/night sweats immediately following premenopausal ovariectomy.

Samsioe, G., V. Dvorak, et al. (2007). "One-year endometrial safety evaluation of a continuous combined transdermal matrix patch delivering low-dose estradiol-norethisterone acetate in postmenopausal women." Maturitas **57**(2): 171-81.

OBJECTIVE: To evaluate the safety and endometrial protection of low-dose transdermal estradiol (E2)/norethisterone acetate (NETA) patches (Estalis 25/125) in terms of post-treatment incidence of endometrial hyperplasia/cancer after 1 year of treatment in postmenopausal women with intact uteri. METHODS: Patients were randomized to receive either transdermal E2/NETA (delivering daily doses of E2 25 microg and NETA 125 microg; applied every 3-4 days) or oral E2/NETA (E2 1mg and NETA 0.5 mg; given daily) in this open-label study. The primary variable was the incidence of endometrial hyperplasia/cancer based on endometrial biopsies; secondary variables included vaginal bleeding/spotting patterns, patch adhesion, safety and tolerability. RESULTS: Six hundred and seventy-seven patients were randomized (507 in the transdermal group and 169 in the oral group; one did not receive study drug) and >80% completed the study. There were no cases of endometrial hyperplasia or cancer in either group and the upper limit of the one-sided 95% confidence interval in the transdermal group was 0.85%. Over time, both treatments were associated with a decreasing frequency of spotting/bleeding days. The overall incidence of adverse events (AEs) was comparable in both groups, and the majority was mild-to-moderate in intensity. Breast tenderness was the most frequently reported AE (transdermal 19.9% versus oral 28.4%). AEs related to the gastrointestinal system were more frequent with oral E2/NETA, and episodes of spotting and bleeding were more frequent with transdermal E2/NETA. Local skin tolerability of the transdermal matrix system was good. CONCLUSIONS: Transdermal E2/NETA (25 and 125 microg) provided adequate endometrial protection in postmenopausal women when evaluated according to CPMP/CHMP criteria, achieved a high rate of amenorrhea, and was well tolerated.

Active-controlled (N=5)

Carmignani, L. O., A. O. Pedro, et al. (2010). "The effect of dietary soy supplementation compared to estrogen and placebo on menopausal symptoms: a randomized controlled trial." Maturitas **67**(3): 262-269.

OBJECTIVES: To compare the effects of daily ingestion of dietary soy supplementation, l ow-dose hormone therapy (HT) and placebo on psychological, somatic and urogenital symptoms in postmenopausal women. STUDY DESIGN: A double-blind, randomized, controlled trial. Sixty healthy, symptomatic, postmenopausal women of 40-60 years of age were allocated to use dietary soy supplementation (containing 90 mg of isoflavone) or HT (1mg estradiol and 0.5mg norethisterone acetate) or placebo. Main outcome measures: the Menopause Rating Scale (MRS) was used to assess menopausal symptoms at baseline and after 16 weeks of treatment. Intention-to-treat analyses were performed using the chi-square test, Fisher's exact test, the Kruskal-Wallis non-parametric test and analysis of variance (ANOVA). RESULTS: No statistically significant differences were found between the groups with respect to baseline clinical and sociodemographic characteristics. The psychological, somatic and urogenital symptoms analyzed in the MRS improved during

treatment in all the groups, except for urogenital symptoms in the placebo group in which no significant changes were detected. Comparison between groups revealed a statistically significant improvement in somatic symptoms (hot flashes and muscle pain) in the users of HT (-45.6%) and dietary soy supplementation (-49.8%). Urogenital symptoms (vaginal dryness) improved significantly in HT users (-38.6%) and in users of the dietary soy supplementation (-31.2%). There was no statistically significant difference between the groups with respect to overall MRS score or to scores obtained in the psychological symptoms subscale. CONCLUSION: Dietary soy supplementation may constitute an effective alternative therapy for somatic and urogenital symptoms of the menopause.

Heiss, G., R. Wallace, et al. (2008). "Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin.[see comment]." JAMA **299**(9): 1036-45.

CONTEXT: The Women's Health Initiative (WHI) trial of estrogen plus progestin vs placebo was stopped early, after a mean 5.6 years of follow-up, because the overall health risks of hormone therapy exceeded its benefits. OBJECTIVE: To report health outcomes at 3 years (mean 2.4 years of follow-up) after the intervention was stopped. DESIGN, SETTING, AND PARTICIPANTS: The intervention phase was a double-blind, placebo-controlled, randomized trial of conjugated equine estrogens (CEE) 0.625 mg daily plus medroxyprogesterone acetate (MPA) 2.5 mg daily, in 16,608 women aged 50 through 79 years, recruited by 40 centers from 1993 to 1998. The postintervention phase commenced July 8, 2002, and included 15 730 women. MAIN OUTCOME MEASURES: Semi-annual monitoring and outcomes ascertainment continued per trial protocol. The primary end points were coronary heart disease and invasive breast cancer. A global index summarizing the balance of risks and benefits included the 2 primary end points plus stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, and death due to other causes. RESULTS: The risk of cardiovascular events after the intervention was comparable by initial randomized assignments, 1.97% (annualized rate) in the CEE plus MPA (343 events) and 1.91% in the placebo group (323 events). A greater risk of malignancies occurred in the CEE plus MPA than in the placebo group (1.56% [n = 281] vs 1.26% [n = 218]; hazard ratio [HR], 1.24; 95% confidence interval [CI], 1.04-1.48). More breast cancers were diagnosed in women who had been randomly assigned to receive CEE plus MPA vs placebo (0.42% [n = 79] vs 0.33% [n = 60]; HR, 1.27; 95% CI, 0.91-1.78) with a modest trend toward a lower HR during the follow-up after the intervention. All-cause mortality was somewhat higher in the CEE plus MPA than in the placebo group (1.20% [n = 233] vs 1.06% [n = 196]; HR, 1.15; 95% CI, 0.95-1.39). The global index of risks and benefits was unchanged from randomization through March 31, 2005 (HR, 1.12; 95% CI, 1.03-1.21), indicating that the risks of CEE plus MPA exceed the benefits for chronic disease prevention. CONCLUSIONS: The increased cardiovascular risks in the women assigned to CEE plus MPA during the intervention period were not observed after the intervention. A greater risk of fatal and nonfatal malignancies occurred after the intervention in the CEE plus MPA group and the global risk index was 12% higher in women randomly assigned to receive CEE plus MPA compared with placebo.

Maki, P. M., L. H. Rubin, et al. (2009). "Effects of botanicals and combined hormone therapy on cognition in postmenopausal women." Menopause **16**(6): 1167-77.

OBJECTIVE: The aim of this study was to characterize the effects of red clover, black cohosh, and combined hormone therapy on cognitive function in comparison to placebo in women with moderate to severe vasomotor symptoms. METHODS: In a phase II randomized, double-blind, placebo-controlled study, 66 midlife women (of 89 from a parent study; mean age, 53 y) with 35

or more weekly hot flashes were randomized to receive red clover (120 mg), black cohosh (128 mg), 0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate (CEE/MPA), or placebo. Participants completed measures of verbal memory (primary outcome) and other cognitive measures (secondary outcomes) before and during the 12th treatment month. A subset of 19 women completed objective, physiological measures of hot flashes using ambulatory skin conductance monitors. RESULTS: Neither of the botanical treatments had an impact on any cognitive measure. Compared with placebo, CEE/MPA led to a greater decline in verbal learning (one of five verbal memory measures). This effect just missed statistical significance (P = 0.057) in unadjusted analyses but reached significance (P = 0.02) after adjusting for vasomotor symptoms. Neither of the botanical treatment groups showed a change in verbal memory that differed from the placebo group (Ps > 0.28), even after controlling for improvements in hot flashes. In secondary outcomes, CEE/MPA led to a decrease in immediate digit recall and an improvement in letter fluency. Only CEE/MPA significantly reduced objective hot flashes. CONCLUSIONS: Results indicate that a red clover (phytoestrogen) supplement or black cohosh has no effects on cognitive function. CEE/MPA reduces objective hot flashes but worsens some aspects of verbal memory.

Moriyama, C. K., B. Oneda, et al. (2008). "A randomized, placebo-controlled trial of the effects of physical exercises and estrogen therapy on health-related quality of life in postmenopausal women.[see comment]." Menopause **15**(4 Pt 1): 613-8.

OBJECTIVE: The purpose of this study was to evaluate the isolated and associated effects of estrogen therapy (estradiol valerate 1 mg/d orally) and physical exercise (moderate aerobic exercise, 3 h/wk) on health-related quality of life (HRQOL) and menopausal symptoms among women who had undergone hysterectomy. DESIGN: A 6-month, randomized, double-blind, placebo-controlled clinical trial with 44 postmenopausal women who had undergone hysterectomy. The interventions were physical exercise and hormone therapy (n = 9), being sedentary and hormone therapy (n = 14), physical exercise and placebo (n = 11), and being sedentary and placebo (n = 10). HRQOL was assessed by a Brazilian standard version of the Medical Outcome Study Short-Form Health Survey and symptoms by Kupperman Index at baseline and after 6 months. RESULTS: There was a decrease in symptoms in all groups, but only groups who performed physical exercise showed an increase in quality of life. Analysis of variance showed that changes in physical functioning (P = 0.001) and bodily pain (P = 0.012) scores over the 6-month period differed significantly between women who exercised and women who were sedentary, regardless of hormone therapy. Hormone therapy had no effect, and there was also no significant association between physical exercise and hormone therapy in HRQOL. CONCLUSIONS: Physical exercises can reduce menopausal symptoms and enhance HRQOL, independent of whether hormone therapy is taken.

Zaborowska, E., J. Brynhildsen, et al. (2007). "Effects of acupuncture, applied relaxation, estrogens and placebo on hot flushes in postmenopausal women: an analysis of two prospective, parallel, randomized studies.[see comment]." Climacteric **10**(1): 38-45.

OBJECTIVE: To assess if transdermal or oral estrogens, acupuncture and applied relaxation decrease the number of menopausal hot flushes/24 h and improve climacteric symptoms, as assessed by the Kupperman index, more than transdermal placebo treatment. SETTING: An outpatient clinic at a Swedish university hospital. METHODS: A total of 102 postmenopausal women were recruited to two studies performed in parallel. In Study I, the women were randomized between transdermal placebo or estrogen treatment and, in Study II, between oral estrogens, acupuncture or applied relaxation for 12 weeks. Climacteric symptoms were measured with daily logbooks on hot flushes. Women completed the assessment questionnaire for the Kupperman index at baseline and after 12 weeks.

RESULTS: The number of flushes/24 h decreased significantly after 4 and 12 weeks in all groups except the placebo group. Both at 4 and 12 weeks, acupuncture decreased the number of flushes more ($p<0.05$; $p<0.01$, respectively) than placebo. At 12 weeks, applied relaxation decreased the number of flushes more ($p<0.05$) than placebo. The Kupperman index score decreased in all groups except the placebo group. The decrease in score was significantly greater in all treatment groups than in the placebo group ($p<0.01$). CONCLUSION: Acupuncture and applied relaxation both reduced the number of hot flushes significantly better than placebo and should be further evaluated as alternatives to hormone therapy in women with menopausal vasomotor complaints.

Placebo-controlled and no treatment-controlled (N=30)

Bachmann, G., C. Bouchard, et al. (2009a). "Efficacy and safety of low-dose regimens of conjugated estrogens cream administered vaginally." Menopause **16**(4): 719-27.

OBJECTIVE: The aim of this study was to evaluate the efficacy and safety of low-dose conjugated estrogens (CE) cream for treatment of atrophic vaginitis. METHODS: Postmenopausal women (N = 423) with moderate-to-severe vaginal atrophy were randomized to CE cream 0.3 mg or placebo once daily (21 days on/7 days off) or twice weekly for 12 weeks, followed by open-label treatment with CE cream for 40 weeks consistent with their prior regimen. Primary endpoints were changes in vaginal maturation index (VMI; percentage of superficial cells), vaginal pH, and severity of participant-reported most bothersome symptom (vaginal dryness, itching, burning, or dyspareunia) at week 12. Endometrial safety was assessed by transvaginal ultrasound and endometrial biopsy for 52 weeks. RESULTS: At week 12, improvements in VMI with daily and twice-weekly use of low-dose CE cream (27.9% and 25.8%, respectively) were significantly greater compared with placebo (3.0% and 1.0%, respectively; $P < 0.001$). Improvements in vaginal pH with daily and twice-weekly CE cream (-1.6 for both) were also significantly greater relative to placebo (-0.4 and -0.3, respectively; $P < 0.001$). VMI and vaginal pH responses were sustained through 52 weeks. Both CE cream regimens significantly reduced most bothersome symptom scores compared with placebo ($P <$ or $= 0.001$), including those for dyspareunia ($P <$ or $= 0.01$). There was no report of endometrial hyperplasia or carcinoma. Adverse events occurred with similar frequency among the active and placebo groups during the double-blind phase. CONCLUSIONS: Daily and twice-weekly use of low-dose CE cream was equally effective in relieving symptoms of vulvovaginal atrophy. Both regimens showed endometrial safety and sustained efficacy during 1 year of therapy.

Bachmann, G., R. A. Lobo, et al. (2008). "Efficacy of low-dose estradiol vaginal tablets in the treatment of atrophic vaginitis: a randomized controlled trial." Obstetrics & Gynecology **111**(1): 67-76.

OBJECTIVE: To evaluate the efficacy of two vaginal doses of estradiol (E2) compared with placebo in the treatment of atrophic vaginitis. METHODS: In a multi-center, randomized, double-blind, parallel-group study, 230 postmenopausal women received treatment with 25 mcg or 10 mcg E2 or placebo for 12 weeks. Efficacy was measured through composite score of three vaginal symptoms and grading of vaginal health. Additional analyses included maturation of vaginal and urethral mucosa. Safety assessments included endometrial biopsy, adverse events, changes in laboratory tests, and physical examinations. After 12 weeks of treatment, all patients were switched to the open-label extension and received treatment with 25 mcg E2 up to week 52. RESULTS: Vaginal tablets with 25 mcg and 10 mcg E2 showed significant ($P<.001$) improvement in composite score of vaginal health. Other results with 10 mcg E2 were not entirely consistent with those for 25 mcg E2. Over 12 weeks, both active treatments resulted in greater decreases in vaginal pH than placebo. There were no significant

differences between the 25 mcg and 10 mcg E2 groups in terms of improvements in maturation value or composite score of three vaginal symptoms. The efficacy was maintained to week 52 with 25 mcg E2. CONCLUSION: Vaginal tablets with 25 mcg and 10 mcg E2 provided relief of vaginal symptoms, improved urogenital atrophy, decreased vaginal pH, and increased maturation of the vaginal and urethral epithelium. Those improvements were greater with 25 mcg than with 10 mcg E2. Both doses were effective in the treatment of atrophic vaginitis.

Bachmann, G. A., M. Schaefers, et al. (2007). "Lowest effective transdermal 17beta-estradiol dose for relief of hot flushes in postmenopausal women: a randomized controlled trial.[see comment]." Obstetrics & Gynecology **110**(4): 771-9.

OBJECTIVE: To investigate the efficacy of micro-dose transdermal estrogen in relieving menopausal vasomotor symptoms. METHODS: A randomized, double-blind, placebo-controlled, multi-center trial. Healthy postmenopausal women with at least seven moderate or severe hot flushes per day for at least 1 week, or at least 50 per week, applied transdermal patches with a nominal delivery of 0.023 mg/d 17beta-estradiol and 0.0075 mg/d levonorgestrel (low-dose E2/levonorgestrel; n=145), 0.014 mg/d E2 (micro-dose; n=147), or placebo (n=133) for 12 weeks. The coprimary efficacy variables were the mean changes from baseline in frequency and severity of moderate and severe hot flushes at the week 4 and 12 endpoints. RESULTS: At the week 12 endpoint, mean weekly frequencies of moderate and severe hot flushes were significantly reduced compared with placebo with low-dose E2/levonorgestrel (-51.80; P<.001) and micro-dose E2 (-38.46; P<.001). Severity scores were also significantly reduced with both treatments compared with placebo. At week 12 endpoint, 41.3% of women receiving micro-dose E2 were treatment responders (75% or more reduction from baseline in hot flush frequency; P=.003 compared with 24.2% placebo). In this group, the mean reduction in moderate and severe hot flushes from baseline was approximately 50% after 2, 70% after 4, 90% after 8, and 95% after 12 weeks. There were no differences between active treatments and placebo regarding adverse events. CONCLUSION: Micro-dose E2 (0.014 mg/d) was clinically and statistically significantly more effective than placebo in reducing the number of moderate and severe hot flushes, with a 41% responder rate, supporting the concept of the lowest effective dose.

Bachmann, G. A., M. Schaefers, et al. (2009b). "Microdose transdermal estrogen therapy for relief of vulvovaginal symptoms in postmenopausal women." Menopause **16**(5): 877-82.

OBJECTIVE: The aim of this study was to investigate the effectiveness of microdose transdermal 17beta-estradiol (E2) therapy in postmenopausal women with moderate to severe vulvovaginal symptoms. METHODS: This report is based on a subset of 121 women who reported most bothersome moderate or severe vulvovaginal symptoms at baseline, from a previous randomized, double-blind, placebo-controlled, multicenter study of 425 healthy, symptomatic, postmenopausal women. Recruits had experienced at least 7 moderate or severe hot flushes daily for at least 1 week or at least 50 moderate or severe hot flushes per week for at least 1 week. Effects on coprimary efficacy variables have been reported previously. Participants received low-dose transdermal E2 plus levonorgestrel (n = 43; nominal delivery 0.023 mg/d E2/0.0075 mg/d levonorgestrel), microdose E2 (n = 42; nominal delivery 0.014 mg/d), or placebo (n = 36) for 12 weeks. Secondary efficacy variables reported herein include mean change from baseline in vaginal pH and vaginal maturation index, the proportion of women with symptoms of vulvar and vaginal atrophy at baseline and week 12, and the proportion of women with moderate-to-severe symptoms of vulvar and vaginal atrophy. RESULTS: Microdose transdermal E2 treatment was associated with a consistent benefit versus placebo in women with vulvovaginal atrophy. There was a statistically significant difference between both E2 versus placebo for changes in vaginal

pH and vaginal maturation index. CONCLUSIONS: Microdose transdermal E2 offers a useful addition to the therapeutic armamentarium for postmenopausal women in whom vulvovaginal symptoms are particularly troublesome.

Baksu, B., A. Baksu, et al. (2009). "Do different delivery systems of hormone therapy have different effects on psychological symptoms in surgically menopausal women? A randomized controlled trial." Maturitas **62**(2): 140-5.

OBJECTIVE: To compare the influence of different delivery forms of estrogen therapy on menopausal and psychological symptoms in surgically menopausal women. STUDY DESIGN: Surgically menopausal women were assigned to a 1-year-therapy with oral conjugated estrogen 0.625mg/day (n=35), intranasal 300microg/day estradiol hemihidrate (n=33), percutaneous gel 1.5mg/day estradiol hemihidrate (n=32) or no treatment (control group, n=32). Serum E(2) and FSH levels, Kupperman's Scale used to assess climacteric symptoms, Hamilton Depression Scale (HDRS) and Hamilton Anxiety Rating Scale (HARS) scores were assessed before and after 1-year-therapy. RESULTS: After 1 year, the greatest increase in E(2) was in the oral group, followed by the transdermal gel, and then the intranasal group (oral vs transdermal gel: p=0.022: oral vs intranasal: p=0.0001; transdermal gel vs intranasal: p=0.0001). All treatment groups improved significantly in total Kupperman index score and HARS ($p<0.05$) with no difference between the groups. With regard to HDRS, all treatment groups improved significantly ($p<0.05$) with the greatest improvement in the oral group, and no difference between transdermal gel and intranasal groups (oral vs transdermal gel: p=0.015; oral vs intranasal: p=0.001; transdermal gel vs intranasal: p=0.735). Control group scored worse in all tests after study ($p<0.05$). All scores correlated significantly with post-treatment serum E(2) and FSH levels ($p<0.001$). CONCLUSION: Oral, intranasal and percutaneous gel estradiol therapies significantly improve menopausal and psychological symptoms in surgically menopausal women with oral route better than transdermal gel and intranasal modalities against depressive mood.

Buster, J. E., W. D. Koltun, et al. (2008). "Low-dose estradiol spray to treat vasomotor symptoms: a randomized controlled trial." Obstetrics & Gynecology **111**(6): 1343-51.

OBJECTIVE: To investigate the safety and efficacy of a transdermal estradiol (E2) spray in women with postmenopausal vasomotor symptoms. METHOD: A randomized, double-blind, placebo-controlled, multicenter, parallel-group clinical trial was conducted. Postmenopausal women (N=454) with at least eight moderate-to-severe hot flushes per day applied daily, one, two, or three E2 (90 microliter spray contains 1.53 mg E2) or matching placebo sprays. The primary efficacy endpoints were mean change from baseline in frequency and severity of moderate-to-severe hot flushes at weeks 4 and 12. RESULTS: All three E2 groups showed a significant decrease in hot flushes at weeks 4 and 12 compared with their placebo groups ($P<.010$). The mean change in frequency at week 12 was eight fewer flushes per day for women in the E2 groups and between four and six fewer flushes for women in the placebo groups. Women in the three- and two-E2 spray groups demonstrated significant ($P<.050$) reductions in severity score at weeks 4 and 12; women in the one-spray group showed significant reductions at week 5. At week 12, the majority (74-85%) of women on E2 showed at least a 50% hot flush frequency reduction as compared with 46% in the placebo group. The systemic E2 delivery rates at week 12 were approximately 0.021 mg/d, 0.029 mg/d, and 0.040 mg/d for the one-, two-, and three-spray doses, respectively. Common adverse events were similar to those previously reported with other transdermal products. Treatment-related application site reaction rate was similar to placebo (1.3% compared with 1.8%). CONCLUSION: The three dose levels of E2 spray achieved efficacy at 0.021-0.040 mg/d delivery rates. The spray is a well-tolerated, new, convenient method of delivering low-dose E2 transdermally.

Endrikat, J., T. Graeser, et al. (2007). "A multicenter, prospective, randomized, double-blind, placebo-controlled study to investigate the efficacy of a continuous-combined hormone therapy preparation containing 1mg estradiol valerate/2mg dienogest on hot flushes in postmenopausal women." Maturitas **58**(2): 201-7.

OBJECTIVES: To evaluate the effects of an estrogen-reduced, continuous-combined hormone therapy preparation (HT) containing 1mg estradiol valerate (1EV) and 2mg dienogest (2DNG) on the number of moderate and severe hot flushes. METHODS: This study compared the effects of an oral continuous-combined HT containing 1mg EV and 2mg DNG (1EV/2DNG) with those of placebo. The planned treatment duration was 12 weeks. Data were obtained from 324 postmenopausal women. The primary efficacy variable was the individual relative change of the mean number of moderate and severe hot flushes per week. Weeks 5-12 of treatment were compared with the 2 weeks preceding the treatment phase. RESULTS: Moderate and severe hot flushes were reduced by 80.8+/-30.9% in the 1EV/2DNG group and by 41.5+/-39.4% in the placebo group. This difference was statistically significant ($p<0.0001$; Wilcoxon's rank sum test). The incidence of all types of hot flushes (mild+moderate+severe) was reduced by 75.2+/-30.2% under 1EV/2DNG and by 35.3+/-37.0% under placebo. In the subset of non-hysterectomized women, exposure to 1EV/2DNG led to 2.4+/-6.2 days with bleeding in the reference period of 84 days of treatment, versus 0.3+/-1.3 days in the placebo group. The safety profile of 1EV/2DNG was very similar to that of placebo. CONCLUSIONS: Continuous-combined HT preparation with 1mg EV and 2mg DNG induced a significant reduction of moderate and severe hot flushes compared to placebo ($p<0.0001$). Thus, this low-estrogen preparation is an effective and safe option for HT.

Fonseca, A. M., V. R. Bagnoli, et al. (2007). "Monophasic estrogen-progestogen therapy and sexuality in postmenopausal women." Clinical Drug Investigation **27**(2): 131-7.

OBJECTIVE: This study aimed to evaluate the effects of monophasic estrogen-progestogen therapy on the sexuality and climacteric symptoms of postmenopausal women. PATIENTS AND METHODS: A prospective, randomised, double-blind, crossover, placebo-controlled, single-centre study was carried out over a total of 12 consecutive months in 40 postmenopausal women with an intact uterus who had no contraindications to hormone therapy. Patients received 17beta-estradiol 2mg in combination with norethisterone acetate 1mg (Cliane) daily for 6 months or one placebo tablet daily for 6 months. The tablets were identical in appearance. After 6 months, the groups were crossed over and the patients were followed up for another 6 months. The groups were homogenous with respect to age, height, bodyweight, body mass index and race. For the statistical analysis, the group receiving hormone therapy was referred to as group A and the placebo group was designated group B, irrespective of the placebo/hormone therapy sequence. RESULTS: In group A there were fewer hot flashes ($F=22.85$, $p<0.01$) and an improvement in sexual interest ($F=5.55$, $p<0.05$). The sequence in which the medication was received resulted in a statistically significant difference with respect to dyspareunia ($F=9.65$, $p<0.01$) and satisfaction with the duration of penetration ($F=6.58$, $p<0.05$). In the intrapatient analysis of variation with respect to orgasmic capability and the presence of dialogue with partner regarding the couple's sexual life, whether the placebo was taken prior to or following hormone therapy was significant ($F=17.12$, $p<0.001$ and $F=7.10$, $p<0.05$, respectively). CONCLUSIONS: Monophasic estrogen-progestogen therapy has a beneficial effect on sexuality and on hot flashes in postmenopausal women.

Freedman, M., A. M. Kaunitz, et al. (2009). "Twice-weekly synthetic conjugated estrogens vaginal cream for the treatment of vaginal atrophy." Menopause **16**(4): 735-41.

OBJECTIVE: The aim of this study was to evaluate low-dose synthetic conjugated estrogens A (SCE-A) cream administered twice weekly for the treatment of moderate to severe vulvovaginal atrophy (VVA) in a symptomatic postmenopausal population. METHODS: In a multicenter, double-blind, randomized, placebo-controlled study, 305 women with symptoms of VVA were treated with either 1 g SCE-A cream (n = 150) or matching placebo (n = 155) for a period of up to 12 weeks. Participants had to have a vaginal pH of greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and at least one of five symptoms of VVA (dryness, soreness, irritation, pain with intercourse, and bleeding after intercourse) that was moderate or severe in intensity. Women had to select one moderate or severe symptom as the most bothersome. RESULTS: Efficacy was assessed at 2, 3, 4, 8, and 12 weeks and included the change from baseline in the severity of the most bothersome symptom (MBS), maturation index, and pH. Most women identified vaginal dryness as the MBS (48%) followed by pain with intercourse (31.3%). A statistically significant increase in the maturation index and significant decreases in pH and severity of the MBS were observed for those treated with SCE-A vaginal cream compared with placebo. CONCLUSIONS: A low dose (1 g = 0.625 mg) of SCE-A vaginal cream administered twice weekly was shown to be effective compared with placebo in treating VVA in postmenopausal women for the three coprimary efficacy measures of maturation index, pH, and severity of the MBS.

Gast, M. J., M. A. Freedman, et al. (2009). "A randomized study of low-dose conjugated estrogens on sexual function and quality of life in postmenopausal women." Menopause **16**(2): 247-56.

OBJECTIVE: To evaluate the effects of combined vaginal and oral low-dose estrogen plus progestogen therapy (EPT) on the frequency and severity of dyspareunia, sexual function, and quality of life in recently postmenopausal women. METHODS: This outpatient, double-blind, randomized, placebo-controlled trial enrolled 285 healthy, sexually active postmenopausal women aged 45 to 65 years. Women received either one daily oral low-dose conjugated estrogens (0.45 mg)/medroxyprogesterone (1.5 mg) tablet for six 28-day cycles along with 1 g conjugated estrogens vaginal cream (0.625 mg), intravaginally for the first 6 weeks of the trial or a placebo cream and placebo tablet. Efficacy was evaluated using the McCoy Female Sexuality Questionnaire, self-reported daily diary cards, the Brief Index of Sexual Functioning-Women (BISF-W), and the Women's Health Questionnaire. RESULTS: The EPT group had a significant decrease in the frequency of dyspareunia compared with baseline and placebo in an analysis of responses to the McCoy Female Sexuality Questionnaire. Also, EPT was associated with a significant improvement in a woman's level of sexual interest, frequency of orgasm, and pleasure of orgasm. There was no effect of EPT use on coital frequency. The EPT group had significant improvement in receptivity/initiation and relationship satisfaction, although not in other BISF-W domains, versus placebo (BISF-W analysis) and significant improvement versus placebo on most Women's Health Questionnaire responses. CONCLUSIONS: EPT provided a statistically significant improvement compared with placebo in dyspareunia, sexual experience, and quality of life as measured in this study. In general, EPT also improved self-reported sexual perception and enjoyment significantly compared with placebo.

Hachul, H., L. R. A. Bittencourt, et al. (2008). "Effects of hormone therapy with estrogen and/or progesterone on sleep pattern in postmenopausal women." International Journal of Gynaecology & Obstetrics **103**(3): 207-12.

OBJECTIVE: To investigate the effects of estrogen and progesterone on sleep in postmenopausal women. METHOD: The 33 participants were randomly assigned to an estrogen or placebo group after undergoing clinical and hormonal assessments and a polysomnogram, and they underwent the same tests again after 12 weeks. Then, while still

taking estrogen or placebo, they all received progesterone for another 12 weeks and underwent a final polysomnogram. RESULTS: Estrogen plus progesterone was more effective than estrogen alone in decreasing the prevalence of periodic limb movement (PLM) (8.1% vs 2.8%), hot flashes (14.2% vs 0%), and bruxism (11.1% vs 0%) at night, or somnolence and attention difficulty during the day. The prevalences of breathing irregularities, arousal from sleep, anxiety, and memory impairment were decreased in both groups following progesterone treatment. CONCLUSION: While not significantly affecting sleep quality, hormone therapy decreased the prevalence of arousal in both groups and that of PLM in the group treated with estrogen plus progesterone.

Haines, C., S. L. Yu, et al. (2009). "Micro-dose transdermal estradiol for relief of hot flushes in postmenopausal Asian women: a randomized controlled trial." Climacteric **12**(5): 419-26.

OBJECTIVES: To compare the effect of micro-dose transdermal estradiol and placebo on the incidence and severity of menopausal symptoms and well-being in postmenopausal Asian women with vasomotor symptoms. DESIGN: Multicenter, double-blind, randomized, placebo-controlled study. RESULTS: Of 165 subjects randomized to estradiol 0.014 mg/day or placebo for 12 weeks, 80 per group were included in the analysis. Groups were comparable at baseline, although time since menopause was slightly shorter in the estradiol group. There was a greater reduction in mean weekly hot flushes at week 12 in the estradiol group (55%) than the placebo group (40%; $p < 0.01$), which was evident by week 4. A similar pattern was seen for moderate and severe hot flushes (-58% vs. -39%, respectively). Reductions were statistically significant at weeks 4, 8, and 12. Vaginal pH fell significantly in the estradiol group by week 4 and then remained stable throughout the treatment period, but there were no significant changes in the placebo group. Vaginal maturation value increased more in the estradiol than the placebo group ($p < 0.001$). Few subjects had vaginal bleeding or spotting. Quality of life improved similarly in both groups. Urogenital symptoms improved considerably from baseline in both treatment groups, with no significant differences. Eight subjects experienced treatment-related adverse events (seven in the estradiol group). CONCLUSIONS: In Asian women, micro-dose estradiol was significantly superior to placebo in improving vasomotor symptoms. The bleeding profile was comparable with that of placebo. Micro-dose estradiol was safe and well tolerated in Asian women.

Hedrick, R. E., R. T. Ackerman, et al. (2009). "Transdermal estradiol gel 0.1% for the treatment of vasomotor symptoms in postmenopausal women." Menopause **16**(1): 132-40.

OBJECTIVE: The objective of this study was to evaluate the efficacy and safety of three doses of estradiol gel 0.1% (Divigel, a novel formulation consisting of 1 mg estradiol per 1 g transdermal gel) to reduce the frequency and severity of vasomotor symptoms and signs of vulvar and vaginal atrophy associated with menopause. DESIGN: A total of 488 postmenopausal women were evaluated in a 12-week study comparing placebo with estradiol gel 0.1% at doses of 1.0, 0.5, and 0.25 mg/day, with estimated daily deliveries of 0.027, 0.009, and 0.003 mg of estradiol, respectively. Primary endpoints were the change from baseline in daily frequency and severity of moderate to severe vasomotor symptoms. Change from baseline in the signs of vulvar and vaginal atrophy (vaginal pH and percentage of superficial cells) was also assessed. RESULTS: Treatment with estradiol gel 0.1% showed statistically significant reductions in frequency and severity of vasomotor symptoms from baseline compared with placebo as early as Week 2 that were maintained throughout treatment. Signs of vulvar and vaginal atrophy were also significantly improved from baseline with all three doses of estradiol gel 0.1% compared with placebo. CONCLUSIONS: Low-dose transdermal estradiol gel 0.1% is an effective treatment for relief of vasomotor symptoms, as well as signs of vulvar and vaginal atrophy, associated with menopause. Estradiol gel 0.1% offers multiple dosing options to individualize patient therapy, including

the lowest available effective dose (0.25 mg estradiol, delivering 0.003 mg/d estradiol) to treat the vasomotor symptoms of menopause.

Honjo, H. and Y. Taketani (2009). "Low-dose estradiol for climacteric symptoms in Japanese women: a randomized, controlled trial." Climacteric **12**(4): 319-28.

OBJECTIVES: To investigate two different doses of oral estradiol to reduce the number of hot flushes in Japanese women with climacteric symptoms. METHODS: Women (n = 211) aged 40-64 years who had experienced natural menopause or bilateral oophorectomy, with > or = three moderate/severe hot flushes per day in the week before study, were randomized to receive micronized estradiol (E2) 0.5 or 1.0 mg or placebo once daily for 8 weeks. The primary efficacy endpoint was percentage change in mean daily number of hot flushes over 7 days from baseline to final examination. RESULTS: Percentage change in mean daily number of hot flushes at final examination was similar for E2 0.5 mg and E2 1.0 mg (-79.58 +/- 28.29% vs. -82.49 +/- 25.31%, p = 0.555) but was significantly lower with placebo (-57.89 +/- 34.15%, p < 0.001 vs. E2, both doses). There was no significant difference in number of treatment-related adverse events occurring in the E2 0.5 and 1.0 mg groups (25% and 36.6%, respectively). The higher E2 dose showed more pronounced effects on symptom severity. CONCLUSIONS: The dose of 0.5 mg/day was effective as the oral E2 starting dose for treatment of hot flushes in Japanese women.

Huang, A. J., B. Ettinger, et al. (2007). "Endogenous estrogen levels and the effects of ultra-low-dose transdermal estradiol therapy on bone turnover and BMD in postmenopausal women." Journal of Bone & Mineral Research **22**(11): 1791-7.

In a randomized controlled trial of a 0.014 mg/d transdermal estradiol patch, serum bone turnover markers decreased to a greater degree in postmenopausal women with lower versus higher endogenous estradiol levels. This suggests that the protective effects of ultra-low-dose estrogen therapy on the postmenopausal skeletal health may depend critically on women's endogenous estrogen levels before treatment. INTRODUCTION: Postmenopausal women with very low or undetectable estradiol levels have lower BMD, increased bone turnover, and increased risk of hip and vertebral fracture. We assessed whether the effects of ultra-low-dose 0.014 mg/d transdermal estradiol (Menostar; Berlex, Montvale, NJ, USA) on bone turnover and BMD are influenced by endogenous estradiol levels. MATERIALS AND METHODS: We analyzed data from postmenopausal women (mean age, 66 yr) randomized to an 0.014-mg/d transdermal estradiol patch or placebo in the ultra-low-dose transdermal estrogen (ULTRA) trial. The free estradiol index (FEI), calculated as the ratio of total estradiol (by mass spectometry) to sex hormone-binding globulin (SHBG; by immunoradiometric assay) x 100, was used to estimate bioavailable estradiol at baseline. Among the 382 women who adhered to >or=80% of study medication, we examined change in serum osteocalcin and bone-specific alkaline phosphatase levels at 12 mo and total hip and lumbar spine BMD at 24 mo in each quintile of FEI. RESULTS: Compared with women in the highest quintile of FEI, those in the lowest quintile of FEI had a 26% greater reduction in bone-specific alkaline phosphatase and 15% greater reduction in osteocalcin in response to ultra-low estradiol treatment (p for trend across quintiles < 0.05). There was a trend toward greater improvement in total hip BMD (p = 0.06) but not spine BMD (p = 0.90) in those with lower versus higher FEI levels. CONCLUSIONS: The beneficial effects of ultra-low-dose 0.014-mg/d transdermal estrogen therapy on skeletal health may depend critically on women's endogenous estrogen levels before treatment.

Huang, A. J., G. F. Sawaya, et al. (2009). "Hot flushes, coronary heart disease, and hormone therapy in postmenopausal women." Menopause **16**(4): 639-43.

OBJECTIVE: The aim of this study was to examine interactions between hot flushes, estrogen plus progestogen therapy (EPT), and coronary heart disease (CHD) events in postmenopausal women with CHD. METHODS: We analyzed data from the Heart and Estrogen/Progestin Replacement Study, a randomized, placebo-controlled trial of 0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate in 2,763 postmenopausal women with CHD. Hot flushes were assessed at baseline using self-administered questionnaires; women reporting bothersome hot flushes "some" to "all" of the time were considered to have clinically significant flushing. Cox regression models were used to examine the effect of EPT on risk of CHD events among women with and without significant flushing at baseline. RESULTS: The mean age of participants was 66.7 +/- 6.8 years, and 89% (n = 2,448) were white. Sixteen percent (n = 434) of participants reported clinically significant hot flushes at baseline. Among women with baseline flushing, EPT increased risk of CHD events nine-fold in the first year compared with placebo (hazard ratio = 9.01; 95% CI, 1.15-70.35); among women without baseline flushing, treatment did not significantly affect CHD event risk in the first year (hazard ratio = 1.32; 95% CI, 0.86-2.03; P = 0.07 for interaction of hot flushes with treatment). The trend toward differential effects of EPT on risk for CHD among women with and without baseline flushing did not persist after the first year of treatment. CONCLUSIONS: Among older postmenopausal women with CHD, EPT may increase risk of CHD events substantially in the first year of treatment among women with clinically significant hot flushes but not among those without hot flushes.

Kalleinen, N., O. Polo, et al. (2008). "The effect of estrogen plus progestin treatment on sleep: a randomized, placebo-controlled, double-blind trial in premenopausal and late postmenopausal women." Climacteric **11**(3): 233-43.

OBJECTIVE: In this prospective randomized, placebo-controlled and double-blind study, the objective was to investigate the effects of estrogen-progestin treatment (EPT) on sleep in pre- and postmenopausal women. DESIGN: Seventeen premenopausal (aged 45-51 years) and 18 postmenopausal (aged 58-70 years) women were studied in a sleep laboratory for two nights (one night for adaptation and one study night) before and after 6 months of treatment with EPT or placebo. During the treatment period, premenopausal women received cyclic EPT or placebo and the postmenopausal women continuous EPT or placebo. Polysomnography and questionnaires were used to evaluate sleep and well-being. RESULTS: At the end of the treatment period, premenopausal women receiving EPT had more awakenings from stage 1 sleep (p = 0.047) and postmenopausal women with EPT had a greater total number of awakenings (p = 0.031) than the corresponding placebo group. Further, sleepiness decreased less in the premenopausal EPT group than in the placebo group (p = 0.031). In postmenopausal women, EPT decreased and placebo slightly increased slow wave activity during the second non-rapid eye movement sleep episode (p = 0.046). CONCLUSIONS: In premenopausal and late postmenopausal women, EPT had only random and marginal effects on sleep. Although the limited findings were mostly unfavorable for EPT, one cannot conclude that EPT deteriorates sleep. Further, neither middle-aged cycling premenopausal women nor older postmenopausal women benefit from estrogen-progestin treatment in terms of their sleep quality.

Lee, B. S., B. M. Kang, et al. (2007). "Efficacy and tolerability of estradiol 1 mg and drospirenone 2 mg in postmenopausal Korean women: a double-blind, randomized, placebo-controlled, multicenter study." Maturitas **57**(4): 361-9.

OBJECTIVES:The aim of this study was to demonstrate that the therapeutic efficacy of an estradiol 1mg/drospirenone 2mg (E2/DRSP) preparation is superior to a placebo in

postmenopausal Korean women with hot flushes and other climacteric symptoms, and to demonstrate that this treatment is both safe and tolerable. METHODS: This was a double-blind, randomized, placebo-controlled, multicenter study over four 28-day treatment cycles. A total of 158 subjects were screened and 90 women were randomized into two treatment groups (E2/DRSP group, n=45; placebo group, n=45). The primary efficacy parameter was the individual relative change of hot flushes. The secondary efficacy parameters such as other climacteric, urogenital symptoms and vaginal bleeding patterns were also evaluated, and the occurrence of any adverse events was noted. In addition, physical, gynecological examinations and laboratory analyses were performed at the beginning and end of the study. RESULTS: The mean number of hot flushes per week during treatment weeks 3-16 decreased by 48.1% during treatment with placebo, and by 84.4% during treatment with E2/DRSP ($p<0.001$). The E2/DRSP combination also reduced the incidence and intensity of menopausal symptoms in postmenopausal women. Most of adverse events was mild or moderate degree of intensity. None of the parameters measured in the study, including laboratory analyses, physical and gynecological examinations, vital signs, and weight, led to any concerns of safety. CONCLUSIONS: The E2 1mg/DRSP 2mg combination tested in the study was efficacious and safe in the treatment of hot flushes and other climacteric symptoms in postmenopausal Korean women.

Maki, P. M., M. J. Gast, et al. (2007). "Hormone therapy in menopausal women with cognitive complaints: a randomized, double-blind trial." Neurology **69**(13): 1322-30.

OBJECTIVE: To evaluate the effects of hormone therapy (HT) on cognition and subjective quality of life (QoL) in recently postmenopausal women with cognitive complaints. METHODS: Cognitive Complaints in Early Menopause Trial (COGENT) was a randomized, double-blind, placebo-controlled, multicenter, pilot study of 180 healthy postmenopausal women aged 45 to 55 years, randomly assigned to receive either placebo or conjugated equine estrogen 0.625 mg/medroxyprogesterone acetate 2.5 mg for 4 months. Outcome measures included memory, subjective cognition, QoL, sexuality, and sleep, which were assessed at baseline and month 4. RESULTS: The study was terminated before the expected final sample size of 275 due to a decrease in enrollment coinciding with the publication of findings from the Women's Health Initiative. There were no differences between groups on any cognitive or QoL measures, except for an increase in sexual interest and thoughts with HT. Modest negative effects on short- and long-term verbal memory approached significance ($p < 0.10$). Women with baseline vasomotor symptoms (VMS) showed a decrease in VMS and an improvement in general QoL, but no cognitive benefit vs placebo. CONCLUSIONS: With the power to detect an effect size of >or=0.45, this study suggests potential modest negative effects on verbal memory that are consistent with previous hormone therapy trials in older women.

Marinho, R. M., J. M. Soares, Jr., et al. (2008). "Effects of estradiol on the cognitive function of postmenopausal women." Maturitas **60**(3-4): 230-4.

OBJECTIVE: To analyze the effect of estrogen on the cognitive function of postmenopausal women through psychometric tests. METHODS: Seventy-four postmenopausal women were divided into two groups: (G1) estrogen group (n = 34), treated with 2 mg 17 beta-estradiol; (G2) placebo group (n = 31), treated with inactive substance. All the participants were submitted, before and after treatment, to psychometric tests, Greene's Scale of Climacteric Symptoms and the Hamilton Scale for depression. Statistical analysis was performed using the Mann-Whitney test and Student's t-test. In order to evaluate the degree of improvement of symptoms or depression after estrogen treatment, Spearman's correlation coefficient was

calculated. RESULTS: A few psychometric tests (immediate and late recall of story, Trailmaking A and B, FAS, Stroop, Bells tests) showed post-intervention improvement, but these were not significant when compared to the placebo group's data. The estrogen group's climacteric symptoms were mitigated in comparison to placebo's, but there was no significant difference between the two groups on the Hamilton Scale. Reduction in climacteric symptoms was associated with improvement in executive function performance as evaluated by the Stroop test. CONCLUSION: Our results suggest estrogen improves the cognitive function, possibly due to a decrease in vasomotor symptoms.

Michael, Y. L., R. Gold, et al. (2010). "Hormone therapy and physical function change among older women in the Women's Health Initiative: a randomized controlled trial." Menopause **17**(2): 295-302.

OBJECTIVE: Although estrogen may be linked to biological pathways that maintain higher physical function, the evidence is derived mostly from observational epidemiology and therefore has numerous limitations. We examined whether hormone therapy affected physical function in women 65 to 79 years of age at enrollment. METHODS: This study involves an analysis of the Women's Health Initiative randomized controlled trials of hormone therapy in which 922 nondisabled women who had previous hysterectomies were randomized to receive estrogen therapy or a placebo and 1,458 nondisabled women with intact uteri were randomized to receive estrogen + progestin therapy or a placebo. Changes in physical function were analyzed for treatment effect, and subgroup differences were evaluated. All women completed performance-based measures of physical function (grip strength, chair stands, and timed walk) at baseline. These measures were repeated after 1, 3, and 6 years. RESULTS: Overall, participants' grip strength declined by 12.0%, chair stands declined by 3.5%, and walk pace slowed by 11.4% in the 6 years of follow-up (all P values <0.0001). Hormone therapy, as compared with placebo, was not associated with an increased or decreased risk of decline in physical function in either the intention-to-treat analyses or in analyses restricted to participants who were compliant in taking study pills. CONCLUSIONS: Hormone therapy provided no overall protection against functional decline in nondisabled postmenopausal women 65 years or older in 6 years of follow-up. This study did not address the influence of hormone therapy for women of younger ages.

Panay, N., O. Ylikorkala, et al. (2007). "Ultra-low-dose estradiol and norethisterone acetate: effective menopausal symptom relief." Climacteric **10**(2): 120-31.

OBJECTIVE: To evaluate the efficacy of two ultra-low-dose 17beta-estradiol plus norethisterone acetate (NETA) treatment regimens for relieving menopausal symptoms. DESIGN: A total of 577 postmenopausal women were enrolled, in three treatment groups in a double-blind, randomized, placebo-controlled study of 0.5 mg 17beta-estradiol + 0.1 mg NETA or 0.5 mg 17beta-estradiol + 0.25 mg NETA or placebo. Participants returned at weeks 4, 8, 12 and 24 for climacteric complaint evaluation based on a daily diary vasomotor symptom record. Patients were assessed by the Greene Climacteric Scale and urogenital symptoms were also evaluated. RESULTS: Treatment with ultra-low-dose 0.5 mg 17beta-estradiol + 0.1 mg NETA (0.1 Group) or 0.5 mg 17beta-estradiol + 0.25 mg NETA (0.25 Group) effectively reduced the severity and number of hot flushes within the initial weeks of therapy. Compared to placebo, a rapid, statistically significant decrease in the frequency and severity of hot flushes was achieved by week 3, followed by further improvement which continued throughout the study. There were no statistically significant differences between the active treatment arms. CONCLUSIONS: The data show that both ultra-low-dose regimens are effective in reducing the severity and number of hot flushes compared to placebo, with good safety profiles.

Pefanco, M. A., A. M. Kenny, et al. (2007). "The effect of 3-year treatment with 0.25 mg/day of micronized 17beta-estradiol on cognitive function in older postmenopausal women." Journal of the American Geriatrics Society **55**(3): 426-31.

OBJECTIVES: To evaluate the effect of ultra-low-dose (0.25 mg/d) micronized 17beta-estradiol on cognitive function in older postmenopausal women. DESIGN: Randomized, placebo-controlled trial conducted for 3 years. SETTING: Academic health center in greater Hartford, Connecticut. PARTICIPANTS: Fifty-seven healthy, community-dwelling, older postmenopausal women. INTERVENTION: Women received 0.25 mg/d of micronized 17beta- estradiol (estrogen therapy (ET), n=32) or placebo (n=25); all women who had not had a hysterectomy received 100 mg/d of oral micronized progesterone for 2-week periods every 6 months. MEASUREMENTS: Neuropsychological measures of memory, language, mood, and executive function were collected at baseline, 3 months, and 36 months. Measures of executive function included the Controlled Oral Word Association Test, the Trail Making Test, and the Wisconsin Card Sorting Test. The Boston Naming Test was used to measure language skills. The Symbol Digit Modalities Test was used as a measure of sustained attention. Measures of memory included the Complex Figure Test, Fuld Object Memory Test, and a selected subtest from the Wechsler Memory Scale. Scores from the Geriatric Depression Scale and the Beck Anxiety Inventory were used to assess symptoms of depression. RESULTS: No differences were found between ET and placebo on any of the neurocognitive measures or depression instruments, nor were there any differences when the groups were stratified according to age. CONCLUSION: This small study, which had adequate power to detect change in some but not all domains of cognition tested, revealed t hat low-dose estrogen neither benefits nor harms cognitive function in older women after 3 years of treatment, but confirmation is needed from larger trials.

Resnick, S. M., M. A. Espeland, et al. (2009). "Effects of conjugated equine estrogens on cognition and affect in postmenopausal women with prior hysterectomy." Journal of Clinical Endocrinology & Metabolism **94**(11): 4152-61.

CONTEXT: Different menopausal hormone therapies may have varied effects on specific cognitive functions. We previously reported that conjugated equine estrogens (CEE) with medroxyprogesterone acetate had a negative impact on verbal memory but tended to impact figural memory positively over time in older postmenopausal women. OBJECTIVE: The objective of the study was to determine the effects of unopposed CEE on changes in domain-specific cognitive function and affect in older postmenopausal women with prior hysterectomy. DESIGN: This was a randomized, double blind, placebo-controlled clinical trial. SETTING: The study was conducted at 14 of 40 Women's Health Initiative (WHI) clinical centers. PARTICIPANTS: Participants were 886 postmenopausal women with prior hysterectomy, aged 65 yr and older (mean 74 yr), free of probable dementia, and enrolled in the WHI and WHI Memory Study (WHIMS) CEE-Alone trial for a mean of 3 yr and followed up for a mean of 2.70 yr. INTERVENTION: Intervention was 0.625 mg of CEE daily or placebo. MAIN OUTCOME MEASURES: Annual rates of change in specific cognitive functions and affect, adjusted for time since randomization, were measured. RESULTS: Compared with placebo, unopposed CEE was associated with lower spatial rotational ability ($P < 0.01$) at initial assessment (after 3 yr of treatment), a difference that diminished over 2.7 yr of continued treatment. CEE did not significantly influence change in other cognitive functions and affect. CONCLUSIONS: CEE did not improve cognitive functioning in postmenopausal women with prior hysterectomy. CEE was associated with lower spatial rotational performance after an average of 3 yr of treatment. Overall, CEE does not appear to have enduring effects on rates of domain-specific cognitive change in older postmenopausal women.

Simon, J. A., C. Bouchard, et al. (2007). "Low dose of transdermal estradiol gel for treatment of symptomatic postmenopausal women: a randomized controlled trial.[see comment]." Obstetrics & Gynecology **109**(3): 588-96.

OBJECTIVE: To investigate safety and efficacy and identify the lowest effective dose of a new transdermal estradiol (E2) gel for relief of menopausal symptoms in a population of postmenopausal women. METHODS: This study was a randomized, double-blind, placebo-controlled, multicenter, parallel-group study. Postmenopausal women with at least 60 hot flushes per week applied 0.87 g/d (n=136), 1.7 g/d (n=142), or 2.6 g/d (n=69) E2 gel or placebo gel (n=137) topically for 12 weeks. The changes from baseline in hot flush frequency and severity at 4 and 12 weeks and changes from baseline in vaginal atrophy symptoms at 12 weeks were examined. RESULTS: With increasing E2 doses, mean trough serum E2 increased from 17 to 29 pg/mL. By weeks 3-5, E2 gel reduced moderate-to-severe hot flush rate by at least seven hot flushes per day (P<.001) and reduced the severity score (P<.01). The numbers needed to treat for benefit for an 80% and 100% decrease in hot flush number were 3.2 and 6.3 for the 0.87-g/d group and 1.3 and 2.3 for the 2.6-g/d group. At week 12, vaginal pH was more acidic and vaginal maturation index more mature compared with placebo (P<.001). The lowest dose improved most bothersome vulvovaginal atrophy symptoms (P<.05). Estradiol gel was well tolerated at the site of application and produced no unexpected adverse effects. The 0.87 g/d dose produced fewest adverse events. CONCLUSION: The 0.87 g/d dose of this new transdermal E2 gel, which delivers an estimated 0.0125 mg E2 daily, delivered the lowest effective dose for treatment of vasomotor symptoms and vulvovaginal atrophy in a population of postmenopausal women.

Simon, J. A. and E. S. Group (2006). "Estradiol in micellar nanoparticles: the efficacy and safety of a novel transdermal drug-delivery technology in the management of moderate to severe vasomotor symptoms." Menopause **13**(2): 222-31.

OBJECTIVE: To assess the efficacy and safety of topical micellar nanoparticle estradiol emulsion (MNPEE; Estrasorb; Novavax, Inc., Malvern, PA) in postmenopausal women with moderate to severe vasomotor symptoms. DESIGN: A multicenter, randomized, double-blind, placebo-controlled study was conducted in 200 postmenopausal women with seven or more moderate to severe hot flushes per day. The study consisted of a 3-week screening period followed by a 1-week placebo emulsion run-in period and a 12-week active or placebo treatment period. Women were randomized (1:1) to receive MNPEE (3.45 g daily dose of emulsion containing 8.6 mg estradiol) or matching placebo emulsion. The primary efficacy variable was the change from baseline in the frequency of moderate and severe hot flushes at weeks 4 and 12. Adverse events were monitored throughout the trial. RESULTS: Topical micellar nanoparticle estradiol emulsion was statistically significantly superior to placebo emulsion in reducing the mean frequency of moderate to severe vasomotor symptoms by week 3 (P = 0.003), with superiority to placebo maintained from weeks 4 to 12 (P < 0.001). At week 12 (peak benefit), MNPEE reduced mean daily frequency of hot flush count by 11.1 (P < 0.001 vs placebo). MNPEE significantly reduced mean symptom severity from weeks 4 to 12 (P < 0.001) compared with placebo. At endpoint, mean serum concentrations of estradiol and estrone were 63 and 89 pg/mL, respectively, in the MNPEE group. The mean endpoint ratio of estradiol to estrone in these patients was 0.774. MNPEE was safe and well tolerated. CONCLUSION: Once-daily application of 3.45 g of micellar nanoparticle estradiol emulsion containing 8.6 mg of estradiol was safe and effective in providing significant relief of vasomotor symptom frequency and severity in postmenopausal women.

Simon, J. A., K. Z. Reape, et al. (2008). "Randomized, multicenter, double-blind, placebo-controlled trial to evaluate the efficacy and safety of synthetic conjugated estrogens B for the treatment of vulvovaginal atrophy in healthy postmenopausal women." Fertility & Sterility **90**(4): 1132-8.

OBJECTIVE: To evaluate the safety and efficacy of synthetic conjugated estrogens B (SCE-B; 0.3 mg/d) for 12 weeks in the treatment of vulvovaginal atrophy in symptomatic, postmenopausal women. DESIGN: Prospective, randomized, multicenter, double-blind, placebo-controlled trial. SETTING: Forty-two participating sites in the United States. PATIENT(S): Postmenopausal women with at least one moderate to severe symptom of vaginal atrophy. INTERVENTION(S): Daily oral administration, in a randomized, placebo-controlled setting, of SCE-B (0.3 mg) or of placebo for 12 weeks. MAIN OUTCOME MEASURE(S): Mean changes in vaginal maturation index, percentage of parabasal and superficial cells, vaginal pH, and severity of the most bothersome symptom (MBS) between baseline and predetermined time points were assessed. Safety and tolerability were evaluated. RESULT(S): A total of 310 women (mean age, 58.6 y) were enrolled. Synthetic conjugated estrogens B yielded statistically significantly greater differences in vaginal maturation index and vaginal pH from baseline to the end of treatment. Vaginal dryness (44.4%) and pain during intercourse (30.2%) were the symptoms most commonly identified as the MBS. A statistically significant mean reduction in the severity of the MBS was noted for SCE-B. There were no clinically significant differences observed between the two groups for findings related to safety. CONCLUSION(S): Synthetic conjugated estrogens B (0.3 mg/d) was effective in treating vulvovaginal atrophy in symptomatic postmenopausal women. Significant improvement was seen in vaginal maturation index, vaginal pH, and severity of MBS from baseline to the end of treatment.

Stevenson, J. C., G. Durand, et al. (2010). "Oral ultra-low dose continuous combined hormone replacement therapy with 0.5 mg 17beta-oestradiol and 2.5 mg dydrogesterone for the treatment of vasomotor symptoms: results from a double-blind, controlled study." Maturitas **67**(3): 227-232.

OBJECTIVES: Guidelines recommend using the lowest effective dose of oestrogen for the management of vasomotor symptoms in postmenopausal women. The primary aim of this double-blind, multi-centre, randomised study was to assess the efficacy of oral ultra-low dose continuous combined hormone replacement therapy with 17beta-oestradiol and dydrogesterone. STUDY DESIGN: 313 women with >=50 moderate to severe hot flushes during the previous week were randomised to 0.5 mg 17beta-oestradiol/2.5 mg dydrogesterone (E 0.5 mg/D 2.5 mg), 1mg 17beta-oestradiol/5mg dydrogesterone (E 1mg/D 5 mg) or placebo for 13 weeks. The placebo group then switched to E 0.5 mg/D 2.5 mg for a further 39 weeks, whilst the other groups continued on the same treatment. RESULTS: After 13 weeks, the reduction in the number of moderate to severe hot flushes/day in the E 0.5 mg/D 2.5 mg group was greater than in the placebo group (-6.4 vs. -4.9, $p<0.001$) and comparable to that in the 1/5 mg group (-6.3). E 0.5 mg/D 2.5 mg and E 1mg/D 5 mg significantly improved the total Menopause Rating Scale score. The number of bleeding/spotting days was lower with E 0.5 mg/D 2.5 mg than with E 1 mg/D 5 mg. The overall amenorrhoea rate with E 0.5 mg/D 2.5 mg was 81%; this increased to 91% in months 10-12. CONCLUSIONS: Continuous combined 0.5 mg 17beta-oestradiol and 2.5mg dydrogesterone was effective in alleviating vasomotor symptoms and improving quality of life, and was associated with a high amenorrhoea rate and a good tolerability profile. Copyright

Veerus, P., K. Fischer, et al. (2008). "Symptom reporting and quality of life in the Estonian Postmenopausal Hormone Therapy Trial." BMC Women's Health **8**: 5.

BACKGROUND: The aim of the study was to determine the effect of postmenopausal hormone therapy on women's symptom reporting and quality of life in a randomized trial.

METHODS: 1823 women participated in the Estonian Postmenopausal Hormone Therapy (EPHT) Trial between 1999 and 2004. Women were randomized to open-label continuous combined hormone therapy or no treatment, or to blind hormone therapy or placebo. The average follow-up period was 3.6 years. Prevalence of symptoms and quality of life according to EQ-5D were assessed by annually mailed questionnaires. RESULTS: In the hormone therapy arms, less women reported hot flushes (OR 0.20; 95% CI: 0.14-0.28), sweating (OR 0.56; 95% CI: 0.44-0.72), and sleeping problems (OR 0.66; 95% CI: 0.52-0.84), but more women reported episodes of vaginal bleeding (OR 19.65; 95% CI: 12.15-31.79). There was no difference between the trial arms in the prevalence of other symptoms over time. Quality of life did not depend on hormone therapy use. CONCLUSION: Postmenopausal hormone therapy decreased vasomotor symptoms and sleeping problems, but increased episodes of vaginal bleeding, and had no effect on quality of life.

Welton, A. J., M. R. Vickers, et al. (2008). "Health related quality of life after combined hormone replacement therapy: randomised controlled trial.[see comment]." BMJ **337**: a1190.

OBJECTIVE: To assess the effect of combined hormone replacement therapy (HRT) on health related quality of life. DESIGN: Randomised placebo controlled double blind trial. SETTING: General practices in United Kingdom (384), Australia (94), and New Zealand PARTICIPANTS: Postmenopausal women aged 50-69 at randomisation; 3721 women with a uterus were randomised to combined oestrogen and progestogen (n=1862) or placebo (n=1859). Data on health related quality of life at one year were available from 1043 and 1087 women, respectively. INTERVENTIONS: Conjugated equine oestrogen 0.625 mg plus medroxyprogesterone acetate 2.5/5.0 mg or matched placebo orally daily for one year. MAIN OUTCOME MEASURES: Health related quality of life and psychological wellbeing as measured by the women's health questionnaire. Changes in emotional and physical menopausal symptoms as measured by a symptoms questionnaire and depression by the Centre for Epidemiological Studies depression scale (CES-D). Overall health related quality of life and overall quality of life as measured by the European quality of life instrument (EuroQol) and visual analogue scale, respectively. RESULTS: After one year small but significant improvements were observed in three of nine components of the women's health questionnaire for those taking combined HRT compared with those taking placebo: vasomotor symptoms (P<0.001), sexual functioning (P<0.001), and sleep problems (P<0.001). Significantly fewer women in the combined HRT group reported hot flushes (P<0.001), night sweats (P<0.001), aching joints and muscles (P=0.001), insomnia (P<0.001), and vaginal dryness (P<0.001) than in the placebo group, but greater proportions reported breast tenderness (P<0.001) or vaginal discharge (P<0.001). Hot flushes were experienced in the combined HRT and placebo groups by 30% and 29% at trial entry and 9% and 25% at one year, respectively. No significant differences in other menopausal symptoms, depression, or overall quality of life were observed at one year. CONCLUSIONS: Combined HRT started many years after the menopause can improve health related quality of life.

Varying dose study (N=4)

Limpaphayom, K. K., M. S. Darmasetiawan, et al. (2006). "Differential prevalence of quality-of-life categories (domains) in Asian women and changes after therapy with three doses of conjugated estrogens/medroxyprogesterone acetate: the Pan-Asia Menopause (PAM) study." Climacteric **9**(3): 204-14.

OBJECTIVES: To assess the prevalence of four categories (domains) of menopausal symptoms as markers for quality of life in nine ethnic groups of Asian women. To evaluate

changes in quality of life (MENQOL scores) in Asian women following hormone therapy. METHODS: A prospective, randomized, double-blind, multinational clinical trial in 1028 healthy postmenopausal women of nine ethnic groups from 11 Asian countries/regions. Following 2 weeks of baseline observation, the women received one of three conjugated estrogens (CE)/medroxyprogesterone acetate (MPA) doses (in mg) daily for 24 weeks: 0.625/2.5, 0.45/1.5, or 0.3/1.5. At baseline and at the end of weeks 4, 12 and 24 following the start of therapy, the study participants were asked to record, on a menopause-specific quality of life (MENQOL) questionnaire, 29 menopausal symptoms, as experienced during the preceding month. The symptoms were categorized into four domains: vasomotor, psychosocial, physical and sexual. RESULTS: The baseline (pretreatment) symptom scores in each of the four domains varied substantially among the different ethnic groups, ranging from 2.21 to 5.71 in the vasomotor, 2.37-5.96 in the psychosocial, 2.66-5.39 in the physical, and 2.11-6.55 in the sexual domain. Overall, Vietnamese and Pakistani women had the highest baseline scores, i.e. were most afflicted by each set of symptoms in a given domain, and Indonesian, Malay, Taiwanese and Thai women were least afflicted. In the overall population, intervention resulted in statistically significant decreases in the scores of all four domains within 4 weeks of intervention. The beneficial effects were similar in the three dose groups. CONCLUSIONS: The prevalence of four domains of menopausal symptoms, representative of quality of life as recorded on a MENQOL questionnaire, varies considerably among ethnic groups of Asian women. The MENQOL scores in the overall population were significantly lowered in the course of the study, indicating an improvement in quality of life. In the absence of a placebo group, the relative contribution of hormones and placebo in our intervention is unknown.

Mattsson, L. A., S. Skouby, et al. (2007). "Efficacy and tolerability of continuous combined hormone replacement therapy in early postmenopausal women." Menopause International **13**(3): 124-31.

OBJECTIVE: Continuous combined hormone replacement therapy (ccHRT) based on estradiol valerate (E2V) and medroxyprogesterone acetate (MPA) is effective for relief of menopausal symptoms three years or more after the menopause. This study was undertaken to examine the efficacy and tolerability of ccHRT in early postmenopausal women (last menstrual period 1.3 years before study entry). STUDY DESIGN: This was a 52-week, randomized, double-blind, multinational study of ccHRT comprising three different dose combinations of E2V/MPA in 459 early postmenopausal non-hysterectomized women experiencing 30 or more moderate to severe hot flushes a week and/or vasomotor symptoms requiring treatment. MAIN OUTCOMES MEASURES: The primary endpoint was change in frequency and severity of moderate to severe hot flushes at 12 weeks. Secondary outcome measures included number of bleeding days and evaluation of tolerability. RESULTS: The frequency of hot flushes was reduced by >or=70% after one month (P<0.001 for all doses at week 2 onwards), with little evidence of statistically different dose effects. Severity of flushing was also attenuated by ccHRT. Mean number of bleeding days fell to <1 per 28-day cycle at 52 weeks. Rates of amenorrhoea approached 80-90% at the end of the study, but were significantly lower at several time points with the highest-dose regimen (2 mg E2V + 5 mg MPA) than with the lower-dose options (1 mg E2V + 2.5 mg MPA and 1 mg E2V + 5 mg MPA; P<0.05). Adverse events declined in frequency over time with all regimens but throughout the study were more numerous with the highest-dose regimen than with lower doses (P= 0.0002). CONCLUSIONS: Continuous combined HRT was effective for the relief of climacteric symptoms in early postmenopausal women and was well tolerated.

Pitkin, J., V. P. Smetnik, et al. (2007). "Continuous combined hormone replacement therapy relieves climacteric symptoms and improves health-related quality of life in early postmenopausal women." Menopause International **13**(3): 116-23.

OBJECTIVE: Hormone replacement therapy (HRT) relieves menopausal symptoms but its effect on health related quality of life (HRQoL) is uncertain. The aim of this study was to assess the effect of three dose regimens of continuous combined HRT, consisting of estradiol valerate (E2V) and medroxyprogesterone acetate (MPA) on HRQoL in early postmenopausal women (last menstrual period 1-3 years before study entry). STUDY DESIGN: This was a 52-week, randomized, double-blind, multinational study comparing E2V (1 mg or 2 mg) plus MPA (2.5 mg or 5 mg) in different dose combinations. The intention-to-treat population comprised 459 women (average age 51.5 years). MAIN OUTCOME MEASURES: HRQoL was assessed by the Women's Health Questionnaire (WHQ), the 15D Questionnaire and a visual analogue scale (VAS). RESULTS: There were improvements on eight of the nine domains of the WHQ with all dose regimens during the first 12 weeks (P<0.0001) and an I mprovement in the remaining domain (menstrual symptoms) with the lower-dose regimens (P<0.05). These initial improvements in HRQoL were then maintained or augmented over the remainder of the study (P<0.0001 for change from baseline at 52 weeks for all domains and dose regimens). Mean 15D total score had improved meaningfully and significantly by 12 weeks (P<0.0001 versus baseline) in all treatment groups and this improvement was maintained thereafter. This improvement in 15D total score was most marked among previous non-users of HRT (P<0.05 versus previous users). VAS scores recorded significant (P<0.05) reductions in hot flushes, sweating and sleep disturbances in all groups after week 1 and highly significant (P<0.0001) relief of all climacteric symptoms at week 52. CONCLUSION: Continuous combined HRT was associated with pronounced improvement of vasomotor symptoms and HRQoL in this population of early postmenopausal women.

Yang, T.-S., Y.-J. Chen, et al. (2007). "A clinical trial of 3 doses of transdermal 17beta-estradiol for preventing postmenopausal bone loss: a preliminary study.[see comment]." Journal of the Chinese Medical Association: JCMA **70**(5): 200-6.

BACKGROUND: It is well documented that a daily oral dose of 0.625 mg of conjugated equine estrogen or 1-2 mg of 17beta-estradiol is needed to prevent postmenopausal bone loss. Recent studies have indicated that a lower dose of estrogen maybe as effective in maintaining bone mass. The purpose of this study was to evaluate the effects of 3 dosages of transdermally administered 17beta-estradiol gel in postmenopausal women stratified by oophorectomy and natural menopause. METHODS: One hundred and twenty postmenopausal women were randomly selected to form 4 groups. Three groups of women were treated with a transdermal administration of estradiol gel at a daily dosage of 1.25, 2.5 and 5.0 g (containing 0.75, 1.5, and 3 mg of 17beta-estradiol/day), respectively. The 4th group of women, receiving estriol 2 mg/day p.o., was studied concurrently as a control. Bone mineral density was measured by quantitative computed tomography of the vertebrae from T12 to L3 at baseline, then at 6-month intervals for 1 year. RESULTS: Women in all groups receiving 17beta-estradiol gel obtained a significant increase in bone mass, with the exception of the 1.25 g/day group, which showed a minimal increment at the 6-month period, compared with the control group. Comparisons of the increments in bone mass after estrogen therapy for both natural and surgical menopausal subjects found that there was a more prominent response in surgical menopausal women receiving a dosage of 2.5 g/day. CONCLUSION: Estradiol gel at the dosage of 1.25 g/day, equivalent to 17beta-estradiol 0.75 mg/day, effectively prevented bone loss in postmenopausal women after a 12-month treatment period. The therapeutic effect of estradiol gel on bone mass was more prominent in

the surgical menopausal groups at the dosage of 2.5 g/day. The atrophic ovaries may therefore play a crucial role in the subsequent decades of postmenopausal women.

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Month/Year of Review: January 2014
PDL Classes: Calcium Channel Blockers

Date of Last Review: January 2012
Source Document: OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: AMLODIPINE, NICARDIPINE, NIFEDIPINE ER 24, NIFEDIPINE ER SA, DILTIAZEM SR 24 HR, DILTIAZEM ER, DILTIAZEM HCL, VERAPAMIL HCL, VERAPAMIL HCL 24H
- Non-Preferred Agents: FELODIPINE, ISRADAPINE, NISOLDIPINE, NIMODIPINE (NIMOTOP®)

Previous Conclusions and Recommendation:

- The current evidence does not allow for comparisons of CCBs for the treatment of hypertension and does not differentiate amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nisoldipine, or verapamil SR for efficacy, adverse effects and in subgroups for the treatment of hypertension. There is no evidence for bepridil and felodipine.
- The current evidence does not differentiate amlodipine, diltiazem, nicardipine, nifedipine, and nisoldipine for efficacy in the treatment of chronic stable angina. There is no evidence for felodipine and isradipine. No difference in efficacy was found between dihydropyridines and non-dihydropyridines for the treatment of angina.
- The current evidence does not differentiate between diltiazem or verapamil for efficacy and adverse effects in the treatment of supraventricular arrhythmias and there is no evidence in subgroups of patients.
- In the setting of CHF (defined as systolic dysfunction with a LVEF of < 45%) there is evidence that amlodipine and felodipine do not decrease survival or cause harm in this patient population, but neither do they improve survival nor decrease nonfatal cardiovascular events. In patients with systolic dysfunction the evidence does not demonstrate differences between amlodipine, felodipine nifedipine and nisoldipine on symptoms and exercise tolerance.

Research Questions:

- Is there any new comparative evidence on calcium channel blockers (CCBs) in the treatment of hypertension, angina, supraventricular arrhythmias, or systolic dysfunction on mortality, cardiovascular events, stroke, or quality of life?
- Is there any new comparative safety evidence of CCBs??
- Are there subpopulations of patients for which one medication or preparation is more effective or associated with fewer adverse effects?

Methods:

The DERP scan was used to identify any new comparative research that has emerged since the last P&T review.[1]

Conclusions and Recommendations:

- There is no new significant comparative evidence on the efficacy or safety of CCBs; no further review or research needed.
- Evaluate comparative costs in executive session.

New Guidelines:
Evidence-based guidelines for the treatment of hypertension were recently released from the Eighth Joint National Committee (JNC8)[2] The following recommendations were made regarding the drug selection for the treatment of hypertension:

- In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, CCB, angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (Moderate recommendation – Grade B).
    - These drug classes had comparable effects on overall mortality and CV, cerebrovascular, and kidney outcomes.
    - Initial treatment with a thiazide-type diuretic was more effective than a CCB or ACEI, and an ACEI was more effective than a CCB in improving heart failure outcomes.
- Calcium channel blockers should be dosed adequately to achieve results similar to those seen in RCTs. Evidence-based target doses for CCBs is as follows:
    - Amlodipine: 10mg
    - Diltiazem ER: 360 mg
    - Nitrendipine: 20 mg
- In the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB (Moderate Recommendation – Grade B).
    - CCB's are recommended over an ACEI as first-line therapy in black patients because there was a 51$ higher rate (RR 1.51; 95% CI 1.22-1.86) of stroke in black persons in ALLHAT with the use of an ACEI compared with the use of a CCB. The ACEI was also less effective in reducing BP in black individuals compared with the CCB.

References:

1. Peterson K. Drug Effectiveness Review Project. Drug Class Review: Calcium Channel Blockers. Preliminary Scan Report #5. October 2013.

2. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the eighth joint national committee (jnc 8). *JAMA*. 2013. doi:10.1001/jama.2013.284427.

Drug Class Review

Calcium Channel Blockers

Preliminary Scan Report #5

October 2013

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Scan conducted by:
Kim Peterson, MS

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Pacific Northwest Evidence-based Practice Center
Roger Chou, MD, Director
Marian McDonagh, PharmD, Associate Director

Oregon Health & Science University

OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations' consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Date of Last Update Report

Update #2, March 2005 (searches through February 2004)

Date of Last Preliminary Update Scan Report

April 2009

Scope and Key Questions

Key Questions

1. Do CCBs differ in effectiveness in the treatment of adult patients with essential hypertension (blood pressure ≥ 140/90 mm Hg), angina, supraventricular arrhythmias, or systolic dysfunction (left ventricular ejection fraction [LVEF] <45%)?
2. Do CCBs differ in their safety or adverse effects in the treatment of adult patients with essential hypertension (blood pressure ≥ 140/90 mm Hg), angina, supraventricular arrhythmias, or systolic dysfunction (LVEF<45%)?
3. Based on demographics (age, racial groups, gender), other medications, or comorbidities, are there subgroups of patients for which one CCB is more effective or is associated with fewer adverse effects?

Inclusion Criteria

POPULATION

Adults with hypertension (blood pressure ≥ 140/90 mm Hg), angina, supraventricular arrhythmia or supraventricular tachycardia (SVT), and systolic dysfunction (LVEF <45%).

Interventions

Amlodipine
Bepridil
Diltiazem
Felodipine

Isradipine
Nicardipine
Nifedipine
Nisoldipine
Verapamil

OUTCOMES

Hypertension
All cause mortality
Cardiovascular (CV) disease mortality
CV events (stroke, MI, development of CHF)
Development of renal failure (end stage renal disease/dialysis/transplant/ clinically significant, permanent increase in serum creatinine or decrease in creatinine clearance)
Quality of Life

Angina (Follow-up duration ≥ 2 months)
All cause mortality
Cardiovascular (CV) disease mortality
CV events (stroke, MI, development of CHF)
Symptoms
Quality of Life

Supraventricular Arrhythmias
All cause mortality
Cardiovascular (CV) disease mortality
Stroke
Symptoms (rate or rhythm control)
Quality of Life

Left-ventricular Dysfunction
All cause mortality
Cardiovascular (CV) disease mortality
CV events (stroke, MI, development of CHF)
Symptoms
Quality of Life

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from January 2009 through October 2013 using terms for included drugs. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, indications, and safety alerts. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) and the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/). All citations were imported into an electronic database (EndNote X3) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

New drugs identified in current Preliminary Update Scan

The current scan did not identify any new drugs.

New drugs identified in previous Preliminary Update Scan

In January 2008, FDA approved a change in the formulation of extended-release nisoldipine to lower the strengths and replace all current tablets (i.e., 10 mg, 20 mg, 30 mg and 40 mg) with new lower, bioequivalent strengths (i.e., 8.5 mg, 17 mg, 25.5 mg and 34 mg)

New Indications

New indications identified in current Preliminary Update Scan

The current scan did not identify any new indications.

New indications identified in previous Preliminary Update Scan

Amlodipine indicated for use in patients with angiographically documented coronary artery disease– expanded population (9/05).

New Black Box Warnings

We did not identify any new black box warnings in this or the previous scan.

Comparative Effectiveness Reviews

We did not identify any new potentially relevant comparative effectiveness reviews in this or the previous scan.

Randomized Controlled Trials

Trials identified since the most recent Full Report

Medline searches from this scan resulted in 341 citations. Of those, there were 20 potentially relevant new trials (see Appendix A for abstracts). Together with the 37 potentially relevant trials identified in the last scan (Appendix B), now there are a total of 57. Characteristics of these trials are shown in Table(s) 2-4, below. The majority are subanalyses from previously included or identified trials (Table 4). Shading indicates publications that are new in this scan.

Table 1. New head-to-head trials

Author Year	Trial Name	Interventions	Population
Melcher 1998	N/A	Nisoldipine Coat-Core vs Diltiazem Retard in Combination with a Beta-Blocker	Angina

Table 2. New active-control trials

Author Year	Trial Name	Interventions	Population
Yamashita 2011	J-RHYTHM II (Japanese Rhythm Management Trial II for Atrial Fibrillation)	Amlodipine vs candesartan	Paroxysmal atrial fibrillation
Ogihara 2008	CASE-J (Candesartan Antihypertensive Survival Evaluation in Japan)	Amlodipine vs candesartan	High-risk Japanese hypertensive patients
Investigators 2006	J-ELAN (The Effect of Losartan and Amlodipine on Left Ventricular Diastolic Function in Patients with Mild-to-Moderate Hypertension)	Amlodipine vs losartan	Hypertension
Nakamura 2008	N/A	Amlodipine vs telmisartan	Hypertension with chronic kidney disease
Fogari 2012	N/A	Amlodipine vs telmisartan	Hypertensive patients with paroxysmal AF and normal or increased left atrial dimension (LAD)
Fogari 2012	N/A	Amlodipine vs telmisartan vs ramipril	Hypertensive patients with metabolic syndrome and recurrent symptomatic

			paroxysmal and persistent atrial fibrillation
Muramatsu 2012	NAGOYA HEART Study	Amlodipine vs valsartan	Hypertensive patients with glucose intolerance
Nakamaya 2008	VART (Valsartan Amlodipine Randomized Trial)	Amlodipine vs valsartan	Hypertensive patients in Japan
Schmieder 2008	VALUE (Valsartan Antihypertensive Long-term Use Evaluation)	Amlodipine vs valsartan	High-risk hypertensive patients
Nissen 2004	CAMELOT (Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis)	Amlodipine vs enalapril vs placebo	Coronary disease and normal blood pressure
Jamerson 2008	ACCOMPLISH (Avoiding Cardiovascular events through COMbination therapy in Patients LIving with Systolic Hypertension)	Amlodipine vs HCTZ added to benazepril	Hypertension
Ruzyllo 2007	N/A	Amlodipine vs ivabradine	Angina
Kojima 2004	N/A	Amlodipine vs cilnidipine	Hypertension with renal disease
Koylan 2004	TTS (Turkish Trimetazidine Study)	Diltiazem vs trimetazidine	Angina
Vora 2004	N/A	Diltiazem vs amiodarone	Rheumatic atrial fibrillation
Frishman 2006	M-FACT (Metoprolol Succinate-Felodipine Antihypertension Combination Trial)	Metoprolol ER, felodipine ER, or their combination	Hypertension
Derosa 2004	N/A	Nifedipine GITS vs telmisartan	Hypertension and type 2 diabetes
Inoue 2004	N/A	Nifedipine vs benidipine	Hypertensive patients with renal dysfunction
Ruggenenti 2004	BENEDICT (Bergamo Nephrologic Diabetes Complications Trial)	Verapamil vs trandolapril vs their combination vs placebo	Hypertension, type 2 diabetes mellitus, and normal urinary albumin excretion
Hemels 2006	VERDICT (Verapamil Versus Digoxin and Acute Versus Routine Serial Cardioversion Trial)	Verapamil vs digoxin	Persistent atrial fibrillation
Vranic 2006	N/A	Verapamil vs adenosine	Paroxysmal supraventricular

	tachycardia

Table 3. New placebo-controlled trials

Author Year	Trial Name	CCB	Population
Tepel 2008	N/A	Amlodipine	Hypertensive hemodialysis patients
Liu 2005	FEVER (Felodipine Event Reduction)	Felodipine	Chinese hypertensive patients

Table 4. Subanalyses from previously included/identified trials

Author Year	Trial Name	CCB	Population	Focus
Bakris 2013	ACCOMPLISH	Amlodipine	Hypertension	High-risk subgroup with known coronary artery disease
Weber 2013	ACCOMPLISH	Amlodipine	Hypertension	Effects of body size
Weir 2012	ACCOMPLISH	Amlodipine	Hypertension	Renal outcomes in Black patients
Bakris 2010	ACCOMPLISH	Amlodipine	Hypertension	Renal outcomes in high-risk subgroup with known coronary artery disease
Weber 2010	ACCOMPLISH	Amlodipine	Hypertension	Subgroup with diabetes
Oparil 2013	ALLHAT	Amlodipine	Hypertension	Results by sex
Rahman 2012	ALLHAT	Amlodipine	Hypertension	Results by baseline estimated GFR
Cushman 2012	ALLHAT	Amlodipine	Hypertension	Persistence of mortality and morbidity differences during extended follow-up
Black 2008	ALLHAT	Amlodipine	Hypertension	Metabolic syndrome subgroup
Davis 2008	ALLHAT	Amlodipine	Hypertension	HF events
Wright 2008	ALLHAT	Amlodipine	Hypertension	Influence of race
Leenen 2006	ALLHAT	Amlodipine	Hypertension	Demographic subgroups
Whelton 2005	ALLHAT	Amlodipine	Hypertension	Influence of type 2 diabetes mellitus or impaired fasting glucose levels
Ostergren 2008	ASCOT	Amlodipine	Hypertension	Type II diabetes subgroup

Collier 2011	ASCOT-BPLA	Amlodipine	Hypertension	Influence of age
Ogihara 2011	CASE-J	Amlodipine	Hypertension	Long-term outcomes
Saruta 2009	CASE-J	Amlodipine	Hypertension	Chronic Kidney Disease subgroup
Ogihara 2008	CASE-J	Amlodipine	Hypertension	Survival evaluation
Takano 2012	VART	Amlodipine	Hypertension	Relationship between home blood pressure (HBP) levels and cardiovascular events
Narumi 2011	VART	Amlodipine	Hypertension	Additional cardiorenal outcomes
Yui 2007	JMIC-B	Nifedipine	Hypertensive Japanese patients with previous myocardial infarction	Role of coronary arteriosclerosis progression
Elliot 2011	ACTION	Long-acting nifedipine GITS	Angina	Diabetes mellitus subgroup
Elliot 2011	ACTION	Long-acting nifedipine GITS	Angina	Angina subgroup
Ruilope 2007	ACTION	Long-acting nifedipine GITS	Angina	Role of renal function
Lubsen 2005	ACTION	Long-acting nifedipine GITS	Angina	Stratified by baseline hypertension
de Leeuw 2004	INSIGHT	Long-acting nifedipine GITS	High-risk hypertension	Role of renal function
Mancia 2004	INSIGHT	Long-acting nifedipine GITS	High-risk hypertension	Isolated systolic hypertension subgroup
Bangalore 2008	INVEST	Verapamil sustained release	Hypertension	Prior myocardial infarction subgroup
Cooper-DeHoff 2007	INVEST	Verapamil sustained release	Hypertension	Influence of Hispanic ethnicity
Cooper-DeHoff 2006	INVEST	Verapamil sustained release	Hypertension	Predictors of diabetes mellitus development
Messerli 2006	INVEST	Verapamil sustained release	Hypertension	Influence of aggressive blood pressure lowering

Ruggenenti 2011	BENEDICT-B	Verapamil	Hypertension	Subgroup with type 2 diabetes and microalbuminuria
Black 2005	CONVINCE	COER verapamil	Hypertension	Influence of geographical region

Appendix A. Abstracts of potentially relevant new trials of Calcium Channel Blockers from current scan

New Head-to-Head Trials

Melcher, A., J. Abelin, et al. (1998). "Efficacy and Tolerability of Nisoldipine Coat-Core vs Diltiazem Retard in Combination with a Beta-Blocker in Patients with Stable Exertional Angina Pectoris." Clinical Drug Investigation **15**(5): 389-396.

A randomised, double-blind, placebo-controlled, parallel-group trial with forced titration study to investigate possible equivalence of efficacy and tolerability between nisoldipine coat-core (CC) 40mg once daily, and diltiazem retard 120mg twice daily, was carried out in 176 patients with stable angina pectoris who were already receiving beta-blocker therapy. A total of 164 patients were included in the tolerability analysis and 135 patients were evaluable for efficacy (nisoldipine CC, n = 69; diltiazem retard, n = 66). During bicycle exercise tolerance tests, time to 1mm ST-segment depression, total exercise time, and time to angina were assessed at baseline and at the end of the treatment period. The number of angina attacks and of consumed nitroglycerin tablets were recorded in weekly diaries. Time to onset of 1mm ST-segment depression increased by 69.4 +/- 100.0 seconds with nisoldipine CC and by 65.9 +/- 87.6 seconds with diltiazem retard. The two treatment regimens were equally effective in time to onset of 1mm ST-segment depression, time to angina pectoris, and in exercise duration. A beneficial effect on angina attacks and nitroglycerin consumption was achieved with both treatments. Patient compliance, as assessed by the number of returned tablets, was high, at over 80%. Six patients withdrew from the treatment because of adverse events. Mild and transient adverse events were reported by 24 patients during treatment. One patient experienced a severe circulatory shock on the combination of diltiazem retard and atenolol. Peripheral oedema and headache were more common on nisoldipine CC. We concluded that the two treatments were equally efficacious and tolerated in patients with stable angina pectoris.

New Active-Control Trials

Fogari, R., A. Mugellini, et al. (2012). "Effect of telmisartan and ramipril on atrial fibrillation recurrence and severity in hypertensive patients with metabolic syndrome and recurrent symptomatic paroxysmal and persistent atrial fibrillation." Journal of Cardiovascular Pharmacology & Therapeutics **17**(1): 34-43.

This study evaluated the effect of telmisartan, ramipril, and amlodipine on atrial fibrillation (AF) recurrence and severity in hypertensive patients with metabolic syndrome. A total of 391 hypertensive outpatients with metabolic syndrome, in sinus rhythm but with at least 2 episodes of AF in the previous 6 months were randomized to telmisartan, ramipril, or amlodipine for 1 year. At the first AF, ventricular rate (VR) and plasma cardiac troponin I (TnI) were evaluated. P-wave dispersion (PWD) and procollagen type I carboxy-terminal peptide (PIP) were evaluated before and after 12 months of treatment. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were similarly and significantly reduced by all treatments ($P < .001$). In all, 49% of patients treated with amlodipine had a recurrence of AF as did 25.5% of patients with ramipril and 12.9% of patients with telmisartan ($P < .01$ vs amlodipine and $P < .05$ vs ramipril). Ventricular rate and TnI at the first AF recurrence were significantly lower with telmisartan and ramipril than with amlodipine. P-wave dispersion was reduced by ramipril (-5.1 ms, $P < .05$) and even more by telmisartan (-11 ms, $P < .01$). Telmisartan and ramipril induced a similar PIP reduction (-52.8 and -49.8 g/L, respectively, $P < .01$). These findings suggested that in these patients telmisartan was more effective than ramipril in reducing AF recurrence and severity as well as in improving PWD, despite a similar BP reduction and a similar improvement in cardiac fibrosis. This could be related to a specific effect of telmisartan on atrial electric remodeling.

Fogari, R., A. Zoppi, et al. (2012). "Effect of telmisartan on paroxysmal atrial fibrillation recurrence in hypertensive patients with normal or increased left atrial size." Clinical Cardiology **35**(6): 359-364.

BACKGROUND: Hypertension is the most prevalent and potentially modifiable risk factor for atrial fibrillation (AF). In a previous secondary prevention study, the authors observed that the angiotensin II receptor blocker telmisartan was more effective than the calcium channel blocker amlodipine in preventing AF relapse in hypertensive patients with normal atrial size.

HYPOTHESIS: Telmisartan may be more effective than amlodipine in preventing AF recurrence in hypertensive patients with paroxysmal AF and normal or increased left atrial dimension (LAD).

METHODS: The authors assigned 378 mild hypertensive outpatients in sinus rhythm, but with >=2 episodes of AF in the previous 6 months, to 1 of 2 groups. Group 1 comprised patients with LAD <40 mm in females and <45 mm in males. Group 2 comprised patients with LAD >40 mm and <45 mm in females and >45 mm and <50 mm in males. In both groups, patients were randomly treated with telmisartan or amlodipine for 1 year.

RESULTS: Systolic and diastolic blood pressure were similarly reduced by telmisartan and amlodipine in both groups. The AF recurrence rate was significantly lower in the telmisartan-treated patients than in the amlodipine-treated patients in both group 1 (12 vs 39, $P < 0.01$) and group 2 (40 vs 59, $P < 0.05$). Under telmisartan, the AF recurrence rate was significantly lower in group 1 than in group 2 (12.9% vs 42.1%, $P < 0.05$). Time to a

first AF relapse was significantly longer with telmisartan than with amlodipine in both group 1 (176 +/- 94 days vs 74 +/- 61 days, P < 0.05) and group 2 (119 +/- 65 days vs 38 +/- 35 days, P < 0.05).

CONCLUSIONS: Telmisartan was more effective than amlodipine in preventing AF recurrences in hypertensive patients with paroxysmal AF. 2012 Wiley Periodicals, Inc.

Muramatsu, T., K. Matsushita, et al. (2012). "Comparison between valsartan and amlodipine regarding cardiovascular morbidity and mortality in hypertensive patients with glucose intolerance: NAGOYA HEART Study." Hypertension **59**(3): 580-586.

It has not been fully examined whether angiotensin II receptor blocker is superior to calcium channel blocker to reduce cardiovascular events in hypertensive patients with glucose intolerance. A prospective, open-labeled, randomized, controlled trial was conducted for Japanese hypertensive patients with type 2 diabetes mellitus or impaired glucose tolerance. A total of 1150 patients (women: 34%; mean age: 63 years; diabetes mellitus: 82%) were randomly assigned to receive either valsartan- or amlodipine-based antihypertensive treatment. Primary outcome was a composite of acute myocardial infarction, stroke, coronary revascularization, admission attributed to heart failure, or sudden cardiac death. Blood pressure was 145/82 and 144/81 mm Hg, and glycosylated hemoglobin was 7.0% and 6.9% at baseline in the valsartan group and the amlodipine group, respectively. Both of them were equally controlled between the 2 groups during the study. The median follow-up period was 3.2 years, and primary outcome had occurred in 54 patients in the valsartan group and 56 in the amlodipine group (hazard ratio: 0.97 [95% CI: 0.66-1.40]; P=0.85). Patients in the valsartan group had a significantly lower incidence of heart failure than in the amlodipine group (hazard ratio: 0.20 [95% CI: 0.06-0.69]; P=0.01). Other components and all-cause mortality were not significantly different between the 2 groups. Composite cardiovascular outcomes were comparable between the valsartan- and amlodipine-based treatments in Japanese hypertensive patients with glucose intolerance. Admission because of heart failure was significantly less in the valsartan group.

Yamashita, T., H. Inoue, et al. (2011). "Randomized trial of angiotensin II-receptor blocker vs. dihydropiridine calcium channel blocker in the treatment of paroxysmal atrial fibrillation with hypertension (J-RHYTHM II study)." Europace **13**(4): 473-479.

AIMS: Atrial fibrillation (AF) is a common arrhythmia frequently associated with hypertension. This study was designed to test the hypothesis that lowering blood pressure by angiotensin II-receptor blockers (ARB) has more beneficial effects than by conventional calcium channel blockers (CCB) on the frequency of paroxysmal AF with hypertension.

METHODS AND RESULTS: The Japanese Rhythm Management Trial II for Atrial Fibrillation (J-RHYTHM II study) is an open-label randomized comparison between an ARB (candesartan) and a CCB (amlodipine) in the treatment of paroxysmal AF associated with hypertension. Using daily transtelephonic monitoring, we examined asymptomatic and symptomatic paroxysmal AF episodes during a maximum 1 year treatment. The primary endpoint was the difference in AF frequency between the pre-treatment period and the final month of the follow-up. The secondary endpoints included cardiovascular events, development of persistent AF, left atrial dimension, and quality-of-life (QOL). The study enrolled 318 patients (66 years, male/female 219/99, 158 in the ARB group and 160 in the CCB group) treated at 48 sites throughout Japan. At baseline, the frequency of AF episodes (days/month) was 3.8 +/- 5.0 in the ARB group vs. 4.8 +/- 6.3 in the CCB group

(not significant). During the follow-up, blood pressure was significantly lower in the CCB group than in the ARB group ($P < 0.001$). The AF frequency decreased similarly in both groups, and there was no significant difference in the primary endpoint between the two groups. There were no significant differences between the two groups in the development of persistent AF, changes in left atrial dimension, occurrence of cardiovascular events, or changes in QOL.

CONCLUSIONS: In patients with paroxysmal AF and hypertension, treatment of hypertension by candesartan did not have an advantage over amlodipine in the reduction in the frequency of paroxysmal AF (umin CTR C000000427).

Subanalyses from previously included/identified trials

Bakris, G., A. Briasoulis, et al. (2013). "Comparison of benazepril plus amlodipine or hydrochlorothiazide in high-risk patients with hypertension and coronary artery disease." American Journal of Cardiology **112**(2): 255-259.

Combination therapy with benazepril 40 mg and amlodipine 10 mg (B+A) has been shown to be more effective than benazepril 40 mg and hydrochlorothiazide (HCTZ) 25 mg (B+H) in reducing cardiovascular (CV) events in high-risk patients with stage 2 hypertension with similar blood pressure reductions. In the present post hoc analysis, we evaluated whether B+A is more effective than B+H for reducing CV events in patients with known coronary artery disease (CAD) at baseline in a subgroup analysis of the Avoiding Cardiovascular events through COMbination therapy in Patients LIving with Systolic Hypertension (ACCOMPLISH) study. The main trial randomized 11,506 patients. Of those, 5,744 received B+A and 5,762 received B+H. Of the 11,506 patients, 5,314 (46%) were classified as having CAD at baseline. The mean patient follow-up period was 35.7 months for the B+A group and 35.6 months for the B+H group. The primary end point was the interval to the first event of composite CV morbidity and mortality. At baseline, significant differences were present between the 5,314 with CAD and the 6,192 without CAD. The patients with CAD had a lower systolic blood pressure and heart rate, a lower incidence of diabetes, and greater incidence of dyslipidemia. However, no baseline differences were found between the randomized B+A and B+H groups. In the patients with CAD, an 18% reduction occurred in the hazard ratio for CV events (primary end point) with B+A versus B+H (p= 0.0016). In a prespecified secondary analysis of the composite end point, including only CV death, myocardial infarction, and stroke, the hazard ratio in the patients with CAD was reduced by 25% (p= 0.0033) in the B+A group compared with the B+H group. B+A was more effective than B+H at comparable blood pressure reductions for reducing CV events in patients, regardless of the presence of CAD. In conclusion, our findings suggest that the combination of B+A should be preferentially used for older patients with high-risk, stage 2 hypertension. Copyright 2013 Elsevier Inc. All rights reserved.

Bakris, G. L., P. A. Sarafidis, et al. (2010). "Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomised controlled trial." Lancet **375**(9721): 1173-1181.

BACKGROUND: The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial showed that initial antihypertensive therapy with benazepril plus amlodipine was superior to benazepril plus hydrochlorothiazide in reducing cardiovascular morbidity and mortality. We assessed the effects of these drug combinations on progression of chronic kidney disease.

METHODS: ACCOMPLISH was a double-blind, randomised trial undertaken in five countries (USA, Sweden, Norway, Denmark, and Finland). 11 506 patients with hypertension who were at high risk for cardiovascular events were randomly assigned via a central, telephone-based interactive voice response system in a 1:1 ratio to receive benazepril (20 mg) plus amlodipine (5 mg; n=5744) or benazepril (20 mg) plus hydrochlorothiazide (12.5 mg; n=5762), orally once daily. Drug doses were force-titrated for patients to attain recommended blood pressure goals. Progression of chronic kidney disease, a prespecified

endpoint, was defined as doubling of serum creatinine concentration or end-stage renal disease (estimated glomerular filtration rate <15 mL/min/1.73 m(2) or need for dialysis). Analysis was by intention to treat (ITT). This trial is registered with ClinicalTrials.gov, number NCT00170950.

FINDINGS: The trial was terminated early (mean follow-up 2.9 years [SD 0.4]) because of superior efficacy of benazepril plus amlodipine compared with benazepril plus hydrochlorothiazide. At trial completion, vital status was not known for 143 (1%) patients who were lost to follow-up (benazepril plus amlodipine, n=70; benazepril plus hydrochlorothiazide, n=73). All randomised patients were included in the ITT analysis. There were 113 (2.0%) events of chronic kidney disease progression in the benazepril plus amlodipine group compared with 215 (3.7%) in the benazepril plus hydrochlorothiazide group (HR 0.52, 0.41-0.65, p<0.0001). The most frequent adverse event in patients with chronic kidney disease was peripheral oedema (benazepril plus amlodipine, 189 of 561, 33.7%; benazepril plus hydrochlorothiazide, 85 of 532, 16.0%). In patients with chronic kidney disease, angio-oedema was more frequent in the benazepril plus amlodipine group than in the benazepril plus hydrochlorothiazide group. In patients without chronic kidney disease, dizziness, hypokalaemia, and hypotension were more frequent in the benazepril plus hydrochlorothiazide group than in the benazepril plus amlodipine group.

INTERPRETATION: Initial antihypertensive treatment with benazepril plus amlodipine should be considered in preference to benazepril plus hydrochlorothiazide since it slows progression of nephropathy to a greater extent.

FUNDING: Novartis.

Collier, D. J., N. R. Poulter, et al. (2011). "Impact of amlodipine-based therapy among older and younger patients in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA)." Journal of Hypertension **29**(3): 583-591.

OBJECTIVES: Older patients experience higher rates of cardiovascular disease than younger patients, but studies have suggested that relative risk reductions due to antihypertensive therapy are lower in older than younger patients. The Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) allowed an evaluation of the efficacy and safety of an amlodipine versus an atenolol-based antihypertensive regimen among older (>= 65 years) and younger (<65 years) patients.

METHODS: In ASCOT-BPLA 19 257 patients (8137 aged >= 65 years and 11 020 <65 years) were randomly assigned to receive amlodipine or atenolol-based antihypertensive therapy. The primary endpoint (nonfatal myocardial infarction and fatal coronary heart disease) and seven secondary endpoints were consistent with the original trial design.

RESULTS: All cardiovascular endpoints evaluated favoured the amlodipine-based regimen, significantly so in seven of the 16 age-stratified endpoints. Compared with the atenolol-based regimen, the amlodipine-based regimen reduced the relative risk of cardiovascular events by 17% in older and 15% in younger patients (P < 0.01). Overall, older patients experienced more cardiovascular events [n = 1625 (20%)] than younger patients [n = 1339 (12%)]. Discontinuations due to serious adverse events were low in both age groups and less frequent in the amlodipine-based versus atenolol-based regimen: 0.6 versus 1.1% among older patients and 0.4 versus 0.8% among younger patients.

CONCLUSIONS: The amlodipine-based regimen reduced the relative risk of cardiovascular events more effectively than the atenolol-based regimen in both older and younger patients. However, because event rates were higher among older patients, the absolute benefits were greater for older compared with younger patients.

Cushman, W. C., B. R. Davis, et al. (2012). "Mortality and morbidity during and after the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial." Journal of Clinical Hypertension **14**(1): 20-31.

A randomized, double-blind, active-controlled, multicenter trial assigned 32,804 participants aged 55 years and older with hypertension and >= 1 other coronary heart disease risk factors to receive chlorthalidone (n=15,002), amlodipine (n=8898), or lisinopril (n=8904) for 4 to 8 years, when double-blinded therapy was discontinued. Passive surveillance continued for a total follow-up of 8 to 13 years using national administrative databases to ascertain deaths and hospitalizations. During the post-trial period, fatal outcomes and nonfatal outcomes were available for 98% and 65% of participants, respectively, due to lack of access to administrative databases for the remainder. This paper assesses whether mortality and morbidity differences persisted or new differences developed during the extended follow-up. Primary outcome was cardiovascular mortality and secondary outcomes were mortality, stroke, coronary heart disease, heart failure, cardiovascular disease, and end-stage renal disease. For the post-trial period, data are not available on medications or blood pressure levels. No significant differences (P<.05) appeared in cardiovascular mortality for amlodipine (hazard ratio [HR], 1.00; 95% confidence interval [CI], 0.93-1.06) or lisinopril (HR, 0.97; CI, 0.90-1.03), each compared with chlorthalidone. The only significant differences in secondary outcomes were for heart failure, which was higher with amlodipine (HR, 1.12; CI, 1.02-1.22), and stroke mortality, which was higher with lisinopril (HR, 1.20; CI, 1.01-1.41), each compared with chlorthalidone. Similar to the previously reported in-trial result, there was a significant treatment-by-race interaction for cardiovascular disease for lisinopril vs chlorthalidone. Black participants had higher risk than non-black participants taking lisinopril compared with chlorthalidone. After accounting for multiple comparisons, none of these results were significant. These findings suggest that neither calcium channel blockers nor angiotensin-converting enzyme inhibitors are superior to diuretics for the long-term prevention of major cardiovascular complications of hypertension. 2011 Wiley Periodicals, Inc.

Elliott, H. L., S. M. Lloyd, et al. (2011). "Improving blood pressure control in patients with diabetes mellitus and high cardiovascular risk." International Journal Of Hypertension **2010**: 490769.

Patients with diabetes mellitus and symptomatic coronary artery disease are also likely to be hypertensive and, overall, are at very high cardiovascular (CV) risk. This paper reports the findings of a posthoc analysis of the 1113 patients with diabetes mellitus in the ACTION trial: ACTION itself showed that outcomes in patients with stable angina and hypertension were significantly improved when a long-acting calcium channel blocking drug (nifedipine GITS) was added to their treatment regimens. This further analysis of the ACTION database in those patients with diabetes has identified a number of practical therapeutic issues which are still relevant because of potential outcome benefits, particularly in relation to BP control. For example, despite background CV treatment and, specifically, despite the widespread use of ACE Inhibitor drugs, the addition of nifedipine

GITS was associated with significant benefits: improvement in BP control by an average of 6/3mmHg and significant improvements in outcome. In summary, this retrospective analysis has identified that the addition of nifedipine GITS resulted in improved BP control and significant outcome benefits in patients with diabetes who were at high CV risk. There is evidence to suggest that these findings are of direct relevance to current therapeutic practice.

Elliott, H. L. and P. A. Meredith (2011). "Preferential benefits of nifedipine GITS in systolic hypertension and in combination with RAS blockade: further analysis of the 'ACTION' database in patients with angina." Journal of Human Hypertension **25**(1): 63-70.

A retrospective analysis of the database from A Coronary Disease Trial Investigating Outcome with Nifedipine (ACTION) evaluated the effectiveness of nifedipine gastrointestinal therapeutic system (GITS) (i) in combination with renin angiotensin system (RAS) blockers and (ii) in patients with isolated systolic hypertension (ISH). Analysed on an intention-to-treat basis, treatment groups were compared by the log-rank test without adjustment for covariates and hazard ratios with 95% CIs were obtained using Cox proportional hazards models. Of 7665 randomized patients, 1732 patients were receiving RAS blockade at baseline, the addition of nifedipine GITS significantly reduced any cardiovascular (CV) event (-20%; P<0.05), the composite of death, any CV event and revascularization (-16%; P<0.05) and coronary angiography (-22%; P<0.01). These benefits were achieved with relatively small differences in systolic (3.2mmHg) and diastolic blood pressure (BP) (2.3mmHg). In 2303 patients (30.0%) who had ISH at baseline (1145 nifedipine GITS and 1158 placebo), nifedipine significantly reduced the primary efficacy end point (-18%; P<0.03), any CV event (-22%; P<0.01) and new heart failure (-40%; P<0.01). The benefits were associated with between-group differences in achieved BP of 4.7 and 3.3mmHg for systolic and diastolic BP, respectively. In summary, the lowest CV event rates were seen in those receiving (i) the combination of RAS blockade and nifedipine GITS and (ii) in those specifically treated for ISH.

Narumi, H., H. Takano, et al. (2011). "Effects of valsartan and amlodipine on cardiorenal protection in Japanese hypertensive patients: the Valsartan Amlodipine Randomized Trial.[Erratum appears in Hypertens Res. 2011 Jan;34(1):152]." Hypertension Research - Clinical & Experimental **34**(1): 62-69.

The Valsartan Amlodipine Randomized Trial, a multicenter, prospective, randomized, open-labeled, blinded-end point trial, was designed to compare the beneficial effects of the angiotensin II receptor blocker valsartan and the calcium channel blocker amlodipine on cardiovascular events in Japanese essential hypertensive patients. The primary end point was a composite of all-cause death, sudden death, cerebrovascular death, cardiac events, vascular events and renal events. The secondary endpoints were effects on left ventricular hypertrophy, cardiac sympathetic nerve activity and renal function. A total of 1021 patients were enrolled in the present trial. The mean follow-up period was 3.4 years. There were no significant differences in blood pressure (BP) levels between the valsartan group and the amlodipine group throughout the trial. There was no significant difference in the primary endpoint between the two groups (hazard ratio: 1.0, P = 0.843). No difference in any event category of the primary endpoint was noted for either group. However, we observed a significant reduction of left ventricular mass index, as determined by echocardiography, in the valsartan group compared with the amlodipine

group. We also observed a significant decrease in cardiac sympathetic nerve activity in the valsartan group but not in the amlodipine group. Moreover, there was a significant reduction in the urinary albumin to creatinine ratio in the valsartan group but not in the amlodipine group. Therefore, although BP levels were well controlled and remained equal in the two groups, valsartan had more protective effects on the heart and kidney than amlodipine in Japanese hypertensive patients.

Ogihara, T., K. Ueshima, et al. (2011). "Long-term effects of candesartan and amlodipine on cardiovascular morbidity and mortality in Japanese high-risk hypertensive patients: the Candesartan Antihypertensive Survival Evaluation in Japan Extension Study (CASE-J Ex)." Hypertension Research - Clinical & Experimental **34**(12): 1295-1301.

In the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial, comparable efficacy was noted between candesartan and amlodipine in the incidence of cardiovascular (CV) morbidity and mortality during 3.2 years of follow up. Candesartan suppressed new-onset diabetes more effectively than amlodipine. In this observational study, we investigated whether or not the efficacy of the two drugs is sustainable for another 3 years beyond the experimental period of the CASE-J trial. Of the 4728 high-risk hypertensive patients initially enrolled in the CASE-J trial, 2232 agreed to further follow up. The primary endpoint was a composite of CV morbidity and mortality. The distribution of demographic characteristics for the 2232 patients in the CASE-J extension was similar to that in the initial 4703 patients in the CASE-J trial. Both drugs controlled blood pressure well over the relatively long period of time. The incidence of CV events was 15.5/1000 patient years in the candesartan group and 16.3/1000 patient years in the amlodipine group (Hazard ratio (HR)=0.95, 95% confidence interval (CI)=0.77-1.18; P=0.650). The incidence of new-onset diabetes was significantly lower in the candesartan group (9.5/1000 patient years) than in the amlodipine group (13.3/1000 patient years), representing a 29% risk reduction for new-onset diabetes (HR=0.71, 95% CI=0.51-1.00, P=0.0495). In conclusion, candesartan and amlodipine showed comparable efficacy against CV events beyond the experimental period of the CASE-J trial in high-risk hypertensive patients. In addition, the effects of candesartan on new-onset diabetes observed during the CASE-J trial were sustained in the CASE-J extension. The CASE-J extension, which covered a 3-year extension of follow-up from the original trial, corroborated the results of the CASE-J trial.

Oparil, S., B. R. Davis, et al. (2013). "Mortality and morbidity during and after Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial: results by sex." Hypertension **61**(5): 977-986.

To determine whether an angiotensin-converting enzyme inhibitor (lisinopril) or calcium channel blocker (amlodipine) is superior to a diuretic (chlorthalidone) in reducing cardiovascular disease incidence in sex subgroups, we carried out a prespecified subgroup analysis of 15 638 women and 17 719 men in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Total follow-up (active treatment + passive surveillance using national administrative databases to ascertain deaths and hospitalizations) was 8 to 13 years. The primary outcome was fatal coronary heart disease or nonfatal myocardial infarction. Secondary outcomes included all-cause mortality, stroke, combined cardiovascular disease (coronary heart disease death, nonfatal myocardial infarction, stroke, angina, coronary revascularization, heart failure [HF], or peripheral vascular disease), and end-stage renal disease. In-trial rates of HF, stroke, and combined cardiovascular disease were significantly higher for lisinopril compared with

chlorthalidone, and rates of HF were significantly higher for amlodipine compared with chlorthalidone in both men and women. There were no significant treatment sex interactions. These findings did not persist through the extension period with the exception of the HF result for amlodipine versus chlorthalidone, which did not differ significantly by sex. For both women and men, rates were not lower in the amlodipine or lisinopril groups than in the chlorthalidone group for either the primary coronary heart disease outcome or any other cardiovascular disease outcome, and chlorthalidone-based treatment resulted in the lowest risk of HF. Neither lisinopril nor amlodipine is superior to chlorthalidone for initial treatment of hypertension in either women or men. Clinical Trial Registration- clinicaltrials.gov; Identifier: NCT00000542.

Rahman, M., C. E. Ford, et al. (2012). "Long-term renal and cardiovascular outcomes in Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) participants by baseline estimated GFR." Clinical Journal of The American Society of Nephrology: CJASN **7**(6): 989-1002.

BACKGROUND AND OBJECTIVES: CKD is common among older patients. This article assesses long-term renal and cardiovascular outcomes in older high-risk hypertensive patients, stratified by baseline estimated GFR (eGFR), and long-term outcome efficacy of 5-year first-step treatment with amlodipine or lisinopril, each compared with chlorthalidone.

DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS: This was a long-term post-trial follow-up of hypertensive participants (n=31,350), aged >=55 years, randomized to receive chlorthalidone, amlodipine, or lisinopril for 4-8 years at 593 centers. Participants were stratified by baseline eGFR (ml/min per 1.73 m(2)) as follows: normal/increased (>=90; n=8027), mild reduction (60-89; n=17,778), and moderate/severe reduction (<60; n=5545). Outcomes were cardiovascular mortality (primary outcome), total mortality, coronary heart disease, cardiovascular disease, stroke, heart failure, and ESRD.

RESULTS: After an average 8.8-year follow-up, total mortality was significantly higher in participants with moderate/severe eGFR reduction compared with those with normal and mildly reduced eGFR (P<0.001). In participants with an eGFR <60, there was no significant difference in cardiovascular mortality between chlorthalidone and amlodipine (P=0.64), or chlorthalidone and lisinopril (P=0.56). Likewise, no significant differences were observed for total mortality, coronary heart disease, cardiovascular disease, stroke, or ESRD.

CONCLUSIONS: CKD is associated with significantly higher long-term risk of cardiovascular events and mortality in older hypertensive patients. By eGFR stratum, 5-year treatment with amlodipine or lisinopril was not superior to chlorthalidone in preventing cardiovascular events, mortality, or ESRD during 9-year follow-up. Because data on proteinuria were not available, these findings may not be extrapolated to proteinuric CKD.

Ruggenenti, P., A. Fassi, et al. (2011). "Effects of verapamil added-on trandolapril therapy in hypertensive type 2 diabetes patients with microalbuminuria: the BENEDICT-B randomized trial." Journal of Hypertension **29**(2): 207-216.

OBJECTIVES: To address whether nondihydropyridine calcium-channel blocker added-on angiotensin-converting-enzyme inhibitor therapy ameliorates albuminuria and cardiovascular outcomes in type 2 diabetes patients.

DESIGN: The Bergamo Nephrologic Diabetes Complications Trial-B was a multicentre, prospective, double-blind, parallel-group trial comparing renal and cardiovascular outcomes in 281 hypertensive type 2 diabetes patients with microalbuminuria randomized to at least 2-year VeraTran (verapamil/trandolapril 180 mg/2 mg daily) or trandolapril (2 mg daily, identical image) treatment. Main outcome was persistent macroalbuminuria (albuminuria >200 g/min in two consecutive visits). Treatment targets were SBP/DBP less than 120/80 mmHg and HbA1C less than 7%.

RESULTS: Over a median follow-up of 4.5 years, 18 patients (13%) on VeraTran vs. 15 (10.5%) on trandolapril [unadjusted hazard ratio (95% confidence interval [CI]) 1.07 (0.54-2.12), P = 0.852] progressed to macroalbuminuria, respectively; 62 (44.9%) vs. 71 (49.7%) [0.80 (0.57-1.12), P = 0.198] regressed to normoalbuminuria (urinary albumin excretion <20 g/min), and 20 (14.5%) vs. 21 (14.7%) [hazard ratio 0.93 (0.50-1.72), P = 0.816] had major cardiovascular events. BP and metabolic control were similar between groups. Patients with cardiovascular events were significantly less [13 (9.8%) vs. 28 (18.9%), hazard ratio: 0.37 (0.19-0.71), P = 0.003] among those regressing to normoalbuminuria than those without regression. Difference was independent of treatment allocation and was significant also after adjusting for baseline characteristics [0.40 (0.20-0.79), P = 0.009], follow-up SBP [0.40 (0.20-0.80), P = 0.010] or DBP [0.36 (0.18-0.73), P = 0.004] BP or HbA1C [0.43 (0.21-0.88), P = 0.021].

CONCLUSION: In hypertensive type 2 diabetes patients with microalbuminuria, verapamil added-on trandolapril did not improve renal or cardiovascular outcomes. Independent of verapamil, trandolapril normalized albuminuria in half of patients and this translated into significant cardioprotection.

Takano, H., H. Hasegawa, et al. (2012). "Effects of valsartan and amlodipine on home blood pressure and cardiovascular events in Japanese hypertensive patients: a subanalysis of the VART." Journal of Human Hypertension **26**(11): 656-663.

The Valsartan Amlodipine Randomized Trial (VART) was performed to compare the beneficial effects of valsartan and amlodipine on cardiovascular events in Japanese hypertensive patients. In this subanalysis of the VART, we assessed the relationship between home blood pressure (HBP) levels and cardiovascular events in the enrolled patients. We enrolled 1021 patients with mild-to-moderate hypertension in the VART. The participants were allocated randomly to either the valsartan group or the amlodipine group. The primary end point was a composite of all-cause death, sudden death, cerebrovascular events, cardiac events, vascular events and renal events. A total of 621 patients (valsartan group: 305 and amlodipine group: 316) completed the measurements of HBP (morning and evening) throughout the trial. Both the agents evenly and significantly lowered morning HBP and evening HBP throughout the trial. There was no significant difference in the primary end point between the two groups. However, we observed significant decreases in the left ventricular mass index and urinary albumin to creatinine ratio in the valsartan group but not in the amlodipine group. There were no significant differences in HBP levels and the main outcome of the cardiovascular events between the valsartan and amlodipine groups. However, in the valsartan group, significant improvements in left ventricular hypertrophy and microalbuminuria were observed.

Weber, M. A., G. L. Bakris, et al. (2010). "Cardiovascular events during differing hypertension therapies in patients with diabetes." Journal of the American College of Cardiology **56**(1): 77-85.

OBJECTIVES: The aim of this study was to determine which combination therapy in patients with hypertension and diabetes most effectively decreases cardiovascular events.

BACKGROUND: The ACCOMPLISH (Avoiding Cardiovascular Events Through COMbination Therapy in Patients Living With Systolic Hypertension) trial compared the outcomes effects of a renin-angiotensin system blocker, benazepril, combined with amlodipine (B+A) or hydrochlorothiazide (B+H). A separate analysis in diabetic patients was pre-specified.

METHODS: A total of 6,946 patients with diabetes were randomized to treatment with B+A or B+H. A subgroup of 2,842 diabetic patients at very high risk (previous cardiovascular or stroke events) was also analyzed, as were 4,559 patients without diabetes. The primary end point was a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for angina, resuscitated arrest, and coronary revascularization.

RESULTS: In the full diabetes group, the mean achieved blood pressures in the B+A and B+H groups were 131.5/72.6 and 132.7/73.7 mm Hg; during 30 months, there were 307 (8.8%) and 383 (11.0%) primary events (hazard ratio [HR]: 0.79, 95% confidence interval [CI]: 0.68 to 0.92, p = 0.003). For the diabetic patients at very high risk, there were 195 (13.6%) and 244 (17.3%) primary events (HR: 0.77, 95% CI: 0.64 to 0.93, p = 0.007). In the nondiabetic patients, there were 245 (10.8%) and 296 (12.9%) primary events (HR: 0.82, 95% CI: 0.69 to 0.97, p = 0.020). In the diabetic patients, there were clear coronary benefits with B+A, including both acute clinical events (p = 0.013) and revascularizations (p = 0.024). There were no unexpected adverse events.

CONCLUSIONS: In patients with diabetes and hypertension, combining a renin-angiotensin system blocker with amlodipine, compared with hydrochlorothiazide, was superior in reducing cardiovascular events and could influence future management of hypertension in patients with diabetes. (Avoiding Cardiovascular Events Through COMbination Therapy in Patients Living With Systolic Hypertension [ACCOMPLISH]; NCT00170950). Copyright (c) 2010 American College of Cardiology Foundation. Published by Elsevier Inc. All rights reserved.

Weber, M. A., K. Jamerson, et al. (2013). "Effects of body size and hypertension treatments on cardiovascular event rates: subanalysis of the ACCOMPLISH randomised controlled trial." Lancet **381**(9866): 537-545.

BACKGROUND: In previous clinical trials in high-risk hypertensive patients, paradoxically higher cardiovascular event rates have been reported in patients of normal weight compared with obese individuals. As a prespecified analysis of the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, we aimed to investigate whether the type of hypertension treatment affects patients' cardiovascular outcomes according to their body size.

METHODS: On the basis of body-mass index (BMI), we divided the full ACCOMPLISH cohort into obese (BMI >=30, n=5709), overweight (>=25 to <30, n=4157), or normal weight (<25, n=1616) categories. The ACCOMPLISH cohort had already been randomised to treatment with single-pill combinations of either benazepril and hydrochlorothiazide or benazepril and amlodipine. We compared event rates (adjusted for age, sex, diabetes, previous cardiovascular events, stroke, or chronic kidney disease) for the primary

endpoint of cardiovascular death or non-fatal myocardial infarction or stroke. The analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00170950.

FINDINGS: In patients allocated benazepril and hydrochlorothiazide, the primary endpoint (per 1000 patient-years) was 30.7 in normal weight, 21.9 in overweight, and 18.2 in obese patients (overall p=0.0034). However, in those allocated benazepril and amlodipine, the primary endpoint did not differ between the three BMI groups (18.2, 16.9, and 16.5, respectively; overall p=0.9721). In obese individuals, primary event rates were similar with both benazepril and hydrochlorothiazide and benazepril and amlodipine, but rates were significantly lower with benazepril and amlodipine in overweight patients (hazard ratio 0.76, 95% CI 0.59-0.94; p=0.0369) and those of normal weight (0.57, 0.39-0.84; p=0.0037).

INTERPRETATION: Hypertension in normal weight and obese patients might be mediated by different mechanisms. Thiazide-based treatment gives less cardiovascular protection in normal weight than obese patients, but amlodipine-based therapy is equally effective across BMI subgroups and thus offers superior cardiovascular protection in non-obese hypertension.

FUNDING: Novartis Pharmaceuticals.

Weir, M. R., G. L. Bakris, et al. (2012). "Renal outcomes in hypertensive Black patients at high cardiovascular risk." Kidney International **81**(6): 568-576.

The ACCOMPLISH trial (Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension) was a 3-year multicenter, event-driven trial involving patients with high cardiovascular risk who were randomized in a double-blinded manner to benazepril plus either hydrochlorothiazide or amlodipine and titrated in parallel to reach recommended blood pressure goals. Of the 8125 participants in the United States, 1414 were of self-described Black ethnicity. The composite kidney disease end point, defined as a doubling in serum creatinine, end-stage renal disease, or death was not different between Black and non-Black patients, although the Blacks were significantly more likely to develop a greater than 50% increase in serum creatinine to a level above 2.6 mg/dl. We found important early differences in the estimated glomerular filtration rate (eGFR) due to acute hemodynamic effects, indicating that benazepril plus amlodipine was more effective in stabilizing eGFR compared to benazepril plus hydrochlorothiazide in non-Blacks. There was no difference in the mean eGFR loss in Blacks between therapies. Thus, benazepril coupled to amlodipine was a more effective antihypertensive treatment than when coupled to hydrochlorothiazide in non-Black patients to reduced kidney disease progression. Blacks have a modestly higher increased risk for more advanced increases in serum creatinine than non-Blacks.

Appendix B: Abstracts from previous scans

Scan #4

Saruta, T., K. Hayashi, et al. (2009). "Effects of candesartan and amlodipine on cardiovascular events in hypertensive patients with chronic kidney disease: subanalysis of the CASE-J Study." Hypertension Research - Clinical & Experimental **32**(6): 505-12.

We examined the effects of candesartan and amlodipine on cardiovascular events in hypertensive patients with chronic kidney disease (CKD) using the data from the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial. CKD was defined as proteinuria and/or decreased GFR (<60 ml per min per 1.73 m(2)) at enrollment. Among 2720 subjects with CKD, there were 1376 and 1344 patients in the candesartan and the amlodipine group, respectively. During a 3.2-year follow-up, cardiovascular event rate did not differ in the two groups (7.2% for candesartan and 7.6% for amlodipine). In the subgroup analysis based on the CKD stage, there were no significant differences in the incidence rates of cardiovascular events between the two groups in stages 1+2 and 3 CKD. In stage 4 CKD, however, candesartan reduced the incidence of cardiovascular events (55% risk reduction), particularly of renal events (81% risk reduction), compared with amlodipine. Furthermore, composite cardiovascular events were increased as the CKD stage progressed, and this effect was exaggerated in the presence of proteinuria. Finally, the new onset of diabetes was less in the candesartan-based regimen in stage 3 CKD. In conclusion, candesartan protected hypertensive patients with CKD more potently against renal events, particularly in moderately-to-severely impaired CKD. Furthermore, candesartan prevented a new onset of diabetes in CKD, which would be favorable for the long-term management of CKD.

Scan #3

New trials

Jamerson, K., M. A. Weber, et al. (2008). "Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients.[see comment]." New England Journal of Medicine **359**(23): 2417-28.

BACKGROUND: The optimal combination drug therapy for hypertension is not established, although current U.S. guidelines recommend inclusion of a diuretic. We hypothesized that treatment with the combination of an angiotensin-converting-enzyme (ACE) inhibitor and a dihydropyridine calcium-channel blocker would be more effective in reducing the rate of cardiovascular events than treatment with an ACE inhibitor plus a thiazide diuretic. METHODS: In a randomized, double-blind trial, we assigned 11,506 patients with hypertension who were at high risk for cardiovascular events to receive treatment with either benazepril plus amlodipine or benazepril plus hydrochlorothiazide. The primary end point was the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization. RESULTS: The baseline characteristics of the two groups were similar. The trial was terminated early after a mean follow-up of 36 months, when the boundary of the prespecified stopping rule was exceeded. Mean blood pressures after dose adjustment were 131.6/73.3 mm Hg in the benazepril-amlodipine group and 132.5/74.4 mm Hg in the benazepril-hydrochlorothiazide group. There were 552 primary-outcome events in the benazepril-amlodipine group (9.6%) and 679 in the benazepril-hydrochlorothiazide group (11.8%), representing an absolute risk reduction with benazepril-amlodipine therapy of 2.2% and a relative risk reduction of 19.6% (hazard ratio, 0.80, 95% confidence interval [CI], 0.72 to 0.90; P<0.001). For the secondary end point of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke, the hazard ratio was 0.79 (95% CI, 0.67 to 0.92; P=0.002). Rates of adverse events were consistent with those observed from clinical experience with the study drugs. CONCLUSIONS: The benazepril-amlodipine combination was superior to the benazepril-hydrochlorothiazide combination in reducing cardiovascular events in patients with hypertension who were at high risk for such events. (ClinicalTrials.gov number, NCT00170950.) 2008 Massachusetts Medical Society

Nakamura, T., T. Inoue, et al. (2008). "Comparison of renal and vascular protective effects between telmisartan and amlodipine in hypertensive patients with chronic kidney disease with mild renal insufficiency." Hypertension Research - Clinical & Experimental **31**(5): 841-50.

The present study was conducted to compare the renal and vascular protective effects of telmisartan and amlodipine in untreated hypertensive chronic kidney disease (CKD) patients with moderate renal insufficiency. Thirty hypertensive CKD patients were randomly assigned to receive telmisartan 40 mg (n = 15) or amlodipine 5 mg (n = 15) once daily for 12 months. Changes in blood pressure, serum creatinine, 24-h creatinine clearance (Ccr), proteinuria, brachial-ankle pulse wave velocity (baPWV), intima-media thickness (IMT), plasma interleukin-6 (IL-6), plasma matrix metalloproteinase (MMP)-9

and lipid profiles were monitored in all patients. Before treatment, there were no significant differences in these parameters between the telmisartan and amlodipine groups. Over the 12 month observation period, blood pressure decreased equally in both groups. However, serum creatinine, proteinuria, baPWV, IMT, plasma levels of IL-6 and MMP-9 and total cholesterol decreased and 24-h Ccr increased more strikingly in the telmisartan group than the amlodipine group. These data suggest that telmisartan is more effective than amlodipine for protecting renovascular functions, and potentially for ameliorating atherosclerosis, in hypertensive CKD patients with moderate renal insufficiency.

Nakayama, K., Y. Kuwabara, et al. (2008). "Valsartan Amlodipine Randomized Trial (VART): design, methods, and preliminary results." Hypertension Research - Clinical & Experimental **31**(1): 21-8.

Antihypertensive therapy has been well established to reduce hypertension related morbidity and mortality, but the optimal therapy for Japanese patients remains unknown. The Valsartan Amlodipine Randomized Trial (VART), a prospective randomized open-label trial, was designed to determine whether treatment with an angiotensin II type 1 receptor blocker (valsartan) or a calcium channel blocker (amlodipine) lowers cardiovascular disease events in essential hypertensives in Japan. Registration, randomization and data entry were performed over the Internet. The minimization method (to control for age, gender, blood pressure level and history) was used at random assignment to ensure that the background factors were equivalent between the groups at baseline. After the registration, patients were followed-up for cardiovascular events (primary endpoints), echocardiography, (123)I-metaiodobenzylguanidine (MIBG) imaging, laboratory tests and blood pressure for 3 years. Currently, 797 patients have been enrolled and assigned to two groups: a valsartan (n=399) and an amlodipine (n=398) group. At baseline, controlled factors (age, gender, blood pressure level, and left ventricular hypertrophy) and the proportions of patients with diabetes and hyperlipidemia were equally allocated. At 12 months, both drugs evenly and significantly lowered blood pressure to the target level (valsartan: 133/79 mmHg; amlodipine: 132/79 mmHg). In conclusion, by combining the data on cardiovascular events with the results of echocardiographic, radionuclide imaging, and blood/urine studies, the VART study will provide mechanistic insights into the clinical outcomes and treatment effects of the trial.

Tepel, M., W. Hopfenmueller, et al. (2008). "Effect of amlodipine on cardiovascular events in hypertensive haemodialysis patients." Nephrology Dialysis Transplantation **23**(11): 3605-12.

BACKGROUND: Hypertensive haemodialysis patients may be at a high risk for cardiovascular events. This study was undertaken to ascertain whether the calcium channel blocker amlodipine reduces mortality and cardiovascular events in these high-risk patients. METHODS: We evaluated the effects of amlodipine on cardiovascular events in 251 hypertensive haemodialysis patients in an investigator-designed, prospective, randomized, double-blind, placebo-controlled, multicenter trial. One hundred and twenty-three patients were randomly assigned to amlodipine (10 mg once daily) and 128 to placebo. The primary endpoint was mortality from any cause. The secondary endpoint was a composite variable consisting of mortality from any cause or cardiovascular event. Analysis was by intention-to-treat. The trial was registered with

ClinicalTrials.gov (number NCT00124969). RESULTS: The median age of patients was 61 years (25% percentile - 75% percentile, 47-69), and the median follow-up was 19 months (8-30). Fifteen (12%) of the 123 patients assigned to amlodipine and 22 (17%) of the 128 patients assigned to placebo had a primary endpoint [hazard ratio 0.65 (95% CI 0.34-1.23); P = 0.19]. Nineteen (15%) of the 123 haemodialysis patients assigned to amlodipine and 32 (25%) of the 128 haemodialysis patients assigned to placebo reached the secondary composite endpoint [hazard ratio 0.53 (95% CI 0.31-0.93); P = 0.03]. CONCLUSION: Amlodipine safely reduces systolic blood pressure and it may have a beneficial effect on cardiovascular outcomes in hypertensive haemodialysis patients.

Publications of final outcomes from previous ongoing trials

Ogihara, T., A. Fujimoto, et al. (2008). "ARB candesartan and CCB amlodipine in hypertensive patients: the CASE-J trial." Expert Review of Cardiovascular Therapy **6**(9): 1195-201.

The Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial was a comparative study of the angiotensin II receptor blocker (ARB), candesartan, and a calcium channel blocker (CCB), amlodipine, regarding the incidence of cardiovascular events in high-risk Japanese hypertensive patients. The study design was a prospective, multicenter, randomized, open-label, active-controlled, two-arm, parallel-group comparison study with a response-dependent dose titration and blinded assessment of the end point. The CASE-J trial enrolled 4728 patients, with a mean age of 63.8 years and a mean BMI of 24.6 kg/m(2), who were randomly assigned to either candesartan- or amlodipine-based treatment regimens. Blood pressure was well controlled to the level of less than 140/80 mmHg in both of the treatment regimens. During 3.2 years of follow-up, primary cardiovascular events occurred in 134 patients in each of the two treatment-based regimens, resulting in no significant difference in the incidence of cardiovascular events between them (hazard ratio: 1.01; 95% confidence interval: 0.79-1.28; p = 0.969). In 404 patients with left ventricular hypertrophy, a significantly larger decrease in left ventricular mass index 3 years after enrollment was observed in candesartan-based (n = 205) than amlodipine-based (n = 199) regimens (-22.9 vs -13.4 g/m(2), respectively; p = 0.023). Furthermore, new-onset diabetes occurred in fewer patients taking candesartan than in those taking amlodipine, resulting in a 36% relative risk reduction (p = 0.030). The CASE-J trial demonstrated that both an ARB, candesartan, and a CCB, amlodipine, equally suppressed the incidence of cardiovascular events. The ARB may confer more beneficial effects to hypertensive patients with left ventricular hypertrophy or for those at-risk of diabetes than CCB.

Ogihara, T., K. Nakao, et al. (2008). "Effects of candesartan compared with amlodipine in hypertensive patients with high cardiovascular risks: candesartan antihypertensive survival evaluation in Japan trial." Hypertension **51**(2): 393-8.

The Candesartan Antihypertensive Survival Evaluation in Japan Trial was designed to compare the long-term effects of the angiotensin II receptor blocker candesartan and the calcium channel blocker amlodipine on the incidence of cardiovascular events, represented as a composite of sudden death and cerebrovascular, cardiac, renal, and vascular events in high-risk Japanese hypertensive patients. We conducted a prospective, randomized, open-label study with blinded assessment of the end point in 4728 Japanese hypertensive patients (mean age: 63.8 years; mean body mass index: 24.6 kg/m(2)). Patients were followed for an average of 3.2 years. Blood pressure was well controlled with both treatment-based regimens (systolic blood pressure/diastolic blood pressure: 136.1/77.3 mm Hg for candesartan-based regimens and 134.4/76.7 mm Hg for amlodipine-based regimens after 3 years). Primary cardiovascular events occurred in 134 patients with both the candesartan- and amlodipine-based regimens. The 2 treatment-based regimens produced no significant differences in cardiovascular morbidity or mortality in the high-risk Japanese hypertensive patients (hazard ratio: 1.01; 95% CI: 0.79 to 1.28; P=0.969). In each primary end point category, there was no significant difference between the 2 treatment-based regimens. New-onset diabetes occurred in

fewer patients taking candesartan (8.7/1000 person-years) than in those taking amlodipine (13.6/1000 person-years), which resulted in a 36% relative risk reduction (hazard ratio: 0.64; 95% CI: 0.43 to 0.97; P=0.033). We disclosed that candesartan-based and amlodipine-based regimens produced no statistical differences in terms of the primary cardiovascular end point, whereas candesartan prevented new-onset diabetes more effectively than amlodipine.

Ostergren, J., N. R. Poulter, et al. (2008). "The Anglo-Scandinavian Cardiac Outcomes Trial: blood pressure-lowering limb: effects in patients with type II diabetes." Journal of Hypertension **26**(11): 2103-11.

OBJECTIVE: To compare the effects of two antihypertensive treatment strategies for the prevention of coronary heart disease and other cardiovascular events in the large subpopulation (n=5137) with diabetes mellitus in the blood pressure-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial. METHODS: Patients had either untreated hypertension or treated hypertension. For those with type II diabetes mellitus, inclusion criteria required at least two additional risk factors. Patients were randomized to amlodipine with addition of perindopril as required (amlodipine-based) or atenolol with addition of thiazide as required (atenolol-based). Therapy was titrated to achieve a target blood pressure of less than 130/80 mmHg. RESULTS: The trial was terminated early due to significant benefits on mortality and stroke associated with the amlodipine-based regimen. In patients with diabetes mellitus, the amlodipine-based treatment reduced the incidence of the composite endpoint--total cardiovascular events and procedures--compared with the atenolol-based regimen (hazard ratio 0.86, confidence interval 0.76-0.98, P=0.026). Fatal and nonfatal strokes were reduced by 25% (P=0.017), peripheral arterial disease by 48% (P=0.004) and noncoronary revascularization procedures by 57% (P<0.001). For the other endpoints included in the composite, the endpoint differences were less clear including coronary heart disease deaths and nonfatal myocardial infarctions (the primary endpoint), which were reduced nonsignificantly by 8% (hazard ratio 0.92, confidence interval 0.74-1.15). CONCLUSION: In the large diabetic subgroup in the blood pressure-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial, the benefits of amlodipine-based treatment, compared with atenolol-based treatment, on the incidence of total cardiovascular events and procedures was significant (14% reduction) and similar to that observed in the total trial population (16% reduction).

New subgroup analyses from previously included trials

Bangalore, S., F. H. Messerli, et al. (2008). "Verapamil-sustained release-based treatment strategy is equivalent to atenolol-based treatment strategy at reducing cardiovascular events in patients with prior myocardial infarction: an INternational VErapamil SR-Trandolapril (INVEST) substudy." American Heart Journal **156**(2): 241-7.

BACKGROUND: In patients with prior myocardial infarction (MI), beta-blockers reduce mortality by 23% to 40%. However, despite this favorable effect, adverse effects limit compliance to this medication. The purpose of the study was to compare a beta-blocker-based strategy with a heart rate-lowering calcium antagonists-based strategy in patients with prior MI. METHODS: We evaluated 7,218 patients with prior MI enrolled in the INternational VErapamil SR-Trandolapril (INVEST) substudy randomized to verapamil-sustained release (SR)- or atenolol-based strategies. Primary outcome was time to first occurrence of death (all-cause), nonfatal MI, or nonfatal stroke. Secondary outcomes included death, total MI (fatal and nonfatal), and total stroke (fatal and nonfatal) considered separately. RESULTS: During the 2.8 +/- 1.0 years of follow-up, patients assigned to the verapamil-SR-based and atenolol-based strategies had comparable blood pressure control, and the incidence of the primary outcome was equivalent. There was no difference between the 2 strategies for the outcomes of either death or total MI. However, more patients reported excellent/good well-being (82.3% vs 78.0%, P = .02) at 24 months with a trend toward less incidence of angina pectoris (12.0% vs 14.3%, adjusted P = .07), nonfatal stroke (1.4% vs 2.0%; P = .06), and total stroke (2.0% vs 2.5%, P = .18) in the verapamil-SR-based strategy group. CONCLUSIONS: In hypertensive patients with prior MI, a verapamil-SR-based strategy was equivalent to a beta-blocker-based strategy for blood pressure control and prevention of cardiovascular events, with greater subjective feeling of well-being and a trend toward lower incidence of angina pectoris and stroke in the verapamil-SR-based group.

Black, H. R., B. Davis, et al. (2008). "Metabolic and clinical outcomes in nondiabetic individuals with the metabolic syndrome assigned to chlorthalidone, amlodipine, or lisinopril as initial treatment for hypertension: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)." Diabetes Care **31**(2): 353-60.

OBJECTIVE: Optimal initial antihypertensive drug therapy in people with the metabolic syndrome is unknown. RESEARCH DESIGN AND METHODS: We conducted a subgroup analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) to compare metabolic, cardiovascular, and renal outcomes in individuals assigned to initial hypertension treatment with a thiazide-like diuretic (chlorthalidone), a calcium channel blocker (CCB; amlodipine), or an ACE inhibitor (lisinopril) in nondiabetic individuals with or without metabolic syndrome. RESULTS: In participants with metabolic syndrome, at 4 years of follow-up, the incidence of newly diagnosed diabetes (fasting glucose >or=126 mg/dl) was 17.1% for chlorthalidone, 16.0% for amlodipine (P = 0.49, chlorthalidone vs. amlodipine) and 12.6% for lisinopril (P < 0.05, lisinopril vs. chlorthalidone). For those without metabolic syndrome, the rate of newly diagnosed diabetes was 7.7% for chlorthalidone, 4.2% for amlodipine, and 4.7% for lisinopril (P < 0.05 for both comparisons). There were no differences in relative risks (RRs) for outcomes with amlodipine compared with chlorthalidone in those with

metabolic syndrome; in those without metabolic syndrome, there was a higher risk for heart failure (RR 1.55 [95% CI 1.25-1.35]). In comparison with lisinopril, chlorthalidone was superior in those with metabolic syndrome with respect to heart failure (1.31 [1.04-1.64]) and combined cardiovascular disease (CVD) (1.19 [1.07-1.32]). No significant treatment group-metabolic syndrome interaction was noted. CONCLUSIONS: Despite a less favorable metabolic profile, thiazide-like diuretic initial therapy for hypertension offers similar, and in some instances possibly superior, CVD outcomes in older hypertensive adults with metabolic syndrome, as compared with treatment with CCBs and ACE inhibitors.

Davis, B. R., J. B. Kostis, et al. (2008). "Heart failure with preserved and reduced left ventricular ejection fraction in the antihypertensive and lipid-lowering treatment to prevent heart attack trial.[see comment]." Circulation **118**(22): 2259-67.

BACKGROUND: Heart failure (HF) developing in hypertensive patients may occur with preserved or reduced left ventricular ejection fraction (PEF [>or=50%] or REF [<50%]). In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), 42 418 high-risk hypertensive patients were randomized to chlorthalidone, amlodipine, lisinopril, or doxazosin, providing an opportunity to compare these treatments with regard to occurrence of hospitalized HFPEF or HFREF. METHODS AND RESULTS: HF diagnostic criteria were prespecified in the ALLHAT protocol. EF estimated by contrast ventriculography, echocardiography, or radionuclide study was available in 910 of 1367 patients (66.6%) with hospitalized events meeting ALLHAT criteria. Cox regression models adjusted for baseline characteristics were used to examine treatment differences for HF (overall and by PEF and REF). HF case fatality rates were examined. Of those with EF data, 44.4% had HFPEF and 55.6% had HFREF. Chlorthalidone reduced the risk of HFPEF compared with amlodipine, lisinopril, or doxazosin; the hazard ratios were 0.69 (95% confidence interval [CI], 0.53 to 0.91; P=0.009), 0.74 (95% CI, 0.56 to 0.97; P=0.032), and 0.53 (95% CI, 0.38 to 0.73; P<0.001), respectively. Chlorthalidone reduced the risk of HFREF compared with amlodipine or doxazosin; the hazard ratios were 0.74 (95% CI, 0.59 to 0.94; P=0.013) and 0.61 (95% CI, 0.47 to 0.79; P<0.001), respectively. Chlorthalidone was similar to lisinopril with regard to incidence of HFREF (hazard ratio, 1.07; 95% CI, 0.82 to 1.40; P=0.596). After HF onset, death occurred in 29.2% of participants (chlorthalidone/amlodipine/lisinopril) with new-onset HFPEF versus 41.9% in those with HFREF (P<0.001; median follow-up, 1.74 years); and in the chlorthalidone/doxazosin comparison that was terminated early, 20.0% of HFPEF and 26.0% of HFREF patients died (P=0.185; median follow-up, 1.55 years). CONCLUSIONS: In ALLHAT, with adjudicated outcomes, chlorthalidone significantly reduced the occurrence of new-onset hospitalized HFPEF and HFREF compared with amlodipine and doxazosin. Chlorthalidone also reduced the incidence of new-onset HFPEF compared with lisinopril. Among high-risk hypertensive men and women, HFPEF has a better prognosis than HFREF.

Schmieder, R. E., S. E. Kjeldsen, et al. (2008). "Reduced incidence of new-onset atrial fibrillation with angiotensin II receptor blockade: the VALUE trial." Journal of Hypertension **26**(3): 403-11.

BACKGROUND: Atrial fibrillation (AF) is the most common arrhythmia and increases cardiovascular risk in hypertensive patients. Therefore, in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) a prespecified objective was to compare the effects of valsartan and amlodipine on new-onset AF. METHODS: A total of 15 245 hypertensive patients at high cardiovascular risk received valsartan 80-160 mg/day or amlodipine 5-10 mg/day combined with additional antihypertensive agents. Electrocardiograms were obtained every year and analyzed centrally for evidence of left ventricular hypertrophy and new-onset AF. RESULTS: At baseline, AF was diagnosed in 2.6% of 7649 valsartan recipients and 2.6% of 7596 amlodipine recipients. During antihypertensive treatment the incidence of at least one documented occurrence of new-onset AF was 3.67% with valsartan and 4.34% with amlodipine [unadjusted hazard ratio 0.843, [95% confidence interval (CI): 0.713, 0.997], P = 0.0455]. The incidence of persistent AF was 1.35% with valsartan and 1.97% with amlodipine [unadjusted hazard ratio 0.683 (95% CI: 0.525, 0.889), P = 0.0046]. CONCLUSIONS: Valsartan-based treatment reduced the development of new-onset AF, particularly sustained AF in hypertensive patients, compared with amlodipine-based therapy. These findings suggest that angiotensin II receptor blockers may result in greater benefits than calcium antagonists in hypertensive patients at risk of new-onset AF.

Wright, J. T., Jr., S. Harris-Haywood, et al. (2008). "Clinical outcomes by race in hypertensive patients with and without the metabolic syndrome: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[see comment]." Archives of Internal Medicine **168**(2): 207-17.

BACKGROUND: Antihypertensive drugs with favorable metabolic effects are advocated for first-line therapy in hypertensive patients with metabolic/cardiometabolic syndrome (MetS). We compared outcomes by race in hypertensive individuals with and without MetS treated with a thiazide-type diuretic (chlorthalidone), a calcium channel blocker (amlodipine besylate), an alpha-blocker (doxazosin mesylate), or an angiotensin-converting enzyme inhibitor (lisinopril). METHODS: A subgroup analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a randomized, double-blind hypertension treatment trial of 42 418 participants. We defined MetS as hypertension plus at least 2 of the following: fasting serum glucose level of at least 100 mg/dL, body mass index (calculated as weight in kilograms divided by height in meters squared) of at least 30, fasting triglyceride levels of at least 150 mg/dL, and high-density lipoprotein cholesterol levels of less than 40 mg/dL in men or less than 50 mg/dL in women. RESULTS: Significantly higher rates of heart failure were consistent across all treatment comparisons in those with MetS. Relative risks (RRs) were 1.50 (95% confidence interval, 1.18-1.90), 1.49 (1.17-1.90), and 1.88 (1.42-2.47) in black participants and 1.25 (1.06-1.47), 1.20 (1.01-1.41), and 1.82 (1.51-2.19) in nonblack participants for amlodipine, lisinopril, and doxazosin comparisons with chlorthalidone, respectively. Higher rates for combined cardiovascular disease were observed with lisinopril-chlorthalidone (RRs, 1.24 [1.09-1.40] and 1.10 [1.02-1.19], respectively) and doxazosin-chlorthalidone comparisons (RRs, 1.37 [1.19-

1.58] and 1.18 [1.08-1.30], respectively) in black and nonblack participants with MetS. Higher rates of stroke were seen in black participants only (RR, 1.37 [1.07-1.76] for the lisinopril-chlorthalidone comparison, and RR, 1.49 [1.09-2.03] for the doxazosin-chlorthalidone comparison). Black patients with MetS also had higher rates of end-stage renal disease (RR, 1.70 [1.13-2.55]) with lisinopril compared with chlorthalidone. CONCLUSIONS: The ALLHAT findings fail to support the preference for calcium channel blockers, alpha-blockers, or angiotensin-converting enzyme inhibitors compared with thiazide-type diuretics in patients with the MetS, despite their more favorable metabolic profiles. This was particularly true for black participants.

Yui, Y., E. Shinoda, et al. (2007). "Nifedipine retard prevents hospitalization for angina pectoris better than angiotensin-converting enzyme inhibitors in hypertensive Japanese patients with previous myocardial infarction (JMIC-B substudy)." Journal of Hypertension **25**(10): 2019-26.

OBJECTIVES AND BACKGROUND: We previously reported that nifedipine retard showed comparable efficacy to angiotensin-converting enzyme (ACE) inhibitors for the prevention of cardiac events in hypertensive patients with coronary artery disease during the Japan Multicenter Investigation for Cardiovascular Diseases B study. In the nifedipine group, patients with a history of myocardial infarction (MI) showed a significant reduction in hospitalization for angina pectoris compared with the ACE inhibitor group. We investigated whether this difference was related to the progression of coronary arteriosclerosis. METHODS: To evaluate coronary arteriosclerosis, we performed coronary angiography (CAG) and a quantitative analysis of coronary angiograms. RESULTS: The cumulative incidence of hospitalization for angina was significantly lower in the nifedipine group (log-rank test P = 0.013). The etiology of angina requiring hospitalization was determined on the basis of CAG findings. Its incidence secondary to the development of new lesions or the progression of existing lesions was significantly lower in the nifedipine group than in the ACE inhibitor group (log-rank test P = 0.042 and P = 0.028, respectively). Using quantitative coronary analysis, changes in the coronary artery luminal diameter were compared between the nifedipine and ACE inhibitor groups. The minimum coronary lumen diameter did not show a significant change in the nifedipine group, whereas it decreased significantly in the ACE inhibitor group (paired t-test P = 0.002), and there was a significant difference between the two groups by analysis of covariance (P = 0.047). CONCLUSION: These results indicate that nifedipine more effectively prevented admission for angina pectoris by inhibiting the progression of coronary artery disease in patients with a history of MI.

Scan #2

Cooper-DeHoff, R. M., Q. Zhou, et al. (2007). "Influence of Hispanic ethnicity on blood pressure control and cardiovascular outcomes in women with CAD and hypertension: findings from **INVEST**." Journal of Women's Health **16**(5): 632-40.

BACKGROUND: Prospective data regarding blood pressure (BP) control and cardiovascular (CV) outcomes in Hispanic women are lacking. METHODS: We analyzed 5017 Hispanic and 4710 non-Hispanic white hypertensive women with coronary artery disease (CAD) in the INternational VErapamil SR/Trandolapril STudy (INVEST) to determine the impact of baseline characteristics and BP control on CV outcomes. RESULTS: At baseline, Hispanic women were younger and a had lower prevalence of most established CV risk factors than non-Hispanic white women. At 24 months, BP control (< 140/90 mm Hg) was achieved in 75% of Hispanic and 68% of non-Hispanic white women, ($p < 0.001$), with most women, regardless of ethnicity, requiring > or =2 antihypertensive agents. Following 26,113 patient-years of follow-up, the primary outcome (first occurrence of nonfatal myocardial infarction [MI], nonfatal stroke, or all cause death) occurred in 5.7% of Hispanic and 12.3% of non-Hispanic white women (adjusted HR = 0.84, 95% CI = 0.71-0.98, $p = 0.03$). There was no difference in outcome in either group of women comparing the randomized antihypertensive treatment strategies. CONCLUSIONS: Despite accounting for a lower risk profile, deployment of protocol-based antihypertensive treatment regimens resulted in superior BP control and fewer CV events in Hispanic women compared with non-Hispanic white women.

Ruilope, L. M., B.-A. Kirwan, et al. (2007). "Uric acid and other renal function parameters in patients with stable angina pectoris participating in the **ACTION** trial: impact of nifedipine GITS (gastro-intestinal therapeutic system) and relation to outcome." Journal of Hypertension **25**(8): 1711-8.

BACKGROUND: Little data is available concerning the prognostic implications of renal function abnormalities, their evolution over time and the effects of nifedipine on such abnormalities in patients with stable angina pectoris. METHODS: The previously published ACTION trial compared long-acting nifedipine GITS 60 mg once daily to placebo among 7,665 patients. Standard laboratory tests including creatinine and uric acid were assessed at baseline, after 6 months, 2 and 4 years, and at the end of follow-up. We assessed the impact of nifedipine on markers of renal dysfunction and determined whether evidence of renal failure alters the impact of nifedipine on the clinical outcome of patients with stable angina. RESULTS: Uric acid was not while creatinine level and estimated creatinine clearance were potent conditionally independent predictors of total mortality and of cardiovascular clinical events. Relative to placebo, nifedipine reduced 6-month uric acid levels by 3% ($P < 0.001$) of the baseline value. This difference was maintained during long-term follow-up, was present both in normotensives and in hypertensives, and was not explained by differences in diuretic therapy or allopurinol use. Nifedipine had no effect on the occurrence of clinical renal failure. Relative to placebo, the effects of nifedipine on cardiovascular death or myocardial infarction [hazard ratio (HR) = 1.01, 95% confidence interval (CI) 0.88-1.17], any stroke or transient ischaemic attack (HR = 0.73, 95% CI 0.60-0.88), new overt heart failure (HR = 0.72, 95% CI 0.55-0.95), and the need for any coronary procedure (HR = 0.81, 95% CI 0.75-0.88) were consistent across strata of markers of renal dysfunction. CONCLUSIONS: We conclude that, in patients with stable angina, nifedipine reduces uric acid levels and does not

affect other markers of renal dysfunction. Renal dysfunction does not alter the effects of nifedipine on clinical outcome.

Ruzyllo, W., M. Tendera, et al. (2007). "Antianginal efficacy and safety of ivabradine compared with amlodipine in patients with stable effort angina pectoris: a 3-month randomised, double-blind, multicentre, noninferiority trial." Drugs **67**(3): 393-405.

BACKGROUND AND OBJECTIVE: Current medical therapies for the symptoms of angina pectoris aim to improve oxygen supply and reduce oxygen demand in the myocardium. Not all patients respond to current antianginal monotherapy, or even combination therapy, and a new class of antianginal drug that complements existing therapies would be useful. This study was undertaken to compare the antianginal and anti-ischaemic effects of the novel heart-rate-lowering agent ivabradine and of the calcium channel antagonist amlodipine. PATIENTS AND METHODS: Patients with a >/=3-month history of chronic, stable effort-induced angina were randomised to receive ivabradine 7.5mg (n = 400) or 10mg (n = 391) twice daily or amlodipine 10mg once daily (n = 404) for a 3-month, double-blind period. Bicycle exercise tolerance tests were performed at baseline and monthly intervals. The primary efficacy criterion was the change from baseline in total exercise duration after 3 months of treatment. Secondary efficacy criteria included changes in time to angina onset and time to 1mm ST-segment depression, rate-pressure product at trough drug activity, as well as short-acting nitrate use and anginal attack frequency (as recorded in patient diaries). RESULTS: At 3 months, total exercise duration was improved by 27.6 +/- 91.7, 21.7 +/- 94.5 and 31.2 +/- 92.0 seconds with ivabradine 7.5 and 10mg and amlodipine, respectively, both ivabradine groups were comparable to amlodipine (p-value for noninferiority < 0.001). Similar results were observed for time to angina onset and time to 1mm ST-segment depression. Heart rate decreased significantly by 11-13 beats/min at rest and by 12-15 beats/min at peak of exercise with ivabradine but not amlodipine, and rate-pressure product decreased more with ivabradine than amlodipine (p-value vs amlodipine <0.001, at rest and at peak of exercise). Anginal attack frequency and short-acting nitrate use decreased substantially in all treatment groups with no significant difference between treatment groups. The most frequent adverse events were visual symptoms and sinus bradycardia with ivabradine (0.8% and 0.4% withdrawals, respectively) and peripheral oedema with amlodipine (1.5% withdrawals). CONCLUSIONS: In patients with stable angina, ivabradine has comparable efficacy to amlodipine in improving exercise tolerance, a superior effect on the reduction of rate-pressure product (a surrogate marker of myocardial oxygen consumption) and similar safety.

Scan #1

Active-Controlled Trials

Black HR, Elliott WJ, Grandits G, et al. Results of the Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints (CONVINCE) trial by geographical region. *Journal of Hypertension.* May 2005;23(5):1099-1106.

OBJECTIVE: To examine regional differences in the Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints (CONVINCE) trial. DESIGN: Double-blind, randomized, international clinical trial. SETTING: Six hundred and sixty-one clinical centers in 15 countries. PATIENTS: Hypertensive volunteers (n = 16,602) with > or =1 additional cardiovascular risk factor, grouped into four regions: USA (n = 8144), Canada (n = 3405), Western Europe (Spain, UK, Italy, Sweden, Germany; n = 2048) or 'other' (Bulgaria, Israel, Mexico, Czech Republic, Hungary, Poland, Slovakia, Brazil; n = 2879); subgroupings included country and state/province within the USA and Canada. INTERVENTIONS: Randomized to COER-verapamil or the investigator's choice of either atenolol or hydrochlorothiazide, titrated and additional drugs added as required. MAIN OUTCOME MEASURES: Baseline characteristics; blood pressure control, medication adherence and lost-to-follow-up at 2 years; and composite primary endpoint (stroke, myocardial infarction, cardiovascular death) by regional groupings. RESULTS: Regional differences were found at baseline for age, gender, blood pressure, percentage receiving antihypertensive drug therapy, initial choice of atenolol or hydrochlorothiazide, and risk factor profile. Blood pressure control rates increased markedly during follow-up in all regions, but varied significantly by region. Blood pressure control, medication adherence and lost-to-follow-up rates were poorest in the USA. After adjustment for baseline differences, the primary-event rate for each region was significantly lower than for the USA. Although baseline factors, blood pressure control and event rates varied by region, treatment differences did not. CONCLUSION: Despite differences in baseline and follow-up measures across geographical regions, the absence of treatment differences by region suggests that the overall findings of CONVINCE are robust.

Cooper-Dehoff R, Cohen JD, Bakris GL, et al. Predictors of development of diabetes mellitus in patients with coronary artery disease taking antihypertensive medications (findings from the INternational VErapamil SR-Trandolapril STudy [INVEST]). *American Journal of Cardiology.* Oct 1 2006;98(7):890-894.

Knowledge of predictors of diabetes mellitus (DM) development in patients with coronary artery disease (CAD) who use antihypertensive therapy could contribute to decreasing this adverse metabolic consequence. This is particularly relevant because the standard of care, beta blockers combined with diuretics, may contribute to adverse metabolic risk. The INternational VErapamil SR-trandolapril STudy compared a calcium antagonist-based (verapamil SR) and a beta-blocker-based (atenolol) strategy with trandolapril and/or hydrochlorothiazide added to control blood pressure (BP) in patients with CAD. The 16,176 patients without DM at entry were investigated with regard to newly diagnosed DM during follow-up. Newly diagnosed DM was less frequent in the verapamil SR

versus atenolol strategy (7.0% vs 8.2%, hazard ratio 0.85, 95% confidence interval 0.76 to 0.95, p <0.01). Characteristics associated with risk for newly diagnosed DM included United States residence, left ventricular hypertrophy, previous stroke/transient ischemic attack, Hispanic ethnicity, coronary revascularization, hypercholesterolemia, greater body mass index, and higher follow-up systolic BP. Addition of trandolapril to verapamil SR decreased DM risk and addition of hydrochlorothiazide to atenolol increased risk. In conclusion, clinical findings associated with more severe vascular disease and Hispanic ethnicity identify a group at high risk for developing DM, whereas lower on-treatment BP and treatment with verapamil SR-trandolapril attenuated this risk.

de Leeuw PW, Ruilope LM, Palmer CR, et al. Clinical significance of renal function in hypertensive patients at high risk: results from the INSIGHT trial.[see comment]. *Archives of Internal Medicine.* Dec 13-27 2004;164(22):2459-2464.

BACKGROUND: Increasing evidence suggests renal involvement in hypertension-related cardiovascular and cerebrovascular complications. To assess this role of renal function in more detail, we studied the evolution of renal function and the relationship of renal function with mortality and morbidity in the Intervention as a Goal in Hypertension Treatment (INSIGHT) study. METHODS: The INSIGHT study was a double-blind, randomized, multicenter trial in patients with hypertension and at least 1 additional cardiovascular risk factor. Treatment consisted of nifedipine gastrointestinal therapeutic system, 30 mg/d, or hydrochlorothiazide-amiloride (25 mg/d of hydrochlorothiazide and 2.5 mg/d of amiloride hydrochloride). Primary outcome was a composite of cardiovascular death, myocardial infarction, heart failure, and stroke. Renal function was assessed by measuring creatinine clearance, serum creatinine level, and serum uric acid level and by the presence of proteinuria. RESULTS: Creatinine clearance fell more in nifedipine recipients than in hydrochlorothiazide-amiloride recipients. Renal insufficiency developed in 2% of nifedipine recipients and 5% of hydrochlorothiazide-amiloride recipients. Primary outcomes occurred in 15% of patients with increased serum creatinine levels and 6% of patients with normal levels (odds ratio [OR] 2.89; 95% confidence interval [CI], 1.92-4.36; P<.001). Primary outcomes were more likely in patients with low creatinine clearance (<60 mL/min) than in those with higher clearances (9% vs 5%, respectively [OR, 1.51, 95%CI, 1.22-1.88; P<.001]). CONCLUSIONS: Renal function is an important predictor of risk in hypertensive patients at high risk. Antihypertensive treatment with a long-acting dihydropyridine calcium channel blocker may better preserve renal function than would treatment with diuretics.

Derosa G, Cicero AFG, Bertone G, et al. Comparison of the effects of telmisartan and nifedipine gastrointestinal therapeutic system on blood pressure control, glucose metabolism, and the lipid profile in patients with type 2 diabetes mellitus and mild hypertension: a 12-month, randomized, double-blind study. *Clinical Therapeutics.* Aug 2004;26(8):1228-1236.

BACKGROUND: Angiotensin receptor blockers (ARBs) provide effective blood pressure control. Whereas none of the ARBs appear to affect glucose homeostasis, some ARBs have been associated with a decrease in cholesterolemia. OBJECTIVE: This study was conducted to evaluate blood pressure control glucose homeostasis, and the plasma lipid profile in patients with type 2 diabetes mellitus and mild hypertension during 12 months

of treatment with the ARB telmisartan or nifedipine gastrointestinal therapeutic system (GITS). METHODS: In this double-blind trial, patients taking oral hypoglycemic agents were randomized to receive telmisartan 40 mg or nifedipine GITS 20 mg once daily for 12 months. At the time of enrollment, patients were given advice on diet (1400-1600 kcal/d) and exercise (stationary bicycle for > or =30 min, 4 d/wk). Assessments of systolic blood pressure (SBP), diastolic blood pressure, body mass index (BMI), fasting plasma glucose concentrations, glycosylated hemoglobin, fasting plasma insulin concentrations, the homeostasis model assessment of insulin resistance, and the lipid profile were performed at baseline and after 6 and 12 months of treatment. RESULTS: One hundred sixteen patients were divided into 2 age- and sex-matched treatment groups (58 men, 58 women; mean [SD] age, 52.5 [5] years). All patients were in good general health at baseline; had achieved adequate glycemic control with diet and oral hypoglycemic agents; were taking antihypercholesterolemic drugs; and had no evidence of macroangiopathy, microalbuminuria, or neuropathy. There were significant reductions from baseline in seated trough SBP after 12 months of treatment with both telmisartan and nifedipine GITS (from 139 [4] to 132 [4] mm Hg and from 140 [4] to 130 [4] mm Hg, respectively; both, P < 0.01). No change in BMI or glucose metabolism was observed with either treatment. After 12 months, there were significant improvements in concentrations of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) with telmisartan (-9% and -11.5%, respectively; both, P < 0.01) compared with nifedipine GITS (-2% and -1.5%). CONCLUSIONS: In this selected sample of patients with type 2 diabetes and mild hypertension, both telmisartan and nifedipine GITS produced significant reductions in blood pressure. Telmisartan was associated with a slight but statistically significant improvement in plasma TC and LDL-C concentrations compared with nifedipine GITS.

Frishman WH, Hainer JW, Sugg J, Group MFS. A factorial study of combination hypertension treatment with metoprolol succinate extended release and felodipine extended release results of the Metoprolol Succinate-Felodipine Antihypertension Combination Trial (M-FACT). *American Journal of Hypertension.* Apr 2006;19(4):388-395.

BACKGROUND: Many hypertensive patients require combination therapy to achieve target blood pressure (BP). beta-Blockers and dihydropyridine calcium channel blockers are effective as monotherapy in hypertensive patients and have complementary mechanisms for lowering BP. METHODS: This multicenter, randomized, placebo-controlled, unbalanced factorial study included a 4- to 5-week single-blind placebo, 9-week, double-blind treatment as well as a 2-week double-blind, down-titration period. Patients (N = 1092) were randomized to one of 16 treatment groups: extended-release (ER) metoprolol succinate (25, 100, or 400 mg), ER felodipine (2.5, 10, or 20 mg), ER felodipine/ER metoprolol succinate (2.5/25, 2.5/100, 2.5/400, 10/25, 10/100, 10/400, 20/25, 20/100, or 20/400 mg), or placebo. RESULTS: At baseline, treatment groups were well balanced; mean sitting BP was 152.6/99.9 mm Hg. Monotherapy with ER metoprolol succinate induced dose-related reductions in sitting systolic/diastolic BP (DBP) (mean 8.1/7.7 to 9.7/11.1 mm Hg) as did ER felodipine (mean 7.7/7.7 to 14.0/11.8) and the combinations reflected additive effects (mean 13.8/11.0 to 19.8/15.2). The decline in the placebo group was 2.1/4.0 mm Hg. All combinations were more effective than their components (P < .05 for all but ER metoprolol succinate 25/ER felodipine 20). When compared with the

highest doses of the individual agents (ER metoprolol succinate 400 mg; ER felodipine 20 mg), the low-dose combination ER metoprolol succinate 25/ER felodipine 2.5 was approximately as effective (differences in DBP <1 mm Hg). The most common adverse events leading to discontinuation were peripheral edema (4%), headache (2%), and fatigue (1%). Higher rates of peripheral edema and flushing were associated with high-dose ER felodipine, either alone or in combination. CONCLUSIONS: The antihypertensive effects of ER metoprolol succinate and ER felodipine are dose-related, and when given in combination, their BP-lowering effects are additive over a wide dose range. Low-dose combination therapy is comparable in effectiveness to high-dose monotherapy but is better tolerated.

Hemels MEW, Van Noord T, Crijns HJGM, et al. Verapamil versus digoxin and acute versus routine serial cardioversion for the improvement of rhythm control for persistent atrial fibrillation. *Journal of the American College of Cardiology.* Sep 5 2006;48(5):1001-1009.

OBJECTIVES: The VERDICT (Verapamil Versus Digoxin and Acute Versus Routine Serial Cardioversion Trial) is a prospective, randomized study to investigate whether: 1) acutely repeated serial electrical cardioversions (ECVs) after a relapse of atrial fibrillation (AF); and 2) prevention of intracellular calcium overload by verapamil, decrease intractability of AF. BACKGROUND: Rhythm control is desirable in patients suffering from symptomatic AF. METHODS: A total of 144 patients with persistent AF were included. Seventy-four (51%) patients were randomized to the acute (within 24 h) and 70 (49%) patients to the routine serial ECVs, and 74 (51%) patients to verapamil and 70 (49%) patients to digoxin for rate control before ECV and continued during follow-up (2 x 2 factorial design). Class III antiarrhythmic drugs were used after a relapse of AF. Follow-up was 18 months. RESULTS: At baseline, there were no significant differences between the groups, except for beta-blocker use in the verapamil versus digoxin group (38% vs. 60%, respectively, p = 0.01). At follow-up, no difference in the occurrence of permanent AF between the acute and the routine cardioversion groups was observed (32% [95% confidence intervals (CI)] 22 to 44) vs. 31% [95% CI 21 to 44], respectively, p = NS), and also no difference between the verapamil- and the digoxin-randomized patients (28% [95% CI 19 to 40] vs. 36% [95% CI 25 to 48] respectively, p = NS). Multivariate Cox regression analysis revealed that lone digoxin use was the only significant predictor of failure of rhythm control treatment (hazard ratio 2.2 [95% CI 1.1 to 4.4], p = 0.02). CONCLUSIONS: An acute serial cardioversion strategy does not improve long-term rhythm control in comparison with a routine serial cardioversion strategy. Furthermore, verapamil has no beneficial effect in a serial cardioversion strategy.

Inoue S, Tomino Y. Effects of calcium antagonists in hypertensive patients with renal dysfunction: a prospective, randomized, parallel trial comparing benidipine and nifedipine. *Nephrology.* Oct 2004;9(5):265-271.

BACKGROUND: Although calcium antagonists, derived from dihydropyridine (DHP), are important agents in achieving control in a majority of patients with high blood pressure and renal disease, there are no comparative data regarding their inhibitory effects on the progression of renal dysfunction in Japan. METHODS: Benidipine and nifedipine retard both calcium antagonists derived from DHP and were compared in terms of their

inhibitory effect on the progression of renal dysfunction in hypertensive patients. The primary end-points were defined as 1.5 times the serum creatinine value at baseline, progression to end-stage renal failure (ESRF) necessitating dialysis or renal transplantation, and death. RESULTS: During the study period, a significant decline in blood pressure was observed in the two groups, with no significant difference between them. The worsening of nephropathy was significantly inhibited in the benidipine group as compared with the nifedipine retard group (log-rank test: P = 0.014, Wilcoxon's test: P = 0.022). Among the subjects who reached a primary end-point, one (33%) in the benidipine group and five (50%) in the nifedipine retard group were placed on haemodialysis within 1 year. CONCLUSION: It appears that benidipine inhibits the progression of hypertensive renal diseases more effectively than nifedipine retard.

Investigators JE, Investigators JE. Effect of Losartan and Amlodipine on Left Ventricular Diastolic Function in Patients With Mild-to-Moderate Hypertension (J-ELAN): rationale and design. *Circulation Journal.* Jan 2006;70(1):124-128.

BACKGROUND: Hypertension is a major underlying disease that may cause left ventricular (LV) diastolic dysfunction, even without LV systolic dysfunction, and antihypertensive drugs could affect LV diastolic function. METHODS AND RESULTS: The Effect of Losartan and Amlodipine on Left Ventricular Diastolic Function in Patients With Mild-to-Moderate Hypertension (J-ELAN) study is a multicenter, prospective, randomized trial designed to assess the effects of losartan and amlodipine on LV diastolic function in hypertensive patients with LV diastolic dysfunction in the absence of systolic dysfunction. A total of 300 patients (150 patients in each group) will be enrolled. In addition to Doppler echocardiographic indices of LV diastolic function, changes in LV structure and atherosclerosis of the carotid arteries will be serially assessed. The maximum follow-up period is 18 months. CONCLUSIONS: This study will provide the characteristic differences in the effects of amlodipine and losartan on LV diastolic dysfunction in hypertensive patients.

Koylan N, Bilge AK, Adalet K, Mercanoglu F, Buyukozturk K, Group TTS. Comparison of the effects of trimetazidine and diltiazem on exercise performance in patients with coronary heart disease. The Turkish trimetazidine study (TTS). *Acta Cardiologica.* Dec 2004;59(6):644-650.

OBJECTIVE: A multicentre, double-blind comparative study was performed to compare the effects of trimetazidine with diltiazem on exercise performance in patients with stable angina pectoris. METHODS AND RESULTS: A total of 116 male patients with documented coronary artery disease at 11 centres were randomized into trimetazidine and diltiazem groups both including 58 men (mean age 55.1+/-8.6 years and 54.9+/-6.6 years, respectively) in a prospective, multicentre, double-blind active treatment trial.The study consisted of a two-week placebo washout period and a four-week active treatment phase. Clinical examinations and exercise tests were performed at the beginning (D0) and at the end (D28) of the active treatment. Laboratory investigations were also performed at the beginning of the washout period (D-14) and at D28. Holter recordings were done in the mid of the washout period (D-7) and D28. Both trimetazidine and diltiazem decreased the

number of anginal attacks per week ($p < 0.0001$ for both drugs) and weekly nitrate consumption ($p = 0.0008$ and $p < 0.0001$, respectively). Both trimetazidine and diltiazem improved the recovery of anginal pain ($p = 0.0188$ and $p = 0.0079$, respectively) and maximal ST-segment depression ($p = 0.0134$ and $p = 0.0214$, respectively) but none of the drugs significantly changed the time to 1 mm ST-segment depression and ST recovery time on exercise test. Diltiazem caused a slight prolongation of PR and QRS durations ($p = 0.039$) on ambulatory ECG whereas trimetazidine did not change these parameters significantly. CONCLUSION: This study suggests that trimetazidine is an effective and safe alternative for diltiazem in the treatment of patients with stable angina pectoris. Although several other trials have shown that this drug can be used in combination with other antianginal drugs or instead of beta blockers or nifedipine in the symptomatic treatment of stable anginal syndromes, this study suggests that trimetazidine can be used instead of diltiazem, a well-known powerful antianginal drug.

Leenen FHH, Nwachuku CE, Black HR, et al. Clinical events in high-risk hypertensive patients randomly assigned to calcium channel blocker versus angiotensin-converting enzyme inhibitor in the antihypertensive and lipid-lowering treatment to prevent heart attack trial.[see comment]. *Hypertension.* Sep 2006;48(3):374-384.

The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) provides a unique opportunity to compare the long-term relative safety and efficacy of angiotensin-converting enzyme inhibitor and calcium channel blocker-initiated therapy in older hypertensive individuals. Patients were randomized to amlodipine (n=9048) or lisinopril (n=9054). The primary outcome was combined fatal coronary heart disease or nonfatal myocardial infarction, analyzed by intention-to-treat. Secondary outcomes included all-cause mortality, stroke, combined cardiovascular disease (CVD), end-stage renal disease (ESRD), cancer, and gastrointestinal bleeding. Mean follow-up was 4.9 years. Blood pressure control was similar in nonblacks, but not in blacks. No significant differences were found between treatment groups for the primary outcome, all-cause mortality, ESRD, or cancer. Stroke rates were higher on lisinopril in blacks (RR=1.51, 95% CI 1.22 to 1.86) but not in nonblacks (RR=1.07, 95% CI 0.89 to 1.28), and in women (RR=1.45, 95% CI 1.17 to 1.79), but not in men (RR=1.10, 95% CI 0.92 to 1.31). Rates of combined CVD were higher (RR=1.06, 95% CI 1.00 to 1.12) because of higher rates for strokes, peripheral arterial disease, and angina, which were partly offset by lower rates for heart failure (RR=0.87, 95% CI 0.78 to 0.96) on lisinopril compared with amlodipine. Gastrointestinal bleeds and angioedema were higher on lisinopril. Patients with and without baseline coronary heart disease showed similar outcome patterns. We conclude that in hypertensive patients, the risks for coronary events are similar, but for stroke, combined CVD, gastrointestinal bleeding, and angioedema are higher and for heart failure are lower for lisinopril-based compared with amlodipine-based therapy. Some, but not all, of these differences may be explained by less effective blood pressure control in the lisinopril arm.

Mancia G, Ruilope L, Palmer C, et al. Effects of nifedipine GITS and diuretics in isolated systolic hypertension--a subanalysis of the INSIGHT study. *Blood Pressure.* 2004;13(5):310-315.

AIMS: This study tested the effects on cardiovascular outcomes of treatments based on nifedipine gastrointestinal therapeutic system (GITS) compared with the diuretic combination co-amilozide in a pre-specified subset of patients with isolated systolic hypertension (ISH) enrolled in the International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) study. MAJOR FINDINGS: Of 6321 randomized patients, 1498 (23.7%) had ISH with a baseline mean BP of 173/88 mmHg in both treatment groups. Mean BP fell by 29/10 mmHg in the nifedipine and 30/10 mmHg in the diuretic group to a mean BP of 144/78 mmHg and 143/79 mmHg, respectively, at endpoint. The percentage of primary outcomes in patients with ISH was not significantly different between the two treatment groups (nifedipine GITS 6.0%, co-amilozide 6.6%). The number of ISH patients with composite secondary outcomes was 90 (12.2%) in the nifedipine GITS group and 110 (14.5%) in the co-amilozide group (not significant). The incidence rates of primary and secondary outcomes were similar in patients without ISH. CONCLUSION: In patients with ISH, nifedipine GITS and co-amilozide had similar effects on clinical outcomes and BP lowering. They lend support to international guidelines for the treatment of hypertension recommending the use of long-acting dihydropyridine calcium-channel blockers as one treatment option for patients with ISH.

Messerli FH, Mancia G, Conti CR, et al. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Annals of Internal Medicine.* Jun 20 2006;144(12):884-893.

BACKGROUND: Because coronary perfusion occurs mainly during diastole, patients with coronary artery disease (CAD) could be at increased risk for coronary events if diastolic pressure falls below critical levels. OBJECTIVE: To determine whether low blood pressure could be associated with excess mortality and morbidity in this population. DESIGN: A secondary analysis of data from the International Verapamil-Trandolapril Study (INVEST), which was conducted from September 1997 to February 2003. SETTING: 862 sites in 14 countries. PATIENTS: 22 576 patients with hypertension and CAD. Interventions: Patients from INVEST were randomly assigned to a verapamil sustained-release- or atenolol-based strategy; blood pressure control and outcomes were equivalent. MEASUREMENTS: An unadjusted quadratic proportional hazards model was used to evaluate the relationship between average on-treatment blood pressure and risk for the primary outcome (all-cause death, nonfatal stroke, and nonfatal myocardial infarction [MI]), all-cause death, total MI, and total stroke. A second model adjusted for differences in baseline covariates. RESULTS: The relationship between blood pressure and the primary outcome, all-cause death, and total MI was J-shaped, particularly for diastolic pressure, with a nadir at 119/84 mm Hg. After adjustment, the J-shaped relationship persisted between diastolic pressure and primary outcome. The MI-stroke ratio remained constant over a wide blood pressure range, but at a lower diastolic blood pressure, there were substantially more MIs than strokes. An interaction between decreased diastolic pressure and history of revascularization was observed; low diastolic pressure was associated with a relatively lower risk for the primary outcome in patients with revascularization than in those without revascularization. LIMITATIONS: This is a post hoc analysis of hypertensive patients with CAD. CONCLUSIONS: The risk for the primary outcome, all-cause death, and MI, but not stroke, progressively increased with

low diastolic blood pressure. Excessive reduction in diastolic pressure should be avoided in patients with CAD who are being treated for hypertension.

Nissen SE, Tuzcu EM, Libby P, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial.[see comment]. *JAMA.* Nov 10 2004;292(18):2217-2225.

CONTEXT: The effect of antihypertensive drugs on cardiovascular events in patients with coronary artery disease (CAD) and normal blood pressure remains uncertain. OBJECTIVE: To compare the effects of amlodipine or enalapril vs placebo on cardiovascular events in patients with CAD. DESIGN, SETTING, AND PARTICIPANTS: Double-blind, randomized, multicenter, 24-month trial (enrollment April 1999-April 2002) comparing amlodipine or enalapril with placebo in 1991 patients with angiographically documented CAD (>20% stenosis by coronary angiography) and diastolic blood pressure <100 mm Hg. A substudy of 274 patients measured atherosclerosis progression by intravascular ultrasound (IVUS). INTERVENTIONS: Patients were randomized to receive amlodipine, 10 mg; enalapril, 20 mg; or placebo. IVUS was performed at baseline and study completion. MAIN OUTCOME MEASURES: The primary efficacy parameter was incidence of cardiovascular events for amlodipine vs placebo. Other outcomes included comparisons of amlodipine vs enalapril and enalapril vs placebo. Events included cardiovascular death, nonfatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina pectoris, hospitalization for congestive heart failure, fatal or nonfatal stroke or transient ischemic attack, and new diagnosis of peripheral vascular disease. The IVUS end point was change in percent atheroma volume. RESULTS: Baseline blood pressure averaged 129/78 mm Hg for all patients; it increased by 0.7/0.6 mm Hg in the placebo group and decreased by 4.8/2.5 mm Hg and 4.9/2.4 mm Hg in the amlodipine and enalapril groups, respectively (P<.001 for both vs placebo). Cardiovascular events occurred in 151 (23.1%) placebo-treated patients, in 110 (16.6%) amlodipine-treated patients (hazard ratio [HR], 0.69; 95% CI, 0.54-0.88 [P = .003]), and in 136 (20.2%) enalapril-treated patients (HR, 0.85; 95% CI, 0.67-1.07 [P = .16]. Primary end point comparison for enalapril vs amlodipine was not significant (HR, 0.81; 95% CI, 0.63-1.04 [P = .10]). The IVUS substudy showed a trend toward less progression of atherosclerosis in the amlodipine group vs placebo (P = .12), with significantly less progression in the subgroup with systolic blood pressures greater than the mean (P = .02). Compared with baseline, IVUS showed progression in the placebo group (P<.001), a trend toward progression in the enalapril group (P = .08), and no progression in the amlodipine group (P = .31). For the amlodipine group, correlation between blood pressure reduction and progression was r = 0.19, P = .07. CONCLUSIONS: Administration of amlodipine to patients with CAD and normal blood pressure resulted in reduced adverse cardiovascular events. Directionally similar, but smaller and nonsignificant, treatment effects were observed with enalapril. For amlodipine, IVUS showed evidence of slowing of atherosclerosis progression.

Ruggenenti P, Fassi A, Ilieva AP, et al. Preventing microalbuminuria in type 2 diabetes.[see comment]. *New England Journal of Medicine.* Nov 4 2004;351(19):1941-1951.

BACKGROUND: The multicenter double-blind, randomized Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) was designed to assess whether angiotensin-converting-enzyme inhibitors and non-dihydropyridine calcium-channel blockers, alone or in combination, prevent microalbuminuria in subjects with hypertension, type 2 diabetes mellitus, and normal urinary albumin excretion. METHODS: We studied 1204 subjects, who were randomly assigned to receive at least three years of treatment with trandolapril (at a dose of 2 mg per day) plus verapamil (sustained-release formulation, 180 mg per day), trandolapril alone (2 mg per day), verapamil alone (sustained-release formulation, 240 mg per day), or placebo. The target blood pressure was 120/80 mm Hg. The primary end point was the development of persistent microalbuminuria (overnight albumin excretion, > or =20 microg per minute at two consecutive visits). RESULTS: The primary outcome was reached in 5.7 percent of the subjects receiving trandolapril plus verapamil, 6.0 percent of the subjects receiving trandolapril, 11.9 percent of the subjects receiving verapamil, and 10.0 percent of control subjects receiving placebo. The estimated acceleration factor (which quantifies the effect of one treatment relative to another in accelerating or slowing disease progression) adjusted for predefined baseline characteristics was 0.39 for the comparison between verapamil plus trandolapril and placebo (P=0.01), 0.47 for the comparison between trandolapril and placebo (P=0.01), and 0.83 for the comparison between verapamil and placebo (P=0.54). Trandolapril plus verapamil and trandolapril alone delayed the onset of microalbuminuria by factors of 2.6 and 2.1, respectively. Serious adverse events were similar in all treatment groups. CONCLUSIONS: In subjects with type 2 diabetes and hypertension but with normoalbuminuria, the use of trandolapril plus verapamil and trandolapril alone decreased the incidence of microalbuminuria to a similar extent. The effect of verapamil alone was similar to that of placebo. Copyright 2004 Massachusetts Medical Society.

Vranic II, Matic M, Perunicic J, Simic T, Soskic L, Milic N. Adenosine cardioprotection study in clinical setting of paroxysmal supraventricular tachycardia. *Prostaglandins Leukotrienes & Essential Fatty Acids.* Jun 2006;74(6):365-371.

PSVT attack of >20min and frequency >160 is well-recognized model of myocardial dysfunction. We measured 6-keto-PGF1alpha and TXB(2) before and after adenosine administration to assess its cardioprotective potential. A total of 64 patients were randomly assigned as having acute episode of PSVT to adenosine or verapamil group. A bolus of 6mg of adenosine up to the maximum dose of 12 or 5mg of verapamil up to the maximum dose of 10mg were given, until the sinus rhythm was restored. The levels of PGI(2), TXA(2) and TAS were measured in three different time intervals. In adenosine group all parameters were normalized after 20min of conversion to sinus rhythm. The ratio of PGI(2)/TXA(2) increased after 5min of conversion to SR (P<0.01). Also, the ratio of TXA(2)/TAS was decreased for ADO (P<0.01). This is the first study to demonstrate that adenosine exerts cardioprotective effect.

Whelton PK, Barzilay J, Cushman WC, et al. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Archives of Internal Medicine.* Jun 27 2005;165(12):1401-1409.

BACKGROUND: Optimal first-step antihypertensive drug therapy in type 2 diabetes mellitus (DM) or impaired fasting glucose levels (IFG) is uncertain. We wished to determine whether treatment with a calcium channel blocker or an angiotensin-converting enzyme inhibitor decreases clinical complications compared with treatment with a thiazide-type diuretic in DM, IFG, and normoglycemia (NG). METHODS: Active-controlled trial in 31 512 adults, 55 years or older, with hypertension and at least 1 other risk factor for coronary heart disease, stratified into DM (n = 13 101), IFG (n = 1399), and NG (n = 17 012) groups on the basis of national guidelines. Participants were randomly assigned to double-blind first-step treatment with chlorthalidone, 12.5 to 25 mg/d, amlodipine besylate, 2.5 to 10 mg/d, or lisinopril, 10 to 40 mg/d. We conducted an intention-to-treat analysis of fatal coronary heart disease or nonfatal myocardial infarction (primary outcome), total mortality, and other clinical complications. RESULTS: There was no significant difference in relative risk (RR) for the primary outcome in DM or NG participants assigned to amlodipine or lisinopril vs chlorthalidone or in IFG participants assigned to lisinopril vs chlorthalidone. A significantly higher RR (95% confidence interval) was noted for the primary outcome in IFG participants assigned to amlodipine vs chlorthalidone (1.73 [1.10-2.72]). Stroke was more common in NG participants assigned to lisinopril vs chlorthalidone (1.31 [1.10-1.57]). Heart failure was more common in DM and NG participants assigned to amlodipine (1.39 [1.22-1.59] and 1.30 [1.12-1.51], respectively) or lisinopril (1.15 [1.00-1.32] and 1.19 [1.02-1.39], respectively) vs chlorthalidone. CONCLUSION: Our results provide no evidence of superiority for treatment with calcium channel blockers or angiotensin-converting enzyme inhibitors compared with a thiazide-type diuretic during first-step antihypertensive therapy in DM, IFG, or NG.

Kojima S, Shida M, Yokoyama H. Comparison between cilnidipine and amlodipine besilate with respect to proteinuria in hypertensive patients with renal diseases. *Hypertension Research - Clinical & Experimental.* Jun 2004;27(6):379-385.

Unlike other dihydropyridine calcium channel blockers (CCBs), cilnidipine has been reported to exert an N-type calcium-channel-blocking activity and to reduce sympathetic hyperactivity. This study compared cilnidipine and amlodipine with respect to their effects on renal function and proteinuria. Twenty-eight proteinuric hypertensive outpatients (13 men and 15 women, aged 62+/-2 years) who had been maintained on CCBs for more than 3 months were randomly assigned to a group receiving amlodipine besilate (14 patients) or a group receiving cilnidipine (14 patients). CCBs were increased in dosage or other drugs were added until blood pressure decreased below 140/90 mmHg, but no inhibitors of the renin-angiotensin (RA) system were added or changed in dosage. Before and at 6 and 12 months after randomization, the concentrations of urine protein, urine albumin, serum and urine creatinine (Cr), and serum beta2-microglobulin were determined. The amlodipine group showed a significant increase in proteinuria, while the increase was suppressed in the cilnidipine group. The rate of increase in proteinuria at 12 months was 87% (95% confidence interval (CI) -10 to 184) of the baseline value with amlodipine and 4% (95% CI -69 to 77) of baseline with cilnidipine, a significant intergroup difference ($p<0.05$). The mean blood pressure remained in the 96-99 mmHg range until 12 months after randomization, showing no significant difference between the two groups. The cilnidipine group showed an increase in serum Cr levels (baseline vs. 12

months, 1.36+/-0.20 vs. 1.50+/-0.23 mg/dl, p<0.01). Overall, an inverse correlation existed between the changes in Cr and proteinuria (r= -0.477, p<0.01). These results suggest that cilnidipine results in a greater suppression of the increase in proteinuria and greater reduction in glomerular filtration rate than amlodipine, and that these effects are similar between cilnidipine and RA inhibitors. However, additional large-cohort and longer-term studies will be needed to clarify whether cilnidipine is superior to other CCBs in maintaining renal function.

Vora A, Karnad D, Goyal V, et al. Control of rate versus rhythm in rheumatic atrial fibrillation: a randomized study.[see comment]. *Indian Heart Journal.* Mar-Apr 2004;56(2):110-116.

BACKGROUND: Patients with rheumatic heart disease and atrial fibrillation incur significant morbidity and mortality. It is not known which approach, rate control or maintenance of sinus rhythm might be most appropriate. The present study was undertaken to compare the strategy of ventricular rate control versus maintenance of sinus rhythm in rheumatic atrial fibrillation, and to evaluate the role of amiodarone in this patient population. METHODS AND RESULTS: We prospectively studied 144 patients with chronic rheumatic atrial fibrillation in a double-blind protocol-rhythm control (group I: 48 patients each with amiodarone -group Ia; and placebo -group Ib) and compared the effects with the ventricular rate control (group II) by diltiazem (n=48, open-label). Direct current cardioversion was attempted in group I. The mean age of the study population was 38.6+/-10.3 years, left atrial size was 4.7+/-0.6 cm, atrial fibrillation duration was 6.1+/-5.4 years, and 72.9% patients had undergone valvular interventions. At 1 year, 45 patients with sinus rhythm in group I compared to 48 patients in group II demonstrated significant increase in exercise to sinus rhythm time, had improvement in functional class and quality of life score. There was no difference in hospitalization rates, systemic bleeds or incidence of thromboembolism. Five patients died in group II but none in group I (p=0.02). In group I, 73/87 (83.9%) patients converted, and 45/86 (52.3%) patients maintained sinus rhythm at 1 year. Conversion rates were 38/43 (88.4%) with amiodarone versus 34/44 (77.3%) with placebo (p=0.49): corresponding rate for maintaining sinus rhythm was 29/42 (69.1%) versus 16/44 (36.4%), p=0.008 respectively. CONCLUSIONS: Maintenance of sinus rhythm appeared to be superior to ventricular rate control in patients with rheumatic atrial fibrillation in terms of an effect on mortality and morbidity. Sinus rhythm could be restored in the majority and amiodarone was superior to placebo in this regard.

Placebo-Controlled Trials

Liu L, Zhang Y, Liu G, et al. The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients.[see comment]. *Journal of Hypertension.* Dec 2005;23(12):2157-2172.

OBJECTIVE: To compare the incidence of stroke and other cardiovascular events in hypertensive patients receiving a low-dose diuretic and low-dose calcium antagonist combination with those receiving low-dose diuretic monotherapy, and assess the effects of a small blood pressure difference at achieved levels lower than those achieved in previous placebo-controlled trials. METHODS: The Felodipine Event Reduction

(FEVER) trial was an investigator-designed, prospective, multicentre, double-blind, randomized, placebo-controlled, parallel group trial. It enrolled 9800 Chinese patients, of either sex, aged 50-79 years, with one or two additional cardiovascular risk factors or disease, whose blood pressure, 6 weeks after switching from previous antihypertensive therapy to low-dose (12.5 mg a day) hydrochlorothiazide, was in the range 140-180 mmHg (systolic) or 90-100 mmHg (diastolic). These patients were randomly assigned either to low-dose felodipine extended release or placebo, and followed at 3-month intervals for an average of 40 months. RESULTS: The intention-to-treat analysis included 9711 randomly selected patients with only 30 (0.3%) lost to follow-up. A total of 31 842 patient-years of follow-up were accumulated, with 85.9% of patients remaining on blinded randomized treatment. Add-on therapy was given to 33.9% of the hydrochlorothiazide-felodipine patients and to 42.3% of the hydrochlorothiazide-placebo patients. In the felodipine group, systolic blood pressure (SBP)/diastolic blood pressure (DBP) decreased (from randomization to study end) from 154.2/91.0 to 137.3/82.5 mmHg, and in the placebo group from 154.4/91.3 to 142.5/85.0 mmHg, with an average difference throughout the trial of 4.2/2.1 mmHg. In the felodipine group, the primary endpoint (fatal and non-fatal stroke) was reduced by 27% (P = 0.001). Among secondary endpoints, all cardiovascular events were reduced by 27% (P < 0.001), all cardiac events by 35% (P = 0.012), death by any cause by 31% (P = 0.006), coronary events by 32% (P = 0.024), heart failure by 30% (P = 0.239), cardiovascular death by 33% (P = 0.019), cancer by 36% (P = 0.017) in the felodipine group. No significant differences were found in new-onset diabetes. Both treatments were very well tolerated. CONCLUSIONS: In moderately complicated hypertensive patients from China even a difference in SBP/DBP as small as 4/2 mmHg, such as that induced by adding low-dose felodipine to low-dose hydrochlorothiazide, is associated with very substantial reductions in the incidence of most types of cardiovascular events. As the SBP achieved in the felodipine group was below the recommended goal of less than 140 mmHg, and SBP in the placebo group was slightly above that level, FEVER provides the required evidence in support of the guidelines recommended goal, even for a hypertensive population not entirely consisting of patients with diabetes or previous cardiovascular events.

Lubsen J, Wagener G, Kirwan B-A, de Brouwer S, Poole-Wilson PA, investigators A. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with symptomatic stable angina and hypertension: the ACTION trial.[see comment]. *Journal of Hypertension.* Mar 2005;23(3):641-648.

OBJECTIVE: To examine the effects of nifedipine GITS on clinical outcome in patients with concurrent stable angina and hypertension. METHODS: Data from the double-blind placebo-controlled ACTION trial was stratified for hypertension (blood pressure > or = 140/90 mmHg), at baseline. RESULTS: A total of 52% of 7665 ACTION patients were hypertensive. Some 80% were on a beta blocker; hypertensives were more often treated with other blood pressure-lowering drugs. Mean baseline blood pressure was 122/74 mmHg among normotensives and 151/85 mmHg among hypertensives. Follow-up blood pressures were reduced by nifedipine (P < 0.001) on the average by 3.9/2.4 and 6.6/3.5 mmHg among normotensives and hypertensives, respectively. Nifedipine GITS significantly (P < 0.05) reduced the combined incidence of all-cause mortality, myocardial infarction, refractory angina, heart failure, stroke and peripheral

revascularization by 13% in hypertensives only. Nifedipine significantly reduced the incidence of any stroke or transient ischemic attack by almost 30% in both subgroups and the need for coronary angiography by 21% in normotensives and 16% in hypertensives. Among hypertensives, the incidence of new overt heart failure was significantly reduced by 38% and of debilitating stroke by 33%. Among normotensives, the need for coronary bypass grafting was significantly reduced by 32%. Nifedipine did not affect all-cause death, cardiovascular death and myocardial infarction in either normo- or hypertensives, but increased the need for peripheral revascularization. CONCLUSION: The salutary effects of the addition of nifedipine GITS to the basic regimen of patients with concurrent stable symptomatic coronary artery disease and hypertension emphasize the need for blood pressure control.

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Month/Year of Review: January 2014
PDL Classes: Beta Blockers

Date of Last Review: January 2012
Source Document: OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: ACEBUTOLOL HCL, ATENOLOL, CARVEDILOL, LABETALOL HCL, METOPROLOL TARTRATE, NADOLOL, PROPRANOLOL HCL
- Non-Preferred Agents: BETAXOLOL, BISOPROLOL, METOPROLOL SUCCINATE, NEBIVOLOL (BYSTOLIC®), PENBUTOLOL (LEVABUTOL®), PINDOLOL, TIMOLOL

Previous Conclusions and Recommendation:

- In patients with mild-moderate HF, bisoprolol, carvedilol or metoprolol succinate (ER) reduce mortality.
- In patients with severe HF, carvedilol or metoprolol succinate (ER) reduce mortality.
- In patients with recent MI, acebutolol, carvedilol, metoprolol tartrate (IR), propranolol, or timolol reduce mortality. It is important that at least one of these drugs be included in the PDL.
- All of the β-Blockers reviewed are effective in the treatment of hypertension, but there is no evidence of differences between β-blockers for blood pressure control, survival, or quality of life.
- All of the β-Blockers reviewed except carteolol reduced anginal attacks in patients in short-term studies that did not allow mortality evaluation.
- Because of their effectiveness in rate control for atrial fibrillation at least one of either atenolol, bisoprolol, carvedilol, metoprolol succinate (ER), nadolol, pindolol, or propranolol should be included in the PDL.
- The current evidence does not distinguish a difference among these beneficial β−Blockers that were tested for preventing recurrence and diminishing the severity of migraine headaches: atenolol, bisoprolol, metoprolol tartrate (IR), metoprolol succinate (ER), propranolol, propranolol LA nadolol, or timolol.
- The current evidence does not distinguish a difference among beneficial β−Blockers that were tested for reducing esophageal variceal re-bleeding: atenolol, nadolol, propranolol, or propranolol LA.
- There is no evidence of significant differences among β-blockers in safety or adverse effects.
- There is no evidence of significant differences found for one β-blocker being more effective or associated with fewer adverse effects in subgroups of patients based on demographics (race, ethnicity, gender), use of other medications, or co-morbidities.

Research Questions:

- Is there any new comparative evidence on Beta Blockers on mortality, cardiovascular events, stroke, or quality of life?
- Is there any new comparative safety evidence of Beta Blockers??
- Are there subpopulations of patients for which one medication or preparation is more effective or associated with fewer adverse effects?

Methods:

The DERP scan was used to identify any new comparative research that has emerged since the last P&T review. [1]

Conclusions and Recommendations:

- There is no new significant comparative evidence on the efficacy or safety of Beta Blockers; no further review or research needed.
- Evaluate comparative costs in executive session.

New Guidelines:

Evidence-based guidelines for the treatment of hypertension were recently released from the Eighth Joint National Committee (JNC8)[2] The following recommendations were made regarding the drug selection for the treatment of hypertension:

- The panel did not recommend Beta Blockers for the initial treatment of hypertension because in one study use of beta blockers resulted in a higher rate of the primary composite outcome of CV death, myocardial infarction, or stroke compared to use of an angiotensin receptor blocker. In other studies, beta blockers performed similar to the other recommended drug classes, or the evidence was insufficient to make a determination.

References:

1. Peterson K. Drug Effectiveness Review Project. Drug Class Review: Beta Adrenergic Blockers. Preliminary Scan Report #2. October 2013.

2. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the eighth joint national committee (jnc 8). *JAMA*. 2013. doi:10.1001/jama.2013.284427.

Drug Class Review

Beta Adrenergic Blockers

Preliminary Scan Report #2

October 2013

Last Report: Update #4 Final Report (July 2009)

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Scan conducted by:
Kim Peterson, MS

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Pacific Northwest Evidence-based Practice Center
Roger Chou, MD, Director
Marian McDonagh, PharmD, Associate Director

Oregon Health & Science University

OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations' consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Date of Last Update Report

Update #4, July 2009 (searches through January 2009)

Date of Last Preliminary Update Scan Report

October 2010

Scope and Key Questions

Key Questions

1. For adult patients with hypertension, angina, coronary artery bypass graft, recent myocardial infarction, heart failure, atrial arrhythmia, migraine or bleeding esophageal varices, do beta blocker drugs differ in effectiveness?
2. For adult patients with hypertension, angina, coronary artery bypass graft, recent myocardial infarction, heart failure, atrial arrhythmia, migraine or bleeding esophageal varices, do beta blocker drugs differ in safety or adverse events?
3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications (drug-drug interactions), or co-morbidities (drug-disease interactions) for which one beta blocker is more effective or associated with fewer adverse effects?

Inclusion Criteria

Populations

Adult patients with hypertension, angina, coronary artery bypass graft, recent myocardial infarction, heart failure, atrial arrhythmia, migraine or bleeding esophageal varices

Interventions

Interventions include an oral beta blocker compared with another beta blocker, another drug (such as calcium channel blocker), or placebo. (Oral beta blockers: acebutolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, carvedilol phosphate, labetalol, metoprolol tartrate, metoprolol succinate, nadolol, nebivolol, penbutolol, pindolol, propranolol, propranolol LA, timolol)

Table 1. Effectiveness outcomes

Hypertension	1. All-cause and cardiovascular mortality 2. Cardiovascular events (stroke, myocardial infarction, or development of heart failure) **3. End-stage renal disease (including dialysis or need for transplantation) or clinically significant and permanent deterioration of renal function (increase in serum creatinine or decrease in creatinine clearance)** 4. Quality-of-life
Chronic stable angina (treatment duration ≥ 2 months)	1. Exercise tolerance 2. Attack frequency 3. Nitrate use
Post-coronary artery bypass graft (long-term treatment)	1. All-cause mortality 2. Ischemic events (MI, unstable angina, need for repeat CABG and PTCA)
Recent myocardial infarction (with and without LV dysfunction)	1. All-cause and cardiovascular mortality 2. Cardiovascular events (usually, development of heart failure)
Symptomatic chronic heart failure	1. All-cause or cardiovascular mortality 2. Symptomatic improvement (heart failure class, functional status, visual analogue scores) 3. Hospitalizations for heart failure
Asymptomatic LV dysfunction	1. All-cause and cardiovascular mortality 2. Cardiovascular events (usually, development of heart failure)
Atrial arrhythmia	1. Rate control 2. Relapse into atrial fibrillation
Migraine	1. Attack frequency 2. Attack intensity/severity 3. Attack duration 4. Use of abortive treatment
Bleeding esophageal varices	1. All-cause mortality 2. Fatal/non-fatal rebleeding

Harms

- Overall adverse events
- Withdrawals due to adverse events
- Serious adverse events reported
- Specific adverse events

Study designs

1. For effectiveness, randomized controlled trials and good-quality systematic reviews
2. For harms, controlled clinical trials and observational studies

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from September 2010 through October 2013 using terms for included drugs. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, indications, and safety alerts. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) and the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/). All citations were imported into an electronic database (EndNote X3) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

We did not identify any new drugs in this or the previous scan.

New Indications

We did not identify any new indications in this or the previous scan.

New Black Box Warnings

We did not identify any new black box warnings in this or the previous scan.

Comparative Effectiveness Reviews

Reviews identified in this Preliminary Update Scan

We did not identify any new potentially relevant comparative effectiveness reviews in this or the previous scan.

Randomized Controlled Trials

Trials identified since the most recent Full Report

Medline searches from this scan resulted in 212 citations. Of those, there were 7 potentially relevant new trials (see Appendix A for abstracts). Together with the 10 potentially relevant trials identified in the last scan (Appendix B), now there are a total of 17. Characteristics of these trials are shown in Table(s) 2 and 3, below.

Table 2.Characteristics of head-to-head trials

Author Year	Beta Blockers	Population
Iliuta 2009	Betaxolol vs metoprolol	Coronary artery bypass grafting
Jabbour 2010	Carvedilol vs metoprolol succinate vs bisoprolol	Heart failure and chronic obstructive pulmonary disease
Shahzamani 2011	Carvedilol vs metoprolol	Coronary artery bypass grafting
Ulimoen 2013	Carvedilol vs metoprolol	Permanent atrial fibrillation
Udelson 2009	Carvedilol vs carvedilol phosphate	Heart failure
Marazzi 2011	Nebivolol vs carvedilol	Hypertensive heart failure
Espinola-Klein 2011	Nebivolol vs metoprolol	Hypertension with intermittent claudication
Sen 2009	Nebivolol vs metoprolol	Cardiac syndrome X

Among the publications of placebo-controlled trials, all involved patients with heart failure and 7 of 9 provide results from subanalyses of previously included trials (Table 2).

Table 3.Characteristics of placebo-controlled trials

Author Year	Beta Blockers	Focus
New Trials		
Hawkins 2009	Bisoprolol	Heart failure and moderate to severe chronic obstructive pulmonary disease
Silberstein 2012	Propranolol	Migraine
Subanalyses from SENIORS trial		
Ambrosio 2011	Nebivolol	Ischemic events
Cohen-Solal 2009	Nebivolol	Influence of renal dysfunction
de Boer 2010	Nebivolol	Influence of diabetes
Mulder 2012	Nebivolol	Influence of atrial fibrillation
van Veldhuisen 2009	Nebivolol	Influence of impaired and preserved left ventricular ejection fraction
Subanalyses from other previous trials		
Castagno 2010	Bisoprolol	Patients with heart failure and renal impairment (CIBIS-II)
Ghali 2009	Metoprolol CR	Patients with heart failure and deceased renal function (MERIT-HF)

Appendix A. Abstracts of potentially relevant new trials of Beta Adrenergic Blockers from current scan

Head-to-head trials

Shahzamani, M., A. Ghanavati, et al. (2011). "Carvedilol compared with metoprolol on left ventricular ejection fraction after coronary artery bypass graft." Journal of PeriAnesthesia Nursing **26**(6): 384-387.

A number of elective coronary artery bypass graft (CABG) surgery patients have impaired underlying left ventricular function (poor ejection fraction). This study was performed to compare the effect of postoperative oral carvedilol versus metoprolol on left ventricular ejection fraction (LVEF) after CABG compared with metoprolol. In a double-blind clinical trial, 60 patients with coronary artery disease, aged 35 to 65 years, who had an ejection fraction of 15% to 35% were included. Either carvedilol or metoprolol was administered the day after CABG. The patients were evaluated by the same cardiologist 14 days before and 2 and 6 months after elective CABG. The results demonstrated better improvements in LVEF in the carvedilol group. No difference regarding postoperative arrhythmias or mortality was detected. The results suggest that carvedilol may exert more of an improved myocardial effect than metoprolol for the low ejection fraction patients undergoing CABG in the early postoperative months.

Ulimoen, S. R., S. Enger, et al. (2013). "Comparison of four single-drug regimens on ventricular rate and arrhythmia-related symptoms in patients with permanent atrial fibrillation." American Journal of Cardiology **111**(2): 225-230.

Rate control of atrial fibrillation (AF) is a main treatment modality. However, data are scarce on the relative efficacy of calcium channel blockers and blockers or between drugs within each class. The purpose of the present study was to compare the effect of 4 rate-reducing, once-daily drug regimens on the ventricular heart rate and arrhythmia-related symptoms in patients with permanent AF. We included 60 patients (mean age 71 +/- 9 years, 18 women) with permanent AF in an investigator-blind cross-over study. Diltiazem 360 mg/day, verapamil 240 mg/day, metoprolol 100 mg/day, and carvedilol 25 mg/day were administered for 3 weeks in a randomized sequence. The 24-hour heart rate was measured using Holter monitoring, and arrhythmia-related symptoms were assessed using the Symptom Checklist questionnaire before randomization and on the last day of each treatment period. The 24-hour mean heart rate was 96 +/- 12 beats/min at baseline (no treatment), 75 +/- 10 beats/min with diltiazem, 81 +/- 11 beats/min with verapamil, 82 +/- 11 beats/min with metoprolol, and 84 +/- 11 beats/min with carvedilol. All drugs reduced the heart rate compared to baseline ($p < 0.001$ for all). The 24-hour heart rate was significantly lower with diltiazem than with any other drug tested ($p < 0.001$ for all). Compared to baseline, diltiazem significantly reduced both the frequency ($p < 0.001$) and the severity ($p = 0.005$) of symptoms. In contrast, verapamil reduced symptom frequency only ($p = 0.012$). In conclusion, diltiazem 360 mg/day was the most effective drug regimen for reducing the heart rate in patients with permanent AF. Arrhythmia-related symptoms were reduced by treatment with the calcium channel blockers diltiazem and verapamil, but not by the blockers.

Marazzi, G., M. Volterrani, et al. (2011). "Comparative long term effects of nebivolol and carvedilol in hypertensive heart failure patients." Journal of Cardiac Failure **17**(9): 703-709.

BACKGROUND: Beta-blockers improve left ventricular (LV) systolic function and prognosis in patients with chronic heart failure (CHF), but their different pleiotropic properties may influence their cardiovascular effects. This open-label study compared the effects of long-term treatment with nebivolol versus carvedilol on LV ejection fraction (LVEF), in hypertensive CHF patients. Secondary end points were to assess the effect of the 2 beta-blockers on exercise capacity and clinical outcome.

METHODS AND RESULTS: A total of 160 hypertensive CHF patients, with LVEF <40% and in New York Heart Association (NYHA) functional class I, II, or III, were randomly assigned to receive nebivolol or carvedilol for 24 months. At baseline and at the end of treatment, all patients underwent clinical evaluation, echocardiography, and 6-minute walking test. The target doses were 10 mg/d for nebivolol and 50 mg/d for carvedilol. Compared with baseline values, LVEF increased by a similar extent in the carvedilol (C) and nebivolol (N) groups (C from 36.1% (SD 1.5%) to 40.9% (SD 1.9%), P < .001; N from 34.1% (SD 1.8%) to 38.5% (SF 2.2%), P < .001). Heart rate and NYHA functional class decreased significantly in both groups, and the 6-minute walking distance increased (C from 420 m (SD 104 m) to 490 m (SD 115m), P < .001; N from 421 m (SD 118 m) to 487 m (SD 138 m), P < .001). During 24 months, 21 carvedilol recipients (26%) and 18 nebivolol recipients (22%) had cardiac events, including 3 and 4deaths, respectively.

CONCLUSION: In the long term, nebivolol and carvedilol appear to be similarly effective in the treatment of hypertensive patients with CHF.

Espinola-Klein, C., G. Weisser, et al. (2011). "-Blockers in patients with intermittent claudication and arterial hypertension: results from the nebivolol or metoprolol in arterial occlusive disease trial." Hypertension **58**(2): 148-154.

The use of -receptor blockers in peripheral arterial disease is controversial for their impact on vasomotor tone. The -blocker nebivolol possesses vasodilating, endothelium-dependent, NO-releasing properties that might be beneficial in peripheral arterial disease. The aim of the study was to evaluate the effects and tolerability of nebivolol in comparison with metoprolol in these patients. A total of 128 patients with intermittent claudication and essential hypertension were included and double-blind randomized to receive 5 mg of nebivolol (N=65) or 95 mg of metoprolol (N=63) once daily. End points were changes in ankle-brachial index, initial and absolute claudication distance, endothelial function assessed by flow-mediated dilatation of the brachial artery, blood pressure, and quality of life using the claudication scale questionnaire. End point analysis was possible in 109 patients (85.2%). After the 48-week treatment period, ankle-brachial index and absolute claudication distance improved significantly in both patient groups (P<0.05 for both), with no difference across treatments. A significant increase of initial claudication distance was found in the nebivolol group. Adjusted mean change of initial claudication distance was 33.9% after nebivolol (P=0.003) and 16.6% after metoprolol (P=0.12) treatment. Quality of life was not influenced by either treatment, and there was no relevant change in flow-mediated dilatation in patients treated with nebivolol or metoprolol (P=0.16). Both drugs were equally effective in lowering blood pressure. In conclusion, -blocker therapy

was well tolerated in patients with intermittent claudication and arterial hypertension during a treatment period of 1 year. In the direct comparison, there was no significant difference between nebivolol and metoprolol.

Placebo-controlled trials

Silberstein, S. D., D. W. Dodick, et al. (2012). "Randomized, placebo-controlled trial of propranolol added to topiramate in chronic migraine." Neurology **78**(13): 976-984.

OBJECTIVE: To assess the efficacy and safety of adding propranolol to topiramate in chronic migraine subjects inadequately controlled with topiramate alone.

METHODS: This was a double-blind, placebo-controlled, randomized clinical trial conducted through the National Institute of Neurological Disorders and Stroke Clinical Research Collaboration, expected to randomize 250 chronic migraine subjects inadequately controlled (>=10 headaches/month) with topiramate (50-100 mg/day) to either propranolol LA (long acting) (240 mg/day) or placebo. Primary outcome was 28-day moderate to severe headache rate reduction at 6 months (weeks 16 to 24) compared with baseline (weeks -4 to 0).

RESULTS: A planned interim analysis was performed after 48 sites randomized 171 subjects. The data and safety monitoring board recommended ending the trial after determining that it would be highly unlikely for the combination to result in a significant reduction in 28-day headache rate compared with topiramate alone if all 250 subjects were randomized. No safety concerns were identified. At study closure, 191 subjects were randomized. The 6-month reduction in moderate to severe 28-day headache rate and total 28-day headache rate for combination therapy vs topiramate alone was not significantly different: 4.0 vs 4.5 days (moderate to severe 28-day headache rate; p = 0.57) and 6.2 vs 6.1 days (total 28-day headache rate; p = 0.91).

CONCLUSIONS: This study does not provide evidence that the addition of propranolol LA to topiramate adds benefit when chronic migraine is inadequately controlled with topiramate alone. Classification of evidence: This study provides Class II evidence that propranolol LA, added to topiramate, is ineffective in chronic migraine patients who fail topiramate monotherapy.

Ambrosio, G., M. D. Flather, et al. (2011). "-blockade with nebivolol for prevention of acute ischaemic events in elderly patients with heart failure." Heart **97**(3): 209-214.

OBJECTIVES: This subanalysis of the Study of the Effects of Nebivolol Intervention on Outcomes and Hospitalisation in Seniors with Heart Failure (SENIORS) investigates whether treatment with nebivolol, a -blocker with nitric oxide-releasing properties, can provide additional benefits besides its effects on heart failure (HF), by reducing cardiac ischaemic events in patients with HF of ischaemic aetiology.

DESIGN: A double-blind, randomised, placebo-controlled, multicentre trial of nebivolol in 2128 elderly patients.

PATIENTS AND INTERVENTIONS: For this analysis, data were extracted for 2128 elderly (>= 70 years) HF patients in whom coronary artery disease (CAD) was the underlying aetiology (68.2%; 717 placebo-treated patients and 735 assigned to nebivolol).

MAIN OUTCOME MEASURES: The main endpoint was the composite of cardiac ischaemic events at 2 year follow-up: death/hospitalisation for myocardial infarction, unstable angina or sudden death, as originally identified in the case report form.

RESULTS: At follow-up, nebivolol treatment was associated with a one-third reduction in the risk of ischaemic events, the composite endpoint occurring in 15.9% of placebo and

10.7% of nebivolol-treated patients (HR 0.68; 95% CI 0.51 to 0.90; p=0.008). This effect was independent of age, gender and ejection fraction. No difference in this composite endpoint was observed in the subgroup of patients of non-ischaemic aetiology.
CONCLUSIONS: Nebivolol was effective in reducing cardiac ischaemic events in patients with HF of ischaemic aetiology. The prevention of ischaemic events can be an additional beneficial effect of -blockade in HF patients with underlying CAD.

Mulder, B. A., D. J. van Veldhuisen, et al. (2012). "Effect of nebivolol on outcome in elderly patients with heart failure and atrial fibrillation: insights from SENIORS." European Journal of Heart Failure **14**(10): 1171-1178.

AIMS: Beneficial effects of beta-blockade remain unclear in heart failure patients who have atrial fibrillation (AF), especially in the elderly. We evaluated the effect of nebivolol on cardiovascular outcomes in elderly patients with heart failure and AF.
METHODS AND RESULTS: The SENIORS trial showed an overall benefit of nebivolol compared with placebo in 2128 heart failure patients >70 years of age. At baseline, AF was present in 738 (34.7%) patients. The primary outcome was all-cause mortality or cardiovascular hospitalizations. After 21 months, the cumulative incidence of the primary outcome was significantly more common in patients with AF compared with those with sinus rhythm (38.5% vs. 30.4%, respectively, P < 0.001). In patients with AF, nebivolol had no beneficial effect on the primary outcome [nebivolol vs. placebo, 37.1% vs. 39.8%, hazard ratio (HR) 0.92, 95% confidence interval (CI), 0.73-1.17, P = 0.46], in contrast to patients with sinus rhythm (28.1% vs. 32.9%, in the nebivolol vs. placebo group, respectively, HR 0.82, 95% CI 0.67-0.99, P = 0.049). In patients with AF, the primary outcome was similar in the impaired and preserved left ventricular ejection fraction (LVEF) groups (39.0% with LVEF <= 35% vs. 37.3% in patients with LVEF > 35%). There was also no evidence of benefit of nebivolol in AF patients stratified by LVEF.
CONCLUSION: Nebivolol failed to improve outcomes in elderly patients with stable heart failure and co-existing AF, irrespective of LVEF. Furthermore, in patients with AF, outcome was comparable between patients with preserved and impaired LVEF.

Appendix B. Abstracts of potentially relevant new trials of Beta Adrenergic Blockers from previous scan in October 2010

Head-to-head trials

Iliuta, L., R. Christodorescu, et al. (2009). "Prevention of perioperative atrial fibrillation with betablockers in coronary surgery: betaxolol versus metoprolol." Interactive Cardiovascular & Thoracic Surgery **9**(1): 89-93.

In this study, we tried to compare the efficacy and safety of betaxolol vs. metoprolol immediately postoperatively in coronary artery bypass grafting (CABG) patients and to determine whether prophylaxy for atrial fibrillation (AF) with betaxolol could reduce hospitalization and economic costs after cardiac surgery. Our trial was open-label, randomized, multicentric enrolling 1352 coronary surgery patients randomized to receive betaxolol or metoprolol. The primary endpoints were the composites of 30-day mortality, in-hospital AF (safety endpoints), duration of hospitalization and immobilization, quality of life, and the above endpoint plus in-hospital embolic event, bradycardia, gastrointestinal symptoms, sleep disturbances, cold extremities (efficacy plus safety endpoint). At the end of the study the incidence and probability of early postoperative AF with betaxolol was lower than with metoprolol in coronary surgery (P<0.0001). In the two study groups minor side effects were similar and no major complication was reported (P<0.001). Patient compliance was good and the general condition improved due to shortened hospitalization and immobilization with subsequent improvement in the psychological status, less arrhythmias and lack of significant side effects. In conclusion, because of its efficacy and safety, betaxolol was superior to metoprolol for the prevention of the early postoperative AF in coronary surgery.

Jabbour, A., P. S. Macdonald, et al. (2010). "Differences between beta-blockers in patients with chronic heart failure and chronic obstructive pulmonary disease: a randomized crossover trial." Journal of the American College of Cardiology **55**(17): 1780-7.

OBJECTIVES: The purpose of this study was to determine the respiratory, hemodynamic, and clinical effects of switching between beta1-selective and nonselective beta-blockers in patients with chronic heart failure (CHF) and chronic obstructive pulmonary disease (COPD). BACKGROUND: Carvedilol, metoprolol succinate, and bisoprolol are established beta-blockers for treating CHF. Whether differences in beta-receptor specificities affect lung or vascular function in CHF patients, particularly those with coexistent COPD, remains incompletely characterized. METHODS: A randomized, open label, triple-crossover trial involving 51 subjects receiving optimal therapy for CHF was conducted in 2 Australian teaching hospitals. Subjects received each beta-blocker, dose-matched, for 6 weeks before resuming their original beta-blocker. Echocardiography, N-terminal pro-hormone brain natriuretic peptide, central augmented pressure from pulse waveform analysis, respiratory function testing, 6-min walk distance, and New York Heart Association (NYHA) functional class were assessed at each visit. RESULTS: Of 51 subjects with a mean age of 66 +/- 12 years, NYHA functional class I (n = 6), II (n = 29), or III (n = 16), and left ventricular ejection fraction mean of 37 +/- 10%, 35 had coexistent COPD. N-terminal pro-hormone brain natriuretic peptide was

significantly lower with carvedilol than with metoprolol or bisoprolol (mean: carvedilol 1,001 [95% confidence interval (CI): 633 to 1,367] ng/l; metoprolol 1,371 [95% CI: 778 to 1,964] ng/l; bisoprolol 1,349 [95% CI: 782 to 1,916] ng/l; $p < 0.01$), and returned to baseline level on resumption of the initial beta-blocker. Central augmented pressure, a measure of pulsatile afterload, was lowest with carvedilol (carvedilol 9.9 [95% CI: 7.7 to 12.2] mm Hg; metoprolol 11.5 [95% CI: 9.3 to 13.8] mm Hg; bisoprolol 12.2 [95% CI: 9.6 to 14.7] mm Hg; $p < 0.05$). In subjects with COPD, forced expiratory volume in 1 s was lowest with carvedilol and highest with bisoprolol (carvedilol 1.85 [95% CI: 1.67 to 2.03] l/s; metoprolol 1.94 [95% CI: 1.73 to 2.14] l/s; bisoprolol 2.0 [95% CI: 1.79 to 2.22] l/s; $p < 0.001$). The NYHA functional class, 6-min walk distance, and left ventricular ejection fraction did not change. The beta-blocker switches were well tolerated. CONCLUSIONS: Switching between beta1-selective beta-blockers and the nonselective beta-blocker carvedilol is well tolerated but results in demonstrable changes in airway function, most marked in patients with COPD. Switching from beta1-selective beta-blockers to carvedilol causes short-term reduction of central augmented pressure and N-terminal pro-hormone brain natriuretic peptide. (Comparison of Nonselective and Beta1-Selective Beta-Blockers on Respiratory and Arterial Function and Cardiac Chamber Dynamics in Patients With Chronic Stable Congestive Cardiac Failure; Australian New Zealand Clinical Trials Registry, ACTRN12605000504617).

Sen, N., Y. Tavil, et al. (2009). "Nebivolol therapy improves endothelial function and increases exercise tolerance in patients with cardiac syndrome X." Anadolu Kardiyoloji Dergisi **9**(5): 371-9.

OBJECTIVE: We sought to determine whether nebivolol affects coronary endothelial function and exercise induced ischemia in patients with cardiac syndrome X (CSX). METHODS: The study protocol undertaken was based on a single-blind randomized controlled prospective study. After a 2-week washout period, 38 patients with cardiac syndrome X were randomized to receive either nebivolol 5 mg daily (n=19) or metoprolol 50 mg daily (n=19) in a single- blind design for 12 weeks. The control group under study was consisted of 16 age- and gender-matched subjects with negative treadmill exercise tests. Plasma endothelial nitric oxide (NOx), L-arginine, and asymmetric dimethylarginine (ADMA) were measured in all patients at baseline and after 12 weeks of treatment. Statistical differences among groups were tested by one-way analysis of variance and unpaired samples t test for parametric; Kruskal-Wallis and Mann-Whitney U tests for non-parametric variables, respectively. A paired samples t test was used to compare continuous variables before and after drug therapy. RESULTS: At baseline, plasma level of NOx, L-arginine, and L-arginine/ADMA ratio were lower ($p<0.001$ for all) in patients with CSX than in the control patients. Whereas, the plasma ADMA levels were increased in the patient group ($p<0.001$). After 12 weeks of drug therapy, the patients taking nebivolol had increased levels of plasma NOx , plasma L-arginine, the L-arginine/ADMA ratio and decreased levels of plasma ADMA compared to those of the patients taking metoprolol ($p<0.001$). In addition, exercise duration to 1-mm ST depression and total exercise duration significantly increased after treatment in the nebivolol group compared to the metoprolol group ($p<0.01$). In the nebivolol group,

Canadian Cardiovascular Society (CCS) angina classification improved by one or more categories in 12 (70%) patients, whereas it deteriorated or remained in the same category in 5 (30%) patients. Meanwhile, in the metoprolol group, the CCS angina classification improved by one or more categories in 7 (41%), whereas it deteriorated or remained in the same category in 10 (59%) patients. CONCLUSION: Circulating endothelial function parameters (plasma ADMA, L-arginine, NOx levels) were impaired in patients with CSX. Nebivolol treatment was associated with better improvements in both circulating endothelial function and exercise stress test parameters than metoprolol. We believe that further studies are needed to evaluate the effects of nebivolol treatment on long-term clinical outcomes in patients with CSX.

Udelson, J. E., S. J. Pressler, et al. (2009). "Adherence with once daily versus twice daily carvedilol in patients with heart failure: the Compliance And Quality of Life Study Comparing Once-Daily Controlled-Release Carvedilol CR and Twice-Daily Immediate-Release Carvedilol IR in Patients with Heart Failure (CASPER) Trial." Journal of Cardiac Failure **15**(5): 385-93.

BACKGROUND: Suboptimal compliance in taking guideline-based pharmacotherapy in patients with chronic heart failure (HF) potentially increases the burden of hospitalizations and diminishes quality of life. By simplifying the medical regimen, once-daily dosing can potentially improve compliance. The Compliance And Quality of Life Study Comparing Once-Daily Controlled-Release Carvedilol CR and Twice-Daily Immediate-Release Carvedilol IR in Patients with Heart Failure (CASPER) Trial was designed to measure differential compliance, satisfaction, and quality of life in chronic HF patients taking carvedilol immediate release (IR) twice daily versus the bioequivalent carvedilol controlled-release (CR) once daily. METHODS AND RESULTS: CASPER was a prospective multicenter, 3-arm, parallel-group, randomized clinical trial for a 5-month period. The primary objective of the study was to evaluate and compare compliance with carvedilol IR twice daily (BID) and carvedilol phosphate CR once daily (QD) in patients with chronic HF who were taking carvedilol IR. Secondary objectives included comparisons of quality of life (Kansas City Cardiomyopathy Questionnaire), satisfaction with medication, and brain natriuretic peptide levels between subjects taking the two formulations. A total of 405 patients with chronic HF and left ventricular dysfunction were randomized to: (A) carvedilol IR twice daily, given double blind; (B) carvedilol CR taken in the morning and placebo in the afternoon, given double blind; or (C) carvedilol CR once daily, open label. Compliance was measured using the medication event monitoring system that captures time of bottle opening. The primary end point was a comparison of taking compliance (doses taken divided by total number of prescribed doses over the actual duration of the study) between the double-blind carvedilol IR BID versus the open-label carvedilol CR QD groups. Sample size estimates were based on assumptions of 75% compliance with BID dosing and 90% compliance with QD dosing. Mean compliance with carvedilol IR BID was 89.3% compared with 88.2% for carvedilol CR QD, and differential mean compliance was 1.1% (95% CI -4.4%, 6.6%; ie, not significant). There were no statistically significant differences in compliance between any of the 3 groups, nor differences in quality of life, treatment satisfaction, or physiologic measures among the 3 study arms. There were also no significant differences in adverse events or side effects among patients switching from carvedilol IR to carvedilol CR in arms B or C over the 5-month study duration compared with patients remaining on

carvedilol IR. CONCLUSIONS: Compliance among chronic HF patients in the CASPER trial was high at baseline and unaffected by QD versus BID dosing. Over the 5-month follow-up period, there were no differences in adverse events among patients switching from carvedilol IR to CR.

Placebo-controlled trials

Castagno, D., P. S. Jhund, et al. (2010). "Improved survival with bisoprolol in patients with heart failure and renal impairment: an analysis of the cardiac insufficiency bisoprolol study II (CIBIS-II) trial." European Journal of Heart Failure **12**(6): 607-16.

AIMS: Information on the effectiveness of beta-blockade in patients with heart failure (HF) and concomitant renal impairment is scarce and beta-blockers are underutilized in these patients. METHODS AND RESULTS: The Cockcroft-Gault formula normalized for body surface-area was used to estimate renal function (eGFR(BSA)) in 2622 patients with HF, left ventricular ejection fraction < or =35%, New York Heart Association class III/IV and serum creatinine <300 micromol/L (3.4 mg/dL) in the second Cardiac Insufficiency Bisoprolol Study II. Patients were divided into four sub-groups according to baseline eGFR(BSA) (<45, 45-60, 60-75 and > or =75 mL/min per 1.73 m(2)). Cox proportional-hazards models adjusted for pre-specified confounders were used to assess the effect of bisoprolol and potential heterogeneity of effect across the eGFR(BSA) sub-groups. Older age, female-sex, diabetes and ischaemic-aetiology were more common in those with reduced eGFR(BSA). The hazard associated with bisoprolol use for all-cause mortality, the composite of all-cause mortality or HF-hospitalization and HF-hospitalization alone was consistently <1.0 across eGFR(BSA) categories with no treatment by renal-function interaction (P = 0.81, P = 0.66, P = 0.71, respectively). The rate of bisoprolol discontinuation was higher in patients with eGFR(BSA) < 45 mL/min per 1.73 m(2). Nevertheless the absolute benefit of bisoprolol was greater for patients with chronic kidney disease compared with those without. CONCLUSION: The beneficial effects of bisoprolol on mortality and hospitalization for worsening heart-failure were not modified by baseline eGFR(BSA). Renal impairment should not prevent the use of bisoprolol in patients with HF.

Cohen-Solal, A., D. Kotecha, et al. (2009). "Efficacy and safety of nebivolol in elderly heart failure patients with impaired renal function: insights from the SENIORS trial." European Journal of Heart Failure **11**(9): 872-80.

AIM: To determine the safety and efficacy of nebivolol in elderly heart failure (HF) patients with renal dysfunction. METHODS AND RESULTS: SENIORS recruited patients aged 70 years or older with symptomatic HF, irrespective of ejection fraction, and randomized them to nebivolol or placebo. Patients (n = 2112) were divided by tertile of estimated glomerular filtration rate (eGFR). Mean age of patients was 76.1 years, 35% of patients had an ejection fraction of >35%, and 37% were women resulting in a unique cohort, far more representative of clinical practice than previous trials. eGFR was strongly associated with outcomes and nebivolol was similarly efficacious across eGFR tertiles. The primary outcome rate (all-cause mortality or cardiovascular hospital admission) and adjusted hazard ratio for nebivolol use in those with low eGFR was 40% and 0.84 (95% CI 0.67-1.07), 31% and 0.79 (0.60-1.04) in the middle tertile, and 29% and 0.86 (0.65-1.14) in the highest eGFR tertile. There was no interaction noted between renal function and the treatment effect (P = 0.442). Nebivolol use in patients with moderate renal impairment (eGFR <60) was not associated with major safety concerns, apart from higher rates of drug-discontinuation due to bradycardia. CONCLUSION:

Nebivolol is safe and has a similar effect in elderly HF patients with mild or moderate renal impairment.

de Boer, R. A., W. Doehner, et al. (2010). "Influence of diabetes mellitus and hyperglycemia on prognosis in patients > or =70 years old with heart failure and effects of nebivolol (data from the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with heart failure [SENIORS])." American Journal of Cardiology **106**(1): 78-86.e1.

The beneficial effects of beta blockers in younger patients with heart failure (HF) due to systolic dysfunction are well established. However, data from patients > or =70 years old with diabetes mellitus and HF are lacking. The Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with heart failure [SENIORS] tested the efficacy of the vasodilator beta blocker nebivolol in patients > or =70 years old with HF and impaired or preserved left ventricular ejection fraction. In the present analysis, we evaluated the association between diabetes mellitus and baseline glucose levels on the primary outcome (all-cause mortality and cardiovascular hospitalization) and secondary end points, including all-cause mortality, cardiovascular hospitalizations, and cardiovascular mortality. Of 2,128 patients, 555 (26.1%) had diabetes mellitus. Of the 555 patients with diabetes mellitus, 223 (40.2%) experienced the primary end point compared to 484 (30.8%) of the 1,573 nondiabetic patients (p <0.001). For the nondiabetic patients, the rate of the primary outcome for placebo compared to nebivolol was 33.7% for the placebo group and 27.8% for the nebivolol group (hazard ratio 0.78, 95% confidence interval 0.65 to 0.93; p = 0.006). In the diabetic subset, the rate was 40.3% for the placebo group and 40.1% for the nebivolol group (hazard ratio 1.04, 95% confidence interval 0.80 to 1.35, p = 0.773). The subgroup interaction p value was 0.073. The baseline glucose levels in the nondiabetic patients did not significantly affect the outcomes. The effect of diabetes mellitus on outcome was independent of the left ventricular ejection fraction and was most pronounced in those with HF due to a nonischemic etiology. In conclusion, in patients > or =70 years old with HF, diabetes mellitus was associated with a worse prognosis. Nebivolol was less effective in the patients with diabetes and HF than in those with HF but without diabetes who were > or =70 years old. Copyright (c) 2010 Elsevier Inc. All rights reserved.

Ghali, J. K., J. Wikstrand, et al. (2009). "The influence of renal function on clinical outcome and response to beta-blockade in systolic heart failure: insights from Metoprolol CR/XL Randomized Intervention Trial in Chronic HF (MERIT-HF)." Journal of Cardiac Failure **15**(4): 310-8.

BACKGROUND: Limited information is available on the risk and impact of renal dysfunction on the response to beta-blockade and mode of death in systolic heart failure (HF). METHODS AND RESULTS: Renal function was estimated with glomerular filtration rate (eGFR) using the simplified Modification of Diet in Renal Disease (MDRD) equation. Patients from the Metoprolol CR/XL Controlled Randomized Intervention Trial in Chronic HF (MERIT-HF) were divided into 3 renal function subgroups (MDRD formula): eGFR(MDRD) > 60 (n = 2496), eGFR(MDRD) 45 to 60 (n = 976), and eGFR(MDRD) < 45 mL/min per 1.73 m(2) body surface area (n = 493). Hazard ratio (HR) was estimated with Cox proportional hazards models adjusted for prespecified risk factors. Placebo patients with eGFR < 45 had significantly higher risk than those with eGFR > 60: HR for all-cause mortality, 1.90 (95% confidence interval

[CI], 1.28 to 2.81) comparing placebo patients with eGFR < 45 and eGFR > 60, and for the combined end point of all-cause mortality/hospitalization for worsening HF (time to first event): HR, 1.91 (95% CI, 1.44 to 2.53). No significant increase in risk with deceased renal function was observed for those randomized to metoprolol controlled release (CR)/extended release (XL) due to a highly significant decrease in risk on metoprolol CR/XL in those with eGFR < 45. For total mortality, metoprolol CR/XL vs placebo: HR, 0.41 (95% CI. 0.25 to 0.68; P < .001) in those with eGFR < 45 compared with HR, 0.71 (95% CI, 0.54 to 0.95; P < .021) for those with eGFR > 60; corresponding data for the combined end point was HR, 0.44 (95% CI, 0.31 to 0.63; P < .0001) and HR, 0.75 (0.62 to 0.92; P = .005, respectively; P = .095 for interaction by treatment for total mortality; P = .011 for combined end point). Metoprolol CR/XL was well tolerated in all 3 renal function subgroups. CONCLUSIONS: Renal function as estimated by eGFR was a powerful predictor of death and hospitalizations from worsening HF. Metoprolol CR/XL was at least as effective in reducing death and hospitalizations for worsening HF in patients with eGFR < 45 as in those with eGFR > 60.

Hawkins, N. M., M. R. MacDonald, et al. (2009). "Bisoprolol in patients with heart failure and moderate to severe chronic obstructive pulmonary disease: a randomized controlled trial." European Journal of Heart Failure **11**(7): 684-90.

AIMS: Heart failure (HF) and chronic obstructive pulmonary disease (COPD) frequently coexist. No study has prospectively examined the effects of beta-blockade in those with both conditions. METHODS AND RESULTS: We randomized 27 patients with HF and coexistent moderate or severe COPD to receive bisoprolol or placebo, titrated to maximum tolerated dose over 4 months. The primary outcome was forced expiratory volume in 1 s (FEV(1)). The study is registered with ClinicalTrials.gov, number: NCT00702156. Patients were elderly and predominantly male. Cardiovascular comorbidity, smoking history, and pulmonary function were similar in each group (mean FEV(1) 1.37 vs. 1.26 L, P = 0.52). A reduction in FEV(1) occurred after 4 months following treatment with bisoprolol compared with placebo (-70 vs. +120 mL, P = 0.01). Reversibility following inhaled beta(2)-agonist and static lung volumes were not impaired by bisoprolol. All measures of health status exhibited a consistent non-significant improvement, including the Short Form 36 physical and mental component scores (2.6 vs. 0.5 and 0.8 vs. -0.3, respectively), Minnesota Living with Heart Failure Questionnaire (-2.5 vs. 3.5) and Chronic Respiratory Questionnaire (0.07 vs. -0.24). The mean number of COPD exacerbations was similar in the bisoprolol and placebo groups (0.50 and 0.31, respectively, P = 0.44). CONCLUSION: Initiation of bisoprolol in patients with HF and concomitant moderate or severe COPD resulted in a reduction in FEV(1). However, symptoms and quality of life were not impaired.

van Veldhuisen, D. J., A. Cohen-Solal, et al. (2009). "Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: Data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure)." Journal of the American College of Cardiology **53**(23): 2150-8.

OBJECTIVES: In this pre-specified subanalysis of the SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure) trial, which examined the effects of nebivolol in elderly heart failure (HF)

patients, we explored the effects of left ventricular ejection fraction (EF) on outcomes, including the subgroups impaired EF (< or =35%) and preserved EF (>35%). BACKGROUND: Beta-blockers are established drugs in patients with HF and impaired EF, but their value in preserved EF is unclear. METHODS: We studied 2,111 patients; 1,359 (64%) had impaired (< or =35%) EF (mean 28.7%) and 752 (36%) had preserved (>35%) EF (mean 49.2%). The effect of nebivolol was investigated in these 2 groups, and it was compared to explore the interaction of EF with outcome. Follow-up was 21 months; the primary end point was all-cause mortality or cardiovascular hospitalizations. RESULTS: Patients with preserved EF were more often women (49.9% vs. 29.8%) and had less advanced HF, more hypertension, and fewer prior myocardial infarctions (all p < 0.001). During follow-up, the primary end point occurred in 465 patients (34.2%) with impaired EF and in 235 patients (31.2%) with preserved EF. The effect of nebivolol on the primary end point (hazard ratio [HR] of nebivolol vs. placebo) was 0.86 (95% confidence interval: 0.72 to 1.04) in patients with impaired EF and 0.81 (95% confidence interval: 0.63 to 1.04) in preserved EF (p = 0.720 for subgroup interaction). Effects on all secondary end points were similar between groups (HR for all-cause mortality 0.84 and 0.91, respectively), and no p value for interaction was <0.48. CONCLUSIONS: The effect of beta-blockade with nebivolol in elderly patients with HF in this study was similar in those with preserved and impaired EF.

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Month/Year of Review: January 2014
PDL Classes: ACEIs/ARBs/DRIs

Date of Last Review: January 2012
Source Document: OSU College of Pharmacy

Current Status of PDL Class:

Current Preferred Agents	Current Non-Preferred Agents
ACEIs	
Benazepril	Perindopril (Aceon®)
Captopril	
Enalapril	
Fosinopril	
Lisinopril	
Moexipril	
Quinapril	
Ramipril	
Trandolapril	
ARBs	
Olmesartan (Benicar®)	Candesartan (Atacand®)
Losartan	Eprosartan (Teveten®)
Telmisartan (Micardis®)	Irbesartan (Avapro®)
	Valsartan (Diovan®)
	Azilsartan medoxomil (Edarbi®)
DRIs	
	Aliskiren (Tekturna®)
Combination Products	
Benazepril-HCTZ	Amlodipine/olmesartan (Azor®)
Olmesartan-hydrochlorothiazide (Benicar HCT®)	Amlodipine/valsartan (Exforge®)
Captopril/HCTZ	Telmisartan/amlodipine (Twynsta®)
Enalapril/HCTZ	Aliskiren/valsartan (Valturna®)
Fosinopril/HCTZ	Aliskiren/amlodipine/HCTZ (Amturnide®)
Lisinopril/HCTZ	Aliskiren/amlodipine (Tekamlo®)
Losartan/HCTZ	Amlodipine/benzepril (Lotrel®)
Telmisartan/HCTZ (Micardis HCT®)	Trandolapril/verapamil (Tarka®)
Quinapril/HCTZ	Tekturna/HCTZ
moexiprilHCTZ	Valsartan/HCTZ (Diovan HCT®)

Abbreviations: ACEI – Ace Inhibitor, ARBs – Angiotensin Receptor Blockers, DRIs-direct renin inhibitor.

Previous Conclusions and Recommendation:

- There are no clinically significant differences among angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs).
- Rates of cough were lower with ARBs than ACEIs. However, overall rates of withdrawal were the same.
- DUE to a lack of comparative effectiveness research for any clinical outcomes, recommend maintaining all DRIs and products containing a DRI as non-preferred on the PDL.
- Due to lack of long term studies demonstrating a reduction of cardiovascular (CV) events and mortality or long-term safety compared to multiple alternatives, recommend making azilsartan a nonpreferred ARB.

Research Questions:

- Is there any new comparative evidence on ACE-Is, ARBs, or DRIs on mortality, cardiovascular events, end-stage renal disease, or quality of life?
- Is there any new comparative safety evidence of Beta Blockers??
- Are there subpopulations of patients for which one medication or preparation is more effective or associated with fewer adverse effects?

Conclusions and Recommendations:

- There is moderate quality evidence that dual blockade of the renin-angiotensin system does not provide any benefit in all-cause mortality and CV mortality compared with monotherapy. There is also an increase in the risk of hyperkalemia, hypotension, renal failure, and withdrawal due to adverse events with dual therapy compared to monotherapy.[1]
- There is moderate quality of evidence of no difference between ACEIs and ARBs in mortality, CV mortality, hospitalizations, and stroke.
- New JNC8 guidelines recommend ACEIs and ARBs (in addition to thiazide diuretics and calcium channel blockers) as initial treatment options in the general nonblack population for the treatment of hypertension (HTN) based on comparable efficacy on overall mortality, CV, and cerebrovascular outcomes. [2]
- There is insufficient evidence evaluating azilsartan/chlorthalidone combination therapy on long term clinical outcomes. Maintain as non-preferred and evaluate comparative costs in executive session.
- There is no new comparative efficacy or safety evidence for preference of one agent over another within each class. Evaluate comparative costs in executive session.

Methods:

The DERP scan was used to identify any new comparative research on the ACEI's that has emerged since the last P&T review. [3] An additional MEDLINE search was conducted using ARBs and DRIs as search terms with limits for human studies and English language, randomized controlled trials (RCTs) and meta-analyses. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. Forty three citations resulted initially for the DRI search. After exclusion due to wrong comparator, poor study design, or wrong outcomes, 3 systematic reviews and 7 RCTs were identified. An initial 322 citations resulted from the ARB literature search, resulting in 4 potentially relevant systematic reviews and 3 RCTs. Poor quality systematic reviews were not included in this review, as well as reviews that only measured surrogate endpoints.[4,5]

Systematic Reviews:

A systematic review evaluated aliskiren/amlodipine vs. aliskiren/HCTZ in hypertension.[6] A MEDLINE search through December 2012 reported on 19 studies (n=13,614). The primary endpoint was reduction from baseline to the end of treatment in mean clinical systolic blood pressure (SBP) and diastolic blood pressure (DMP). The quality of the RCTs was assessed by the Jada scale. All but one study were given a quality score of 4 or 5. An indirect comparison showed that aliskiren/amlodipine was more effective than aliskiren/HCTZ in both mean SBP (weighted mean difference [WMD] -3.36 mm Hg; p=0.97) and mean DBP (WMD -3.39 mm Hg; p=0.78). There was no difference in adverse events or withdrawals due to adverse events.

The effect of combination treatment with aliskiren and blockers of the renin-angiotensin system on hyperkalemia and acute kidney injury was assessed in a systematic review and meta-analysis.[7] Two reviewers used the Cochrane checklist to assess the risk of bias in included studies. Ten RCTs were identified and included in the review. The risk of bias was low. The risk of hyperkalemia was significantly higher among those given aliskiren in combination with an ACEI or ARB than among those given ACEI or ARB monotherapy (RR 1.58; 95% CI 1.24-2.02; NNH 43) as well as compared to aliskiren

monotherapy (RR 1.67, 95% CI 1.01-2.79; NNH50). The risk of acute kidney injury was not significantly increased with aliskiren in combination with an ACEI or ARB compared to ACEI or ARB monotherapy (RR 1.14; 95% CI 0.68-1.89) or aliskiren monotherapy (RR 0.80; 95% CI 0.31-2.04). Many of these studies were small and not designed to measure safety outcomes.

A systematic review was done to compare the long term efficacy and adverse events of dual blockade of the renin-angiotensin system with monotherapy.[1] A total of 33 trials met the inclusion criteria. A combination of an ACEI and ARB was used in 22 trials. Eighteen trials were deemed to be at low risk of bias and the remainder to be at high risk. Seven trials reported on all-cause mortality. When compared with monotherapy alone, dual therapy had no benefit on all-cause mortality (RR 0.97; 95% CI 0.89-1.06, p=0.50). In a subgroup analysis, mortality was increased in the cohort of patients without heart failure (15.3% vs. 15.0%; RR 1.07, 95% CI 1.00-1.14; p=0.04) but not in the group with heart failure. Dual therapy also had no significant benefit on CV mortality (14.7% vs. 15.7%; RR 0.96; 95% CI 0.88-1.05; p=0.38. Based on 5 trials, dual therapy was associated with a reduction in admissions to hospital for heart failure compared with monotherapy (10.3% vs. 18%; RR 0.82; 95% CI 0.74-0.92; p=0.0003). For observed safety outcomes, dual therapy was associated with a significant increase in the risk of hyperkalemia (RR 1.55; 95% CI 1.32-1.82, p<0.001) compared with monotherapy, as well as an increased risk of renal failure (RR 1.41; 95% CI 1.09-1.85; p=0.01). There was also an increase seen in withdrawals due to adverse events in the dual group compared to monotherapy (17.1% vs. 14.5%; RR 1.27; 95% CI 1.21-1.32; p<0.001).

A Cochrane Systematic Review assessed the benefits and harms of ARBs compared with ACEIs or placebo in their use for chronic heart failure.[8] A total of 24 studies met the inclusion criteria for review. Results demonstrated that, in patients with left ventricular ejection fraction (LVEF) of 40% or lower, the reduction in total mortality with ARB therapy was of borderline statistical significance compared to placebo (RR 0.87; 95% CI 0.76-1.00). However, when including only the trials with full reporting, there was no statistically significant difference (RR 0.91; 95% CI 0.79-1.04) between ARBs and placebo. There was no difference between ARBs and placebo for CV and non-CV mortality. Eight studies compared ARBs to ACEIs and showed no difference between them in total mortality, CV mortality, or non-CV mortality. There was also no difference between ACEIs and ARBs in total hospitalizations (RR 1.00; 95% CI 0.92-1.08), MI (RR 1.00; 95% CI 0.62-1.63), and stoke (RR 1.63; 95% CI 0.77-3.44) but withdrawals due to adverse effects were lower with ARBs (RR 0.63; 95% CI 0.52-0.76). Combinations of ARBs and ACEIs increased the risk of withdrawals due to adverse effects, but did not reduce total mortality or hospitalizations versus ACEI's alone.

A review by Savarese et al., assessed the effects of ACEIs and ARBs on the composite outcome of CV death, MI, and stroke, and on all-cause death, new-onset HF, and new-onset diabetes mellitus.[9] Using the PRISMA methods, RCTs comparing either an ARB or an ACEI with placebo were considered for the analysis and were assessed for quality using the Detsky method. ACEIs significantly reduced the risk of the composite outcome by 14.9% compared with placebo (OR 0.830; 95% CI 0.74-0.93/ p=0.001). They significantly reduced the risk of MI (OR 0.81; 95% CI 0.75-0.88; p<0.001) and stroke (OR 0.8; 95% CI 0.7-0.9/ p-0.004), but did not show a difference in reduction in CV death (OR 0.9; 95% CI 0.8-1.03; p=0.112). ACEIs significantly reduced the risk of all-cause death, new-onset HF and new-onset diabetes mellitus. ARBs also reduced the risk of the composite outcome (OR 0.92; 95% CI 0.9-0.98/ p=0.005). ARBs did not reduce the risk of CV death (OR 1.033; 95% CI 0.9-1.3, p=0.75), but did significantly reduce the risk of stroke (OR 0.9; 95% CI 0.8-0.98; p=0.011). There was no difference seen in risk of MI, all-cause death, or new-onset HF.

A meta-analysis evaluated the effect of ARBs on the development of new-onset type 2 diabetes. RCTs were included and assessed for quality using the Cochrane handbook.[10] Eleven RCTs with 79,773 patients were included. Overall, new onset diabetes was significantly lowered in the ARB group compared to the control group (9.9% vs. 11.9%; OR 0.79; 95% CI 0.74-084; p<0.000001). ARBs were associated with a reduction in the risk of new-onset diabetes compared with placebo, beta-blockers, calcium channel blockers, and non-ARBs. However, diabetes was defined differently among the trials and the incidence of diabetes was not the primary outcome of the trials.

New Guidelines:

JNC8:

Evidence-based guidelines for the treatment of hypertension were recently released from the Eighth Joint National Committee (JNC8)[2] The following recommendations were made regarding the drug selection for the treatment of hypertension:

- In the general nonblack population, initial antihypertensive treatments should include a thiazide-type diuretic, calcium channel blocker, ACEI, or ARB (Moderate recommendation – Grade B).
    - Each of these classes had comparable effects on overall mortality and CV, cerebrovascular, and kidney outcomes.
    - No preference of a specific agent in each class was given.

Canadian Hypertension Education Program

The Canadian guidelines for the management of Hypertension were updated in 2012 with the following main recommendations regarding drug selection:[11]

- An ACEI or ARB is recommended for most patients with HTN and coronary artery disease (Grade A).
- For patients with stable angina, Beta blockers are preferred as initial therapy (Grade B).
- For patients with coronary artery disease, but without coexisting systolic heart failure, the combination of an ACEI and ARB is not recommended (Grade B).
- For patients who have had a recent myocardial infarction (MI), initial therapy should include both a Beta blocker and an ACE inhibitor (Grade A).
- An ARB can be used if the patient is intolerant of an ACEI (Grade A).
- After acute stroke, treatment with an ACEI and diuretic combination is preferred (Grade B).

Safety Alerts:

In April 2012, the FDA released a safety announcement warning of possible risks when using medicines containing aliskiren with ACEIs and ARBs in patients with diabetes or kidney impairment.[12] These drug combinations should not be used in patients with diabetes. This is a result of preliminary data from a clinical trial (ALLTITUDE).[13] In ALLTITUDE, the risks of kidney impairment, low blood pressure, and hyperkalemia in a group of patients taking aliskiren plus an ARB or ACEI increased relative to a group of patients taking placebo plus an ARB or ACEI. There was also a slight excess of CV events in the aliskiren group.

New Drugs:

The combination of azilsartan medoximil and cholrthalidone (Edarbyclor®) was recently FDA approved as a fixed-dose combination medication for patients with an inadequate response to monotherapy or those in whom multiple drugs are required to achieve blood pressure control.[14] This is the only ARB found in combination with the diuretic, chlorthalidone. There are no head to head trials comparing hydrochlorothiazide to chlorthalidone in CV events.

A double-blind RCT compared the antihypertensive efficacy of azilsartan/chlorthalidone versus azilsartan or chlorthalidone monotherapy in 1714 patient with stage 2 HTN over 8 weeks.[15] Azilsartan/chlorthalidone 40mg/25mg and 40mg/12.5mg significantly lowered SBP compared to monotherapy.

A second RCT evaluated the efficacy of azilsartan/chlorthalidone with olmesartan/hydrochlorothiazide in 1071 patients with stage 2 HTN.[16] Twenty four SBP was reduced by 5.3 mm Hg more in the azilsartan group compared to the olmesartan group (95% CI -7.6 to -3.1 mmHg; $p<0.001$) at the end of 12 weeks. Reductions in 24-hour mean DBP with azilsartan/chlorthalidone were also superior to olmesartan/hydrochlorothiazide ($p<0.001$). Lastly, a larger percentage of patients receiving azilsartan/chlorthalidone 40/25 mg than olmesartan/hydrochlorothiazide 40/25 mg reached target BP

of less than 140/90 mm Hg (81.4% vs. 74.6%; p<0.05). However, these were not therapeutically equivalent doses of chlorthalidone and hydrochlorothiazide which limits the ability to effectively compare the two.

Lastly, a study compared different thiazide diuretics in combination with azilsartan.[17] Patients (n=609) with a mean SBP of 160-190 mm Hg started azilsartan 40 mg with addition of chlorthalidone 12.5 mg or hydrochlorothiazide 12.5 mg at week 2. Fewer patients required titration to higher doses of azilsartan/chlorthalidone than did those on azilsartan/hydrochlorothiazide (30.8% vs. 345.9%; p<0.001). Also, trough SBP after 10 weeks responded significantly better to chlorthalidone combination than with hydrochlorothiazide (-37.8 vs. -32.8; p<0.001).

There are no clinical trials assessing clinical outcomes for azilsartan/chlorthalidone.

Study	Comparison	Population	Primary Outcome	Results
DRI's				
Littlejohn et al.[18] RCT, DB	Aliskiren/amlodipine combination vs. aliskiren vs. amlodipine vs. placebo	Adults with primary hypertension (n=1688)	Change in mean sitting DBP from baseline to week 8	All four aliskiren/amlodipine combination doses provided significantly greater reductions in mean DBP than the monotherapies (p>0.05).
Nicholls et al.[19] RCT, DB	Aliskiren vs. placebo	Adults with CAD, SBP 125-139 mm Hg, and 2 additional CV risk factors (n=613)	Percent atheroma volume (PAV) (progression of coronary atherosclerosis)	PAV did not differ between participants treated with aliskiren (−0.33%; 95%CI, 0.68%to 0.02%) and placebo (0.11%; 95%CI, −0.24%to 0.45%) (between-group difference, −0.43%[95%CI, −0.92%to 0.05%]; P = .08).
Vakris et al.[20] DB	Aliskiren/valsartan vs. valsartan	Adults with hypertension, type 2 diabetes, and stage 1 or 2 chronic kidney disease (n=1143)	Ambulatory blood pressure	the addition of aliskiren to valsartan was associated with an incremental benefit of 4.0 mm Hg of lowering in 24-hour SBP and 2.4 mm Hg of lowering in 24-hour DBP (both P<.001).
Lizakowski et al.[21] RCT, DB	Aliskiren vs. perindopril vs. placebo	Patients with non-diabetic chronic kidney disease (n=14)	24 hour proteinuria	<u>24-h proteinuria decrease compared to placebo:</u> Alis 150mg: 23% Alis: 300mg 36% P=0.001 Perin 5mg: 7.1%

				Perin 10 mg: 25.1% P=0.04
Gheorghiade et al.[22] RCT, DB, PC	Aliskiren vs. placebo in addition to standard therapy	Hemodynamically stable hospitalized heart failure patients (n=1639)	CV death or HF rehospitalization	<u>DV death + HF rehospitalization at 6 mo:</u> Alisk: 24.9% Plac: 26.5% HR 0.92; 95% CI 0.76-1.12; p=0.41
ALTITUDE[13] RCT, DB	Aliskiren vs.placebo as an adjunct to ACEI or ARB		Composite of the time to CV death or first occurrence of cardiac arrest; nonfatal MI; nonfatal stroke; HF hospitalization; ESRD, death due to kidney disease, or doubling of the baseline serum creatinine level	Interim analysis Composite outcome: Alis: 18.3% Plac: 17.1% HR 1.08; 95% CI 0.98-1.20; p=0.12 Trial was stopped prematurely
ASSERTIVE[23] RCT, DB, DD	Aliskiren 150 mg vs. telmisartan 40mg (n=822)	Adults with hypertension and a 7-day treatment withdrawal	24 h mean ambulatory SBP after a 7-day treatment withdrawal	<u>Change in SBP:</u> Alisk: +2.7 ± 0.466 mm HG Telm: + 6.5 ± 0.461 mmHg Difference : -3.8 mmg Hg; p<0.0001 in favor of aliskiren
ARBs				
Bonner et al.[24] RCT, DB	Azilsartan vs. Ramipril	Patients with stage 1 or 2 HTN (n=884)	Change from baseline to week 24 in trough, seated, clinic SBP	<u>SBP Change from Baseline:</u> AZL 40mg: -20.6 mmHg AZL 80 mg: -21.2 mmHg RAM 10mg: -12.2 mmHg P<0.001 for both AZL doses vs. RAM 10mg
Lee et al.[25] RCT, DB, noninferiority	Amlodipine/benazepril vs. valsartan/HCTZ	Patients with DM and HTN and Microalbuminuria (n=169)	Mean change in DBP at 16 weeks	<u>Mean change in DBP:</u> Amlodipine/benazepril is noninferior to valsartan/HCTZ in blood pressure lowing (difference, -0.9 mm HG; 95% CI -3.5 to 1.6)
Rakugi et al.[26] RCT, DB	Azilsartan vs. candesartan	Japanese patients with essential HTN	Change from baseline in the sitting DBP at week 16	<u>Mean change in DBP:</u> Azil: -12.4 mmHg Cand: -9.8 mm Hg Least squares means -2.6 mm HG (95% CI -4.08 to -1.22), p=0.0003

References:

1. Makani H, Bangalore S, Desouza KA, Shah A, Messerli FH. Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials. *BMJ*. 2013;346:f360.

2. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the eighth joint national committee (jnc 8). *JAMA*. 2013. doi:10.1001/jama.2013.284427.

3. Thakurta S. Drug Effectiveness Review Project. Drug Class Review on ACE Inhibitors. Preliminary Scan Report #4. November 2013.

4. Zaiken K, Hudd TR, Cheng JWM. A review of the use of angiotensin receptor blockers for the prevention of cardiovascular events in patients with essential hypertension without compelling indications. *Ann Pharmacother*. 2013;47(5):686–693. doi:10.1345/aph.1R273.

5. Xu F-Y, Yang B, Shi D, Li H, Zou Z, Shi X-Y. Antihypertensive effects and safety of eprosartan: a meta-analysis of randomized controlled trials. *Eur J Clin Pharmacol*. 2012;68(2):195–205. doi:10.1007/s00228-011-1107-3.

6. Liu Y, Yan R, Song A, et al. Aliskiren/Amlodipine vs. Aliskiren/Hydrochlorothiazide in Hypertension: Indirect Meta-Analysis of Trials Comparing the Two Combinations vs. Monotherapy. *Am J Hypertens*. 2014;27(2):268–278. doi:10.1093/ajh/hpt210.

7. Harel Z, Gilbert C, Wald R, et al. The effect of combination treatment with aliskiren and blockers of the renin-angiotensin system on hyperkalaemia and acute kidney injury: systematic review and meta-analysis. *BMJ*. 2012;344:e42.

8. Heran BS, Musini VM, Bassett K, Taylor RS, Wright JM. Angiotensin receptor blockers for heart failure. *Cochrane Database Syst Rev*. 2012;4:CD003040. doi:10.1002/14651858.CD003040.pub2.

9. Savarese G, Costanzo P, Cleland JGF, et al. A meta-analysis reporting effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients without heart failure. *J Am Coll Cardiol*. 2013;61(2):131–142. doi:10.1016/j.jacc.2012.10.011.

10. Geng D, Jin D, Wu W, Xu Y, Wang J. Angiotensin receptor blockers for prevention of new-onset type 2 diabetes: a meta-analysis of 59,862 patients. *Int J Cardiol*. 2012;155(2):236–242. doi:10.1016/j.ijcard.2010.10.011.

11. Daskalopoulou SS, Khan NA, Quinn RR, et al. The 2012 Canadian hypertension education program recommendations for the management of hypertension: blood pressure measurement, diagnosis, assessment of risk, and therapy. *Can J Cardiol*. 2012;28(3):270–287. doi:10.1016/j.cjca.2012.02.018.

12. U.S. Food and Drug Administration. FDA Drug Safety Communication: New Warning and Contraindication for blood pressure medicines containing aliskiren (Tekturna). 2012. Available at: http://www.fda.gov/drugs/drugsafety/ucm300889.htm.

13. Parving H-H, Brenner BM, McMurray JJV, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med*. 2012;367(23):2204–2213. doi:10.1056/NEJMoa1208799.

14. Pierini D, Anderson KV. Azilsartan medoxomil/chlorthalidone: a new fixed-dose combination antihypertensive. *Ann Pharmacother*. 2013;47(5):694–703. doi:10.1345/aph.1R618.

15. Sica D, Bakris GL, White WB, et al. Blood pressure-lowering efficacy of the fixed-dose combination of azilsartan medoxomil and chlorthalidone: a factorial study. *J Clin Hypertens (Greenwich)*. 2012;14(5):284–292. doi:10.1111/j.1751-7176.2012.00616.x.

16. Cushman WC, Bakris GL, White WB, et al. Azilsartan medoxomil plus chlorthalidone reduces blood pressure more effectively than olmesartan plus hydrochlorothiazide in stage 2 systolic hypertension. *Hypertension*. 2012;60(2):310–318. doi:10.1161/HYPERTENSIONAHA.111.188284.

17. Bakris GL, Sica D, White WB, et al. Antihypertensive efficacy of hydrochlorothiazide vs chlorthalidone combined with azilsartan medoxomil. *Am J Med*. 2012;125(12):1229.e1–1229.e10. doi:10.1016/j.amjmed.2012.05.023.

18. Littlejohn TW 3rd, Jones SW, Zhang J, Hsu H, Keefe DL. Efficacy and safety of aliskiren and amlodipine combination therapy in patients with hypertension: a randomized, double-blind, multifactorial study. *J Hum Hypertens*. 2013;27(5):321–327. doi:10.1038/jhh.2012.42.

19. Nicholls SJ, Bakris GL, Kastelein JJP, et al. Effect of aliskiren on progression of coronary disease in patients with prehypertension: the AQUARIUS randomized clinical trial. *JAMA*. 2013;310(11):1135–1144. doi:10.1001/jama.2013.277169.

20. Bakris GL, Oparil S, Purkayastha D, Yadao AM, Alessi T, Sowers JR. Randomized study of antihypertensive efficacy and safety of combination aliskiren/valsartan vs valsartan monotherapy in hypertensive participants with type 2 diabetes mellitus. *J Clin Hypertens (Greenwich)*. 2013;15(2):92–100. doi:10.1111/jch.12032.

21. Lizakowski S, Tylicki L, Renke M, et al. Effect of aliskiren on proteinuria in non-diabetic chronic kidney disease: a double-blind, crossover, randomised, controlled trial. *Int Urol Nephrol*. 2012;44(6):1763–1770.

22. Gheorghiade M, Böhm M, Greene SJ, et al. Effect of aliskiren on postdischarge mortality and heart failure readmissions among patients hospitalized for heart failure: the ASTRONAUT randomized trial. *JAMA*. 2013;309(11):1125–1135. doi:10.1001/jama.2013.1954.

23. Düsing R, Brunel P, Baek I, Baschiera F. Sustained decrease in blood pressure following missed doses of aliskiren or telmisartan: the ASSERTIVE double-blind, randomized study. *J Hypertens*. 2012;30(5):1029–1040. doi:10.1097/HJH.0b013e328351c263.

24. Bönner G, Bakris GL, Sica D, et al. Antihypertensive efficacy of the angiotensin receptor blocker azilsartan medoxomil compared with the angiotensin-converting enzyme inhibitor ramipril. *J Hum Hypertens*. 2013;27(8):479–486. doi:10.1038/jhh.2013.6.

25. Lee I-T, Hung Y-J, Chen J-F, Wang C-Y, Lee W-J, Sheu WH-H. Comparison of the efficacy and safety profiles of two fixed-dose combinations of antihypertensive agents, amlodipine/benazepril versus valsartan/hydrochlorothiazide, in patients with type 2 diabetes mellitus and hypertension: a 16-week, multicenter, randomized, double-blind, noninferiority study. *Clin Ther*. 2012;34(8):1735–1750. doi:10.1016/j.clinthera.2012.06.014.

26. Rakugi H, Enya K, Sugiura K, Ikeda Y. Comparison of the efficacy and safety of azilsartan with that of candesartan cilexetil in Japanese patients with grade I-II essential hypertension: a randomized, double-blind clinical study. *Hypertens Res*. 2012;35(5):552–558. doi:10.1038/hr.2012.8.

Drug Class Review
on
ACE Inhibitors

Preliminary Scan Report 4

November 2013

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Update scan prepared by Sujata Thakurta, MPA:HA

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Pacific Northwest Evidence-based Practice Center
Roger Chou, MD, Director
Marian McDonagh, PharmD, Associate Director

Oregon Health & Science University

Copyright © 2013 by Oregon Health & Science University
Portland, Oregon 97239. All rights reserved.

OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations' consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Date of Last Update

Update 2 June 2005 (searches through February 2005)

Date of Last Update Scans

Scan #1: February 2007
Scan #2: February 2008
Scan #3: November 2008

Scope and Key Questions

The Pacific Northwest Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

Key Questions

1. For adult patients with essential hypertension, heart failure, high cardiovascular risk factors, diabetic nephropathy, nondiabetic nephropathy, or recent myocardial infarction, do angiotensin converting enzyme (ACE) inhibitors differ in effectiveness?

2. For adult patients with essential hypertension, heart failure, high cardiovascular risk factors, diabetic nephropathy, nondiabetic nephropathy, or recent myocardial infarction, do ACE inhibitors differ in safety or adverse events?

3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one ACE inhibitor is more effective or associated with fewer adverse events?

Inclusion Criteria

Populations

Adult patients with any of the following indications:

- Hypertension without compelling indications. This refers to patients with hypertension who do not have any of the following indications:
  a. a history of coronary heart disease (CHD)
  b. other cardiovascular diseases (CVD), such as cerebrovascular (carotid) disease, peripheral vascular disease, or a history of stroke
  c. other risk factors for CAD/CVD, such as diabetes, smoking or hyperlipidemia
  d. renal insufficiency
- Hypertension with compelling indications. This refers to patients with hypertension who also have one of the conditions listed above.
- High cardiovascular risk. This group includes patients who have a history of CHD/CVD, or a combination of other risk factors for CHD/CVD, such as diabetes, smoking, and hyperlipidemia. These patients may or may not have hypertension as well.
- Recent myocardial infarction. This group includes patients who have had a recent myocardial infarction and who have normal left ventricular function or asymptomatic left ventricular dysfunction.
- Heart failure. This group includes patients who have symptomatic heart failure due to left ventricular systolic dysfunction, with or without hypertension.
- Diabetic nephropathy. This group includes patients with Type 1 or Type 2 diabetes who have laboratory evidence of nephropathy, such as albuminuria or decreased creatinine clearance.

Interventions

- benazepril
- captopril
- enalapril
- fosinopril
- lisinopril
- moexipril
- quinapril
- ramipril
- perindopril
- trandolapril

Effectiveness outcomes

Effectiveness measures varied according to the clinical condition:

Hypertension

- All-cause and cardiovascular mortality
- Cardiovascular events (stroke, myocardial infarction, or development of heart failure)
- End-stage renal disease (including dialysis or need for transplantation) or clinically significant and permanent deterioration of renal function (increase in serum creatinine or decrease in creatinine clearance)
- Quality-of-life

(Trials that focused on blood pressure reduction but not on any health outcomes were excluded from the effectiveness review)

High cardiovascular risk

- All-cause and cardiovascular mortality
- Cardiovascular events (stroke, myocardial infarction, or development of heart failure)

Recent myocardial infarction

- All-cause and cardiovascular mortality
- Cardiovascular events (usually, development of heart failure)

Heart failure

- All-cause or cardiovascular mortality
- Symptomatic improvement (heart failure class, functional status, visual analogue scores)
- Hospitalizations for heart failure

Diabetic nephropathy/non-diabetic nephropathy

- End-stage renal disease (including dialysis or need for transplantation)
- Clinically significant and permanent deterioration of renal function (increase in serum creatinine or decrease in creatinine clearance)

Safety outcomes

- Withdrawals
- Withdrawals due to adverse effects
- Specific adverse effects or withdrawals due to specific adverse events, for example, symptomatic hypotension

Study designs

1. Randomized controlled trials that compared one of the included ACE inhibitors to another.
2. Systematic reviews of the clinical effectiveness or adverse event rates of ACE inhibitors for included clinical conditions that reported an included outcome.
3. Large (> 100 patients) placebo-controlled trials for included clinical conditions that reported an included outcome.
4. Randomized controlled trials and large, good-quality observational studies that evaluated adverse event rates for one or more of the included ACE Inhibitors.

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE from October 2008 through October 2013, using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. We also searched FDA (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, indications, and safety alerts. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) and the Canadian Agency

for Drugs and Technology in Health (http://www.cadth.ca/). All citations were imported into an electronic database (EndNote X3) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

New drugs identified in this Preliminary Update Scan
Epaned™ (enalapril maleate) oral solution approved on August 2013 is indicated for the treatment of hypertension, to lower blood pressure in adults and children older than one month.

New drugs identified in previous Preliminary Update Scan(s)
None identified.

New Indications
New indications identified in this Preliminary Update Scan
None identified.
Identified in previous Preliminary Update Scan(s)
New indication for perindopril in patients with stable coronary artery disease to reduce the risk of cardiovascular mortality or non-fatal myocardial infarction.

New Boxed Warnings
Identified in this Preliminary Update Scan
In January 2012, a new boxed warning was issued for Mavik® (trandolapril tablets). Similar boxed warnings were also issued for other included Ace Inhibitors including Accupril® (Quinapril), Altace®(Ramipril), Lotensin®(Benazepril) and Univasc® (Moexipril) in 2012.

WARNING: FETAL TOXICITY

When pregnancy is detected, discontinue MAVIK as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus (See WARNINGS: Fetal Toxicity).

Identified in previous Preliminary Update Scan(s)
Prior to January 2012, for most Ace Inhibitors the black box warnings were directed against use of the drugs in second and third trimesters.

Comparative Effectiveness Reviews
Reviews identified in this Preliminary Update Scan
A guideline on the "Administration of Angiotensin Converting Enzyme Inhibitors Following Acute Myocardial Infarction" was produced by Canadian Agency for Drugs and Technologies in Health in May of 2010. The details of the guideline is included in Appendix A below.

Reviews identified in previous Preliminary Update Scan(s)

None

Overview

Medline searches resulted in 511 new citations. No relevant head to head trials comparing one ACE inhibitor against the other were found in this scan. There were 8 new potentially relevant placebo controlled trials (see Appendix B, attached) obtained from this scan and are shaded in table 1 below. There was 1 potentially relevant head to head trial and 16 placebo controlled trials that were found in previous scans (Appendix C). Cumulatively, 1 head to head trial and 24 placebo controlled trials that are available at this time. Majority of the trials focused on perindopril. Several of them were subgroup or secondary analyses of trials included in the DERP ACE Inhibitor report like EUROPA, PROGRESS, PEACE, GISSI.

Table 1. Potentially relevant trials of ACE Inhibitors

Author, Year	Drugs	Population	Outcomes	NOTES
Head to head trial				
Tumanan-Mendoza, 2007	Elanalapril, Perindopril	Hypertension	Cough	
Placebo control trials				
Arima, 2005	Perindopril	Atrial Fibrillation and prior stroke, transient ischemic attack	Mortality, major vascular outcomes	PROGRESS
Arima, 2011	Perindopril	Patients with diastolic hypertension	Major vascular events	PROGRESS
Bertrand, 2009	Perindopril	Subpopulation of patients with a history of myocardial infarction and revascularization	composite of cardiovascular mortality, myocardial infarction and resuscitated cardiac arrest	EUROPA
Brugts, 2007	Perindopril	Subgroup of patients with stable coronary artery disease	Cardiovascular death, nonfatal myocardial infarction, or resuscitated cardiac arrest	EUROPA
Coppo, 2007	Benazepril	Nephropathy	Progression of kidney disease	
Daly, 2005	Perindopril	Diabetes	Cardiovascular death, non-fatal myocardial infarction, and resuscitated cardiac arrest	EUROPA
Daly, 2005	Perindopril	Coronary artery disease	Metabolic syndrome and its effect on cardiovascular morbidity and mortality	EOROPA
De Mello, 2008	Enalapril	Type 2 diabetes with microalbuminuria	Urinary albumin excretion rate, blood pressure	
Deckers, 2006	Perindopril	Coronary artery disease	Cardiovascular death, non-fatal myocardial infarction in male patients over 65 years	
Gianni, 2007	Benazepril	Elderly patients	Cardiovascular death, srtoke,	

		with chronic stable vascular disease	myocardial infarction	
Hermida, 2009	Ramipril	Hypertension	Blood pressure reduction	
Hou,2006	Benazepril	Renal insufficiency	Doubling of the serum creatinine level, end-stage renal disease, or death.	
Investigators, 2006	Ramipril	Diabetes	Development of diabetes or death	
Jones-Burton 2010	Enalapril	Hypertension in African American patients	Change in blood pressure	
Kostis, 2005	Enalapril	Hypertension	Angioedema in black and older patients	
Luders, 2008	Ramipril	High-normal blood pressure	Manifest hypertension, cerebrovascular and cardiovascular events	
Mauer, 2009	Enalapril	Type 1 diabetes patients with nephropathy	Microalbuminuria	
Pedrazzini, 2008	Lisinopril	Acute MI	Mortality up to 5 years	GISSI-3
Potter, 2009	Lisinopril	Patients with hypertension who had cerebral infarction and hemorrhage	Death and dependency at 2 weeks	CHHIPS
Ninomiya, 2008	Perindopril	Chronic kidney disease	Recurrent stroke	PROGRESS
Rossignol, 2012	Fosinopril	Hemodyalsis patients	composite of cardiovascular death, nonfatal myocardial infarction, unstable angina, stroke, revascularization, hospitalization for heart failure, and resuscitated cardiac arrest.	
Rouleau, 2008	Quinapril	Low-risk, post-CABG	Composite of cardiovascular death, resuscitated cardiac arrest, nonfatal myocardial infarction, coronary revascularization, unstable angina or heart failure requiring hospitalization, documented angina, and stroke	
Solomon, 2006	Trandolapril	Chronic stable coronary disease	Mortality, reduced renal function	PEACE
Zannad, 2006	Fosinopril	End stage renal disease	Combined fatal and nonfatal first major CVEs	

Appendix A.

TITLE: Administration of Angiotensin Converting Enzyme Inhibitors Following Acute Myocardial Infarction: Guidelines

http://www.cadth.ca/media/pdf/k0187_ace_inhibitors_post-mi_management_htis1-5.pdf

DATE: 13 May 2010

RESEARCH QUESTION:
What are the guidelines for the administration of angiotension converting enzyme inhibitors following acute myocardial infarction?

OVERALL SUMMARY OF FINDINGS:
One systematic review[1] found that the use of ACE inhibitors in patients with acute MI improved both diastolic and systolic volumes over a term of six to twelve months. Another systematic review reported that in patients with a prior cardiovascular event or those who were at high risk of such an event, ACE inhibitors reduced the risk of all-cause mortality, cardiovascular mortality, acute MI, and stroke.
Several guidelines[6-9] recommend that ACE inhibitors be offered to all patients presenting with acute MI or acute coronary syndrome. Others recommend the use of ACE inhibitors under more stringent conditions: ACE inhibitors are recommended as first-line therapy for hypertension in patients with recent MI; long-term management with ACE inhibitors should be used in patients with left ventricular dysfunction;ACE inhibitor use should be considered but not mandatory for patients presenting with ST elevation MI; ACE inhibitor dosages may have to be reduced or discontinued in patients with milder right ventricular dysfunction after MI.[4] Most of the identified guidelines recommend angiotensin receptor blockers be used only when a patient is intolerant or allergic to ACE inhibitors.

Appendix B: Potentially relevant abstracts of trials from current scan 4

Arima, H., C. Anderson, et al. (2011). "Effects of blood pressure lowering on major vascular events among patients with isolated diastolic hypertension: the perindopril protection against recurrent stroke study (PROGRESS) trial." Stroke 42(8): 2339-2341.

BACKGROUND AND PURPOSE: Despite clear evidence that blood pressure (BP) lowering is effective for prevention of cardiovascular events among patients with isolated systolic hypertension and systolic-diastolic hypertension, there is ongoing uncertainty about its effects in those with isolated diastolic hypertension. The objective of the present analysis is to determine whether BP lowering provides benefits to patients with isolated diastolic hypertension.

METHODS: Patients with cerebrovascular disease and hypertension at baseline (n=4283) were randomly assigned to either active treatment (perindopril in all participants plus indapamide for those with neither an indication for nor a contraindication to a diuretic) or matching placebo(s). The primary outcome was total major vascular events.

RESULTS: There were 1923 patients with isolated systolic hypertension (systolic BP >= 140 mm Hg and diastolic BP < 90 mm Hg), 315 with isolated diastolic hypertension (systolic BP <140 mm Hg and diastolic BP >= 90 mm Hg), and 2045 with systolic-diastolic hypertension (systolic BP >= 140 mm Hg and diastolic BP >= 90 mm Hg) at baseline. Active treatment reduced the relative risk of major vascular events by 27% (95% CI, 10% to 41%) among patients with isolated systolic hypertension, by 28% (-29% to 60%) among those with isolated diastolic hypertension, and by 32% (17% to 45%) among those with systolic-diastolic hypertension. There was no evidence of differences in the magnitude of the effects of treatment among different types of hypertension (P homogeneity=0.89).

CONCLUSIONS: BP lowering is likely to provide a similar level of protection against major vascular events for patients with isolated diastolic hypertension as for those with isolated systolic hypertension and systolic-diastolic hypertension. Clinical Trial Registration Information- This trial was not registered because patients were enrolled before July 1, 2005.

Bertrand, M. E., K. M. Fox, et al. (2009). "Angiotensin-converting enzyme inhibition with perindopril in patients with prior myocardial infarction and/or revascularization: a subgroup analysis of the EUROPA trial." Archives of cardiovascular diseases 102(2): 89-96.

BACKGROUND: The European trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease (EUROPA) demonstrated the benefits of perindopril with respect to secondary prevention of cardiovascular risk in patients with stable coronary artery disease.

AIMS: To describe the clinical effects of perindopril in a subpopulation of patients from EUROPA with a history of myocardial infarction and/or revascularization.

PATIENTS AND METHODS: Of the 12,218 patients in the EUROPA study, 10,962 had a history of myocardial infarction and/or revascularization. In this EUROPA subpopulation, 7910 patients had a history of myocardial infarction and 6709 had a history of revascularization. Patients were randomized to treatment with perindopril 8mg/day or placebo. The primary endpoint was a composite of cardiovascular mortality, myocardial infarction and resuscitated cardiac arrest.

RESULTS: After a mean follow-up of 4.2 years, treatment with perindopril 8mg/day was associated with a 22.4% reduction in the primary endpoint compared with placebo ($p<0.001$) in patients with a history of myocardial infarction. Patients with a history of myocardial revascularization showed a 17.3% reduction in the primary endpoint with perindopril versus placebo ($p<0.05$). In the combined population of patients with a history of myocardial infarction and/or revascularization, treatment with perindopril produced a 22.4% reduction in the primary endpoint compared with placebo ($p<0.001$).
CONCLUSIONS: This study confirms the benefits of a high dose of angiotensin-converting enzyme inhibitor for the secondary prevention of cardiovascular risk among patients with a history of myocardial infarction and/or revascularization.

de Mello, V. D. F., T. Zelmanovitz, et al. (2008). "Long-term effect of a chicken-based diet versus enalapril on albuminuria in type 2 diabetic patients with microalbuminuria." Journal of Renal Nutrition 18(5): 440-447.

OBJECTIVE: In short-term studies, the replacement of red meat in the diet with chicken reduced the urinary albumin excretion rate (UAER) and improved lipid profile in type 2 diabetic patients with diabetic nephropathy. The present study sought to assess these effects over a long-term period, comparing the effects of a chicken-based diet (CD) versus enalapril on renal function and lipid profile in microalbuminuric type 2 diabetic patients.
DESIGN: This was a randomized, open-label, controlled clinical trial with a follow-up of 1 year.
SETTING: The trial involved outpatients with type 2 diabetes attending a clinic of the Division of Endocrinology at a tertiary-care hospital.
PATIENTS: Twenty-eight microalbuminuric patients completed the study and were evaluated.
INTERVENTIONS: Patients were randomized to an experimental diet (CD plus active placebo) or to treatment with enalapril (10 mg/day plus usual diet).
MAIN OUTCOME MEASURES: The main outcome measure was UAER (according to immunoturbidimetry). Blood pressure, anthropometric indices, and compliance were also evaluated monthly. The glomerular filtration rate ((51)Cr-EDTA), and lipid, glycemic, and nutritional indices, were measured at baseline and quarterly.
RESULTS: The UAER was reduced after CD (n = 13; from 62.8 [range, 38.4 to 125.1] to 49.1 [range, 6.2 to 146.5] microg/min; $P < .001$) and after enalapril (n = 15; from 55.8 [range, 22.6 to 194.3] to 23.1 [range, 4.0 to 104.9] microg/min; $P < .001$), and this was already significant at month 4. The reduction in UAER after CD (32%; 95% confidence interval, 6.7% to 57.6%) and after enalapril treatment (44.7%; 95% confidence interval, 28.3% to 61.1%; $P = .366$) were not significantly different.
CONCLUSIONS: The CD and the angiotensin-converting enzyme inhibitor enalapril promoted a similar reduction of UAER in patients with type 2 diabetes and microalbuminuria in a 12-month follow-up period.

Hermida, R. C. and D. E. Ayala (2009). "Chronotherapy with the angiotensin-converting enzyme inhibitor ramipril in essential hypertension: improved blood pressure control with bedtime dosing." Hypertension 54(1): 40-46.

Clinical studies have demonstrated a different effect on blood pressure of some angiotensin-converting enzyme inhibitors when administered in the morning versus the evening. Their administration at bedtime resulted in a higher effect on nighttime blood pressure as compared with morning dosing. This study investigated the administration

time-dependent effects of ramipril on ambulatory blood pressure. We studied 115 untreated hypertensive patients, 46.7+/-11.2 years of age, randomly assigned to receive ramipril (5 mg/d) as a monotherapy either on awakening or at bedtime. Blood pressure was measured for 48 hours before and after 6 weeks of treatment. The blood pressure reduction during diurnal activity was similar for both treatment times. Bedtime administration of ramipril, however, was significantly more efficient than morning administration in reducing asleep blood pressure. The awake:asleep blood pressure ratio was decreased after ramipril on awakening but significantly increased toward a more dipping pattern after bedtime dosing. The proportion of patients with controlled ambulatory blood pressure increased from 43% to 65% (P=0.019) with bedtime treatment. Nocturnal blood pressure regulation is significantly better achieved at bedtime as compared with morning administration of ramipril, without any loss in efficacy during diurnal active hours. This might be clinically important, because nighttime blood pressure has been shown to be a more relevant marker of cardiovascular risk than diurnal mean values. The change in the dose-response curve, increased proportion of controlled patients, and improved efficacy on nighttime blood pressure with administration of ramipril at bedtime should be taken into account when prescribing this angiotensin-converting enzyme inhibitor for treatment of essential hypertension.

Jones-Burton, C., J. Rubino, et al. (2010). "Effects of the renin inhibitor MK-8141 (ACT-077825) in patients with hypertension." Journal of the American Society of Hypertension 4(5): 219-226.

The renin inhibitor MK-8141 (ACT-077825) demonstrates substantial immunoreactive active renin (ir-AR) increase (sevenfold) without a persistent plasma renin activity (PRA) decrease. The present study assessed the antihypertensive efficacy of MK-8141 in hypertensive patients. In this double-blind, placebo- and active comparator-controlled study, 195 patients with hypertension (trough sitting diastolic blood pressure >=92 to <105 mm Hg, trough sitting systolic blood pressure <170 mm Hg, and 24-hour mean diastolic blood pressure [DBP] >=80 mm Hg) were randomized to one of four treatments (stratified by race, black versus others): MK-8141 250 mg, MK-8141 500 mg, enalapril 20 mg, or placebo. Blood pressure was measured at trough and as 24-hour ambulatory blood pressure monitoring. The primary end point was change from baseline in 24-hour mean ambulatory DBP measured after 4 weeks. At week 4, the change from baseline in 24-hour mean (95% CI) ambulatory DBP compared with placebo was -1.6 mm Hg (-4.2, 1.1), -1.1 mm Hg (-3.9, 1.6), and -4.9 (-7.5, -2.2) for MK-8141 250 mg, MK-8141 500 mg, and enalapril 20 mg, respectively. Only mean ambulatory DBP-lowering with enalapril 20 mg was statistically significant. Enalapril, but not MK-8141, also significantly lowered 24-hour mean ambulatory systolic blood pressure (SBP) compared with placebo (-6.7 mm Hg [-10.5, -2.8]). Neither enalapril nor MK-8141 significantly lowered trough DBP and SBP compared with placebo. MK-8141 was generally well tolerated. In patients with hypertension, MK-8141 (ACT-077825) did not produce significant blood pressure-lowering efficacy despite a demonstrated effect of the drug on ir-AR, in the absence of durable PRA suppression. Copyright 2010 American Society of Hypertension. Published by Elsevier Inc. All rights reserved.

Mauer, M., B. Zinman, et al. (2009). "Renal and retinal effects of enalapril and losartan in type 1 diabetes." New England Journal of Medicine 361(1): 40-51.

BACKGROUND: Nephropathy and retinopathy remain important complications of type 1 diabetes. It is unclear whether their progression is slowed by early administration of drugs that block the renin-angiotensin system.

METHODS: We conducted a multicenter, controlled trial involving 285 normotensive patients with type 1 diabetes and normoalbuminuria and who were randomly assigned to receive losartan (100 mg daily), enalapril (20 mg daily), or placebo and followed for 5 years. The primary end point was a change in the fraction of glomerular volume occupied by mesangium in kidney-biopsy specimens. The retinopathy end point was a progression on a retinopathy severity scale of two steps or more. Intention-to-treat analysis was performed with the use of linear regression and logistic-regression models.

RESULTS: A total of 90% and 82% of patients had complete renal-biopsy and retinopathy data, respectively. Change in mesangial fractional volume per glomerulus over the 5-year period did not differ significantly between the placebo group (0.016 units) and the enalapril group (0.005, P=0.38) or the losartan group (0.026, P=0.26), nor were there significant treatment benefits for other biopsy-assessed renal structural variables. The 5-year cumulative incidence of microalbuminuria was 6% in the placebo group; the incidence was higher with losartan (17%, P=0.01 by the log-rank test) but not with enalapril (4%, P=0.96 by the log-rank test). As compared with placebo, the odds of retinopathy progression by two steps or more was reduced by 65% with enalapril (odds ratio, 0.35; 95% confidence interval [CI], 0.14 to 0.85) and by 70% with losartan (odds ratio, 0.30; 95% CI, 0.12 to 0.73), independently of changes in blood pressure. There were three biopsy-related serious adverse events that completely resolved. Chronic cough occurred in 12 patients receiving enalapril, 6 receiving losartan, and 4 receiving placebo.

CONCLUSIONS: Early blockade of the renin-angiotensin system in patients with type 1 diabetes did not slow nephropathy progression but slowed the progression of retinopathy. (ClinicalTrials.gov number, NCT00143949.) 2009 Massachusetts Medical Society

Potter, J. F., T. G. Robinson, et al. (2009). "Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial." Lancet Neurology 8(1): 48-56.

BACKGROUND: Raised blood pressure is common after acute stroke and is associated with an adverse prognosis. We sought to assess the feasibility, safety, and effects of two regimens for lowering blood pressure in patients who have had a stroke.

METHODS: Patients who had cerebral infarction or cerebral haemorrhage and were hypertensive (systolic blood pressure [SBP] >160 mm Hg) were randomly assigned by secure internet central randomisation to receive oral labetalol, lisinopril, or placebo if they were non-dysphagic, or intravenous labetalol, sublingual lisinopril, or placebo if they had dysphagia, within 36 h of symptom onset in this double-blind pilot trial. The doses were titrated up if target blood pressure was not reached. Analysis was by intention to treat. This trial is registered with the National Research Register, number N0484128008.

FINDINGS: 179 patients (mean age 74 [SD 11] years; SBP 181 [SD 16] mm Hg; diastolic blood pressure [DBP] 95 [SD 13] mm Hg; median National Institutes of Health stroke scale [NIHSS] score 9 [IQR 5-16] points) were randomly assigned to receive labetolol (n=58), lisinopril (n=58), or placebo (n=63) between January, 2005, and December, 2007. The primary outcome--death or dependency at 2 weeks--occurred in 61% (69) of the active and 59% (35) of the placebo group (relative risk [RR] 1.03, 95% CI 0.80-1.33; p=0.82).

There was no evidence of early neurological deterioration with active treatment (RR 1.22, 0.33-4.54; p=0.76) despite the significantly greater fall in SBP within the first 24 h in this group compared with placebo (21 [17-25] mm Hg vs 11 [5-17] mm Hg; p=0.004). No increase in serious adverse events was reported with active treatment (RR 0.91, 0.69-1.12; p=0.50) but 3-month mortality was halved (9.7%vs 20.3%, hazard ratio [HR] 0.40, 95% CI 0.2-1.0; p=0.05).

INTERPRETATION: Labetalol and lisinopril are effective antihypertensive drugs in acute stroke that do not increase serious adverse events. Early lowering of blood pressure with lisinopril and labetalol after acute stroke seems to be a promising approach to reduce mortality and potential disability. However, in view of the small sample size, care must be taken when these results are interpreted and further evaluation in larger trials is needed.

Rossignol, P., J. Cridlig, et al. (2012). "Visit-to-visit blood pressure variability is a strong predictor of cardiovascular events in hemodialysis: insights from FOSIDIAL." Hypertension 60(2): 339-346.

Optimal blood pressure (BP) targets are still controversial in end-stage renal disease. Recent data have highlighted shortcomings of the usual BP hypothesis in other patient populations and emphasized the importance of visit-to-visit variability of BP in predicting cardiovascular events. The Fosinopril in Dialysis Study failed to demonstrate the efficacy of 2-year angiotensin-converting enzyme inhibition with fosinopril versus placebo in 397 hemodialysis patients with left ventricular hypertrophy but provided an opportunity to assess the influence of BP variability on cardiovascular events. The primary end point was the occurrence of a composite of cardiovascular death, nonfatal myocardial infarction, unstable angina, stroke, revascularization, hospitalization for heart failure, and resuscitated cardiac arrest. The variations in BP throughout the 17 visits were assessed by within-patient overall variability of systolic, diastolic, and pulse pressures between adjacent readings, by within-patient overall variability of systolic/diastolic/pulse pressures, and the residual of the linear fit. Compared with our previous predictive model of cardiovascular events occurrence based on stroke, peripheral arterial disease, coronary artery disease, diabetes mellitus, left ventricular mass, and age (which exhibited similar coefficients herein), the percentage of explained variance improved by 30.1% (R(2)=0.141-0.183) when adding the coefficient of variation of within-patient overall variability of systolic BP. Usual BP parameters were neither cardiovascular events predictors nor correlated to BP variability. Visit-to-visit BP variability was extremely high in hemodialysis patients compared with other populations and a major determinant of cardiovascular events. Such assessments should be prioritized for testing prevention strategies in end-stage renal disease.

Appendix C: Potentially relevant abstracts of trials from previous scans 1-3

Head to head trial

Tumanan-Mendoza, B. A., A. L. Dans, et al. (2007). "Dechallenge and rechallenge method showed different incidences of cough among four ACE-Is." Journal of Clinical Epidemiology 60(6): 547-553.

> OBJECTIVE: To determine the incidence of cough secondary to (1) Cilazapril, (2) Enalapril, (3) Imidapril, and (4) Perindopril and their efficacy in the control of hypertension. STUDY DESIGN AND SETTING: Randomized double-blind study conducted in selected medical centers in the Philippines from the first quarter of 1999 to March, 2001. RESULTS: A total of 301 patients, aged 28-86 years with stage I or II hypertension were included. Patients were randomized to Cilazapril 2.5-5.0 mg/day (n=70), Enalapril 10-20 mg/day (n=82), Perindoril 4-8 mg/day (n=73), or Imidapril 10-20 mg/day (n=76). Hydrochlorothiazide 12.5 mg/day was added if needed. Using a dechallenge and rechallenge method, a strict criteria to attribute cough to angiotensin converting enzyme inhibitors (ACE-Is) not yet used in previous reports, the cough incidence were as follows: (1) Cilazapril--22.86% (16/70), (2) Enalapril--21.95% (18/82), (3) Perindopril--10.96% (6/73), and (4) Imidapril--13.16% (10/76) (P=0.041). Control of hypertension was significantly better with Enalapril during the first follow-up period.

CONCLUSION: Statistically significant differences in the incidence of cough among the studied ACE-Is were noted. Control of hypertension was observed to be better in those with a higher incidence of cough; however, the mean change of both systolic and diastolic blood pressure levels were not significantly different.

Placebo control trial

Arima, H., R. G. Hart, et al. (2005). "Perindopril-based blood pressure-lowering reduces major vascular events in patients with atrial fibrillation and prior stroke or transient ischemic attack." Stroke 36(10): 2164-2169.

BACKGROUND AND PURPOSE: Patients with atrial fibrillation have a high risk of stroke and other vascular events even if anticoagulated. The primary objective here is to determine whether routine blood pressure-lowering provides additional protection for this high-risk patient group. METHODS: This study was a subsidiary analysis of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS)--a randomized, placebo-controlled trial that established the beneficial effects of blood pressure--lowering in a heterogeneous group of patients with cerebrovascular disease. A total of 6105 patients were randomly assigned to either active treatment (2 to 4 mg perindopril for all participants plus 2.0 to 2.5 mg indapamide for those without an indication for or a contraindication to a diuretic) or matching placebo(s). Outcomes are total major vascular events, cause-specific vascular outcomes, and death from any cause. RESULTS: There were 476 patients with atrial fibrillation at baseline, of whom 51% were taking anticoagulants. In these patients, active treatment lowered mean blood pressure by 7.3/3.4 mm Hg and was associated with a 38% (95% confidence interval [CI], 6 to 59) reduction in major vascular events and 34% (95% CI, -13 to 61) reduction in stroke. The benefits of blood pressure-lowering in patients with atrial fibrillation were achieved irrespective of the use of anticoagulant therapy (P homogeneity=0.8) or the presence of hypertension (P homogeneity=0.4). CONCLUSIONS: For most patients with atrial fibrillation, routine blood pressure-lowering is likely to provide protection against major vascular events additional to that conferred by anticoagulation.

Brugts, J. J., E. Boersma, et al. (2007). "The cardioprotective effects of the angiotensin-converting enzyme inhibitor perindopril in patients with stable coronary artery disease are not modified by mild to moderate renal insufficiency: insights from the EUROPA trial." Journal of the American College of Cardiology 50(22): 2148-2155.

OBJECTIVES: This study sought to examine whether the cardioprotective effects of angiotensin-converting enzyme (ACE) inhibitor therapy by perindopril are modified by renal function in patients with stable coronary artery disease. BACKGROUND: A recent study reported that an impaired renal function identified a subgroup of patients with stable coronary artery disease more likely to benefit from ACE inhibition therapy. In light of the growing interest in tailored therapy for targeting medications to specific subgroups, remarks on the consistency of the treatment effect by ACE inhibitors are highly important. METHODS: The present study involved 12,056 patients with stable coronary artery disease without heart failure randomized to perindopril or placebo. Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease equation. Cox regression analysis was used to estimate

multivariable-adjusted hazard ratios. RESULTS: The mean eGFR was 76.2 (+/-18.1) ml/min/1.73 m2. During follow-up, the primary end point (cardiovascular death, nonfatal myocardial infarction, or resuscitated cardiac arrest) occurred in 454 of 5,761 patients (7.9%) with eGFR > or =75 and in 631 of 6,295 patients (10.0%) with eGFR <75. Treatment benefits of perindopril were apparent in both patient groups either with eGFR > or =75 (hazard ratio 0.77; 95% confidence interval 0.64 to 0.93) or eGFR <75 (hazard ratio 0.84; 95% confidence interval 0.72 to 0.98). We observed no significant interaction between renal function and treatment benefit (p = 0.47). Using different cutoff points of eGFR at the level of 60 or 90 resulted in similar trends. CONCLUSIONS: The treatment benefit of perindopril is consistent and not modified by mild to moderate renal insufficiency.

Coppo, R., L. Peruzzi, et al. (2007). "IgACE: a placebo-controlled, randomized trial of angiotensin-converting enzyme inhibitors in children and young people with IgA nephropathy and moderate proteinuria.[see comment]." Journal of the American Society of Nephrology 18(6): 1880-1888.

This European Community Biomedicine and Health Research-supported, multicenter, randomized, placebo-controlled, double-blind trial investigated the effect of an angiotensin-converting enzyme inhibitor (ACE-I) in children and young people with IgA nephropathy (IgAN), moderate proteinuria (>1 and <3.5 g/d per 1.73 m(2)) and creatinine clearance (CrCl) >50 ml/min per 1.73 m(2). Sixty-six patients who were 20.5 yr of age (range 9 to 35 yr), were randomly assigned to Benazepril 0.2 mg/kg per d (ACE-I) or placebo and were followed for a median of 38 mo. The primary outcome was the progression of kidney disease, defined as >30% decrease of CrCl; secondary outcomes were (1) a composite end point of >30% decrease of CrCl or worsening of proteinuria until > or =3.5 g/d per 1.73 m(2) and (2) proteinuria partial remission (<0.5 g/d per 1.73 m(2)) or total remission (<160 mg/d per 1.73 m(2)) for >6 mo. Analysis was by intention to treat. A single patient (3.1%) in the ACE-I group and five (14.7%) in the placebo group showed a worsening of CrCl >30%. The composite end point of >30% decrease of CrCl or worsening of proteinuria until nephrotic range was reached by one (3.1%) of 32 patients in the ACE-I group, and nine (26.5%) of 34 in the placebo group; the difference was significant (log-rank P = 0.035). A stable, partial remission of proteinuria was observed in 13 (40.6%) of 32 patients in the ACE-I group versus three (8.8%) of 34 in the placebo group (log-rank P = 0.033), with total remission in 12.5% of ACE-I-treated patients and in none in the placebo group (log-rank P = 0.029). The multivariate Cox analysis showed that treatment with ACE-I was the independent predictor of prognosis; no influence on the composite end point was found for gender, age, baseline CrCl, systolic or diastolic BP, mean arterial pressure, or proteinuria.

Daly, C. A., K. M. Fox, et al. (2005). "The effect of perindopril on cardiovascular morbidity and mortality in patients with diabetes in the EUROPA study: results from the PERSUADE substudy.[see comment]." European Heart Journal 26(14): 1369-1378.

AIMS: The aim of this study was to assess the effect of the angiotensin converting enzyme inhibitor perindopril on cardiovascular events in diabetic patients with coronary artery disease. METHODS AND RESULTS: A total of 1502 diabetic patients with known coronary artery disease and without heart failure of 12 218 overall in the EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery

(EUROPA) disease were randomized in a double-blinded manner to perindopril 8 mg once daily or placebo. Follow-up was for a median of 4.3 years. The primary end point was cardiovascular death, non-fatal myocardial infarction, and resuscitated cardiac arrest. Perindopril treatment was associated with a non-significant reduction in the primary endpoint in the diabetic population, 12.6 vs. 15.5%, relative risk reduction 19% [(95% CI, -7 to 38%), P=0.13]. This was of similar relative magnitude to the 20% risk reduction observed in the main EUROPA population. CONCLUSION: Perindopril tends to reduce major cardiovascular events in diabetic patients with coronary disease in addition to other preventive treatments and the trend towards reduction was of a similar relative magnitude to that observed the general population with coronary artery disease.

Daly, C. A., P. Hildebrandt, et al. (2007). "Adverse prognosis associated with the metabolic syndrome in established coronary artery disease: data from the EUROPA trial." Heart 93(11): 1406-1411.

OBJECTIVE: To assess the prevalence of metabolic syndrome, and its effect on cardiovascular morbidity and mortality in patients with established coronary disease and to explore the inter-relationships between metabolic syndrome, diabetes, obesity and cardiovascular risk. METHODS: The presence of metabolic syndrome was determined in 8397 patients with stable coronary disease from the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease, with mean follow-up of 4.2 years. Metabolic syndrome was defined using a modified version of the National Cholesterol Education Programme criteria. RESULTS: Metabolic syndrome was present in 1964/8397 (23.4%) of the population and significantly predicted outcome; relative risk (RR) of cardiovascular mortality = 1.82 (95% CI 1.40 to 2.39); and fatal and non-fatal myocardial infarction RR = 1.50 (95% CI 1.24 to 1.80). The association with adverse outcomes remained significant after adjustment, RR of cardiovascular mortality after adjustment for conventional risks and diabetes = 1.39 (95% CI 1.03 to 1.86). In comparison with normal weight subjects without diabetes or metabolic syndrome, normal weight dysmetabolic subjects (with either diabetes or metabolic syndrome) were at substantially increased risk of cardiovascular death (RR = 4.05 (95% CI 2.38 to 6.89)). The relative risks of cardiovascular death for overweight and obese patients with dysmetabolic status were nominally lower (RR = 3.01 (95% CI 1.94 to 4.69) and RR = 2.35 (95% CI 1.50 to 3.68), respectively). CONCLUSIONS: Metabolic syndrome is associated with adverse cardiovascular outcome, independently of its associations with diabetes and obesity. A metabolic profile should form part of the risk assessment in all patients with coronary disease, not just those who are obese.

Deckers, J. W., D. M. Goedhart, et al. (2006). "Treatment benefit by perindopril in patients with stable coronary artery disease at different levels of risk." European Heart Journal 27(7): 796-801.

AIMS: Patients with stable coronary artery disease (CAD) are at increased risk. Estimation of individual risk is difficult. We developed a cardiovascular risk model based on the EUROPA study population and investigated whether benefit of long-term administration of the angiotensin-converting enzyme (ACE)-inhibitor perindopril was modified by risk level. METHODS AND RESULTS: A total of 12 218 patients with stable CAD were treated with 8 mg perindopril or placebo. Baseline patient characteristics were assessed for association with 1091 cardiovascular deaths or non-fatal myocardial infarction (MI). Risk factors were age over 65 years, male gender [hazard

ratio (HR) 1.2], previous MI (HR 1.5), previous stroke and/or peripheral vascular disease (HR 1.7), diabetes, smoking, angina (all HR 1.5), and high serum cholesterol and systolic blood pressure. Treatment benefit by perindopril was consistent among high, intermediate, and low risk patients (HRs 0.88, 0.68, and 0.83, respectively). Risk reduction was thus not modified by absolute risk level. CONCLUSION: Risk factors such as age, male gender, smoking, total cholesterol, and blood pressure continue to play an important role once clinical sequellae of coronary heart disease have developed. Patients at moderate-to-high risk because of uncontrolled risk factors and those with other indications for ACE-inhibitors have the most to gain from ACE-inhibition.

Gianni, M., J. Bosch, et al. (2007). "Effect of long-term ACE-inhibitor therapy in elderly vascular disease patients.[see comment]." European Heart Journal 28(11): 1382-1388.

AIMS: Cardiovascular (CV) disease is the leading cause of death in the elderly. The use of ACE-inhibitors in elderly patients with chronic stable vascular disease has not been previously reported. METHODS AND RESULTS: The HOPE trial evaluated the effects of ramipril and vitamin E in high-risk vascular disease patients. We report the effects of ramipril in the elderly HOPE study patients, defined as those > or =70 years of age. A total of 2755 elderly patients with vascular disease or diabetes and at least one additional CV risk factor and without heart failure or low ejection fraction were randomized to ramipril 10 mg daily or placebo. Those assigned to ramipril had fewer major vascular events compared to those assigned to placebo [18.6 vs. 24.0%, hazard ratio (HR) = 0.75, P = 0.0006], CV deaths (9.3 vs. 13.0%, HR = 0.71, P = 0.003), myocardial infarctions (12.0 vs. 15.6%, HR = 0.75, P = 0.006), and strokes (5.4 vs. 7.7%, HR = 0.69, P = 0.013). Treatment was safe and generally well tolerated. CONCLUSION: Ramipril reduces the risk of major vascular events in elderly patients with vascular disease and is safe and well tolerated by most.

Hou, F. F., X. Zhang, et al. (2006). "Efficacy and safety of benazepril for advanced chronic renal insufficiency.[see comment]." New England Journal of Medicine 354(2): 131-140.

BACKGROUND: Angiotensin-converting-enzyme inhibitors provide renal protection in patients with mild-to-moderate renal insufficiency (serum creatinine level, 3.0 mg per deciliter or less). We assessed the efficacy and safety of benazepril in patients without diabetes who had advanced renal insufficiency. METHODS: We enrolled 422 patients in a randomized, double-blind study. After an eight-week run-in period, 104 patients with serum creatinine levels of 1.5 to 3.0 mg per deciliter (group 1) received 20 mg of benazepril per day, whereas 224 patients with serum creatinine levels of 3.1 to 5.0 mg per deciliter (group 2) were randomly assigned to receive 20 mg of benazepril per day (112 patients) or placebo (112 patients) and then followed for a mean of 3.4 years. All patients received conventional antihypertensive therapy. The primary outcome was the composite of a doubling of the serum creatinine level, end-stage renal disease, or death. Secondary end points included changes in the level of proteinuria and the rate of progression of renal disease. RESULTS: Of 102 patients in group 1, 22 (22 percent) reached the primary end point, as compared with 44 of 108 patients given benazepril in group 2 (41 percent) and 65 of 107 patients given placebo in group 2 (60 percent). As compared with placebo, benazepril was associated with a 43 percent reduction in the risk of the primary end point in group 2 (P=0.005). This benefit did not appear to be attributable to blood-pressure control. Benazepril therapy was associated with a 52 percent reduction in the level of

proteinuria and a reduction of 23 percent in the rate of decline in renal function. The overall incidence of major adverse events in the benazepril and placebo subgroups of group 2 was similar. CONCLUSIONS: Benazepril conferred substantial renal benefits in patients without diabetes who had advanced renal insufficiency. (ClinicalTrials.gov number, NCT00270426.) Copyright 2006 Massachusetts Medical Society.

Investigators, D. T., J. Bosch, et al. (2006). "Effect of ramipril on the incidence of diabetes.[see comment]." New England Journal of Medicine 355(15): 1551-1562.

BACKGROUND: Previous studies have suggested that blockade of the renin-angiotensin system may prevent diabetes in people with cardiovascular disease or hypertension. METHODS: In a double-blind, randomized clinical trial with a 2-by-2 factorial design, we randomly assigned 5269 participants without cardiovascular disease but with impaired fasting glucose levels (after an 8-hour fast) or impaired glucose tolerance to receive ramipril (up to 15 mg per day) or placebo (and rosiglitazone or placebo) and followed them for a median of 3 years. We studied the effects of ramipril on the development of diabetes or death, whichever came first (the primary outcome), and on secondary outcomes, including regression to normoglycemia. RESULTS: The incidence of the primary outcome did not differ significantly between the ramipril group (18.1%) and the placebo group (19.5%; hazard ratio for the ramipril group, 0.91; 95% confidence interval [CI], 0.81 to 1.03; P=0.15). Participants receiving ramipril were more likely to have regression to normoglycemia than those receiving placebo (hazard ratio, 1.16; 95% CI, 1.07 to 1.27; P=0.001). At the end of the study, the median fasting plasma glucose level was not significantly lower in the ramipril group (102.7 mg per deciliter [5.70 mmol per liter]) than in the placebo group (103.4 mg per deciliter [5.74 mmol per liter], P=0.07), though plasma glucose levels 2 hours after an oral glucose load were significantly lower in the ramipril group (135.1 mg per deciliter [7.50 mmol per liter] vs. 140.5 mg per deciliter [7.80 mmol per liter], P=0.01). CONCLUSIONS: Among persons with impaired fasting glucose levels or impaired glucose tolerance, the use of ramipril for 3 years does not significantly reduce the incidence of diabetes or death but does significantly increase regression to normoglycemia. (ClinicalTrials.gov number, NCT00095654 [ClinicalTrials.gov].). Copyright 2006 Massachusetts Medical Society.

Kostis, J. B., H. J. Kim, et al. (2005). "Incidence and characteristics of angioedema associated with enalapril." Archives of Internal Medicine 165(14): 1637-1642.

BACKGROUND: Angioedema is a rare but potentially serious adverse event of angiotensin-converting enzyme inhibitor therapy. However, no prospective, controlled studies have reported on its incidence and clinical characteristics. METHODS: We studied the occurrence of angioedema in a randomized, double-blind, controlled trial of 12 557 persons with hypertension treated with enalapril maleate, 5 to 40 mg/d, using a prospective ascertainment and adjudication of angioedema by an expert committee. RESULTS: Angioedema occurred in 86 (0.68%) of the subjects. Stepwise logistic regression identified black race (odds ratio [OR], 2.88; 95% confidence interval [CI], 1.72-4.82), history of drug rash (OR, 3.78; 95% CI, 1.80-7.92), age greater than 65 years (OR, 1.60; 95% CI, 1.02-2.53), and seasonal allergies (OR, 1.79; 95% CI, 1.06-3.00) as independent risk factors for angioedema. The incidence of angioedema was higher after initiation of therapy (3.6/1000 patients per month) and declined to 0.4/1000 patients per month. Treatment was not given in 44 (51%) of the cases; antihistamines were

administered in 35 (41%); corticosteroids, in 20 (23%); and epinephrine, in 1 (1%). Two patients were hospitalized but none had airway compromise. CONCLUSIONS: Enalapril-related angioedema is uncommon. Although it is most likely to occur early after initiation of therapy, it may occur at any time. It is more likely to occur in black patients, those older than 65 years, and those with a history of drug rash or seasonal allergies. Fatal angioedema or angioedema requiring airway protection did not occur in this study.

Luders, S., J. Schrader, et al. (2008). "The PHARAO study: prevention of hypertension with the angiotensin-converting enzyme inhibitor ramipril in patients with high-normal blood pressure: a prospective, randomized, controlled prevention trial of the German Hypertension League." Journal of Hypertension 26(7): 1487-96.

BACKGROUND: The prevention of hypertension with the angiotensin-converting enzyme inhibitor ramipril in patients with high-normal blood pressure study addresses the issue of whether progression to manifest hypertension in patients with high-normal blood pressure can be prevented with treatment. METHODS: A total of 1008 participants with high-normal office blood pressure were randomized to ramipril treatment group (n = 505) and a control group (n = 503). The patients were followed up for 3 years. Primary endpoint was to prevent or delay the progression to manifest hypertension. Secondary endpoints were reduction in the incidence of cerebrovascular and cardiovascular events, as well as the development of hypertension as defined by ambulatory blood pressure monitoring. FINDINGS: One hundred and fifty-five patients (30.7%) in the ramipril group, and 216 (42.9%) in the control group reached the primary endpoint (relative risk reduction 34.4%, P = 0.0001). Ramipril also proved to be more effective in reducing the incidence of manifest office hypertension in patients with baseline ambulatory blood pressure monitoring high-normal blood pressure. The incidence of cerebrovascular and cardiovascular events showed no statistically significant differences between the two groups. Cough was more frequent in the ramipril group (4.8 vs. 0.4%). INTERPRETATION: There is now good clinical evidence that patients with high-normal blood pressure (prehypertension) are more likely to progress to manifest hypertension than patients with optimal or normal blood pressure. Additional ambulatory blood pressure monitoring seems to be essential to achieve correct diagnosis. Treatment of patients with high-normal office blood pressure with the angiotensin-converting enzyme inhibitor was well tolerated, and significantly reduced the risk of progression to manifest hypertension.

Ninomiya, T., V. Perkovic, et al. (2008). "Lower blood pressure and risk of recurrent stroke in patients with chronic kidney disease: PROGRESS trial." Kidney International 73(8): 963-70.

Recent epidemiological studies have shown a J-shaped association between the risk of stroke and systolic blood pressure (SBP) levels in people with chronic kidney disease (CKD). The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was a randomized, placebo-controlled trial demonstrating that perindopril-based blood pressure (BP) lowering reduced the risk of stroke in 6105 participants with prior cerebrovascular disease. We estimated the effects of therapy on the risk of recurrent stroke in 1757 of these participants with stage 3 or greater CKD according to baseline BP and the relationship between achieved follow-up BP and the risk of stroke. Active therapy produced comparable and significant reductions in the risk of stroke across all baseline

SBP levels. The age- and gender-adjusted incidence of stroke increased significantly in a log-linear relationship for achieved SBP levels and strokes per 1000 person-years. This association persisted after adjusting for potential confounding factors. We found that perindopril-based BP lowering effectively prevented recurrent stroke in people with CKD, across a wide range of BP levels, without evidence of an increased risk of stroke in people with low BP levels.

Pedrazzini, G., E. Santoro, et al. (2008). "Causes of death in patients with acute myocardial infarction treated with angiotensin-converting enzyme inhibitors: findings from the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto (GISSI)-3 trial." American Heart Journal 155(2): 388-94.

BACKGROUND: The causes of death occurring in clinical trials of myocardial infarction (MI) are scarcely reported in the literature. The present analysis is aimed to describe the inhospital causes of death in patients with acute MI stratified to angiotensin converting enzyme (ACE) inhibitor treatment/no treatment, as described in the GISSI-3 trial. Furthermore, the 5-year survival analysis of GISSI-3 patients is reported. METHODS AND RESULTS: An independent committee assigned the definition of causes of death of GISSI-3 based on clinical and/or anatomical data. Univariate and multivariable analyses were performed to identify the predictors of early and late deaths. Kaplan-Meier mortality curves were used to describe the effects of ACE-I treatment on mortality on a median follow-up period of 56 months. Patients receiving lisinopril had fewer inhospital cardiac deaths than patients allocated to the no-lisinopril group (4.7% vs 5.3%, P = .052), corresponding to a 12% relative risk reduction. The risk of dying from cardiac rupture was reduced by 39% by lisinopril treatment. The improvement in survival associated with the lisinopril treatment was mainly due to a reduction in cardiac rupture, electromechanical dissociation, and pump failure occurring early (within 4 days) from the onset of MI symptoms. The beneficial effects of lisinopril observed at 6 weeks (8 fewer deaths per 1000 treated patients) were maintained up to nearly 5 years (10 fewer deaths per 1000). CONCLUSIONS: Early administration of ACE inhibitors in unselected patients with acute MI should be considered standard therapy to reduce early deaths, specifically those due to cardiac rupture. The early beneficial effect persisted up to nearly 5 years.

Rouleau, J. L., W. J. Warnica, et al. (2008). "Effects of angiotensin-converting enzyme inhibition in low-risk patients early after coronary artery bypass surgery.[see comment]." Circulation 117(1): 24-31.

BACKGROUND: Early after coronary artery bypass surgery (CABG), activation of numerous neurohumoral and endogenous vasodilator systems occurs that could be influenced favorably by angiotensin-converting enzyme inhibitors. METHODS AND RESULTS: The Ischemia Management with Accupril post-bypass Graft via Inhibition of the coNverting Enzyme (IMAGINE) trial tested whether early initiation (< or = 7 days) of an angiotensin-converting enzyme inhibitor after CABG reduced cardiovascular events in stable patients with left ventricular ejection fraction > or = 40%. The trial was a

double-blind, placebo-controlled study of 2553 patients randomly assigned to quinapril, target dose 40 mg/d, or placebo, who were followed up to a maximum of 43 months. The mean (SD) age was 61 (10) years. The incidence of the primary composite end point (cardiovascular death, resuscitated cardiac arrest, nonfatal myocardial infarction, coronary revascularization, unstable angina or heart failure requiring hospitalization, documented angina, and stroke) was 13.7% in the quinapril group and 12.2% in the placebo group (hazard ratio 1.15, 95% confidence interval 0.92 to 1.42, P=0.212) over a median follow-up of 2.95 years. The incidence of the primary composite end point increased significantly in the first 3 months after CABG in the quinapril group (hazard ratio 1.52, 95% confidence interval 1.03 to 2.26, P=0.0356). Adverse events also increased in the quinapril group, particularly during the first 3 months after CABG. CONCLUSIONS: In patients at low risk of cardiovascular events after CABG, routine early initiation of angiotensin-converting enzyme inhibitor therapy does not appear to improve clinical outcome up to 3 years after CABG; however, it increases the incidence of adverse events, particularly early after CABG. Thus, early after CABG, initiation of angiotensin-converting enzyme inhibitor therapy should be individualized and continually reassessed over time according to risk.

Solomon, S. D., M. M. Rice, et al. (2006). "Renal function and effectiveness of angiotensin-converting enzyme inhibitor therapy in patients with chronic stable coronary disease in the Prevention of Events with ACE inhibition (PEACE) trial.[see comment]." Circulation 114(1): 26-31.

BACKGROUND: Patients with reduced renal function are at increased risk for adverse cardiovascular outcomes. In the post-myocardial infarction setting, angiotensin-converting enzyme (ACE) inhibitors have been shown to be as effective in patients with impaired renal function as in those with preserved renal function. METHODS AND RESULTS: We assessed the relation between renal function and outcomes, the influence of ACE inhibition on this relation, and whether renal function modifies the effectiveness of ACE inhibition in patients with stable coronary artery disease and preserved systolic function enrolled in the Prevention of Events with ACE inhibition trial (PEACE). Patients (n=8290) were randomly assigned to receive trandolapril (target, 4 mg/d) or placebo. Clinical creatinine measures were available for 8280 patients before randomization. The estimated glomerular filtration rate (eGFR) was calculated with the 4-point Modification of Diet in Renal Disease equation. Renal function was related to outcomes, and the influence of ACE-inhibitor therapy was assessed with formal interaction modeling. The mean eGFR in PEACE was 77.6+/-19.4, and 1355 (16.3%) patients had reduced renal function (eGFR <60 mg.mL(-1).1.73 m(-2)). We observed a significant interaction between eGFR and treatment group with respect to cardiovascular and all-cause mortality (P=0.02). Trandolapril was associated with a reduction in total mortality in patients with reduced renal function (adjusted HR, 0.73; 95% CI, 0.54 to 1.00) but not in patients with preserved renal function (adjusted HR, 0.94; 95% CI, 0.78 to 1.13). CONCLUSIONS: Although trandolapril did not improve survival in the overall PEACE cohort, in which mean eGFR was relatively high, trandolapril reduced mortality in patients with reduced eGFR. These data suggest that reduced renal function may define a subset of patients most likely to benefit from ACE-inhibitor therapy for cardiovascular protection.

Zannad, F., M. Kessler, et al. (2006). "Prevention of cardiovascular events in end-stage renal disease: results of a randomized trial of fosinopril and implications for future studies." Kidney International 70(7): 1318-1324.

Cardiovascular events (CVEs) are the leading cause of death in chronic hemodialysis patients. Results of trials in non-end-stage renal disease (ESRD) patients cannot be extrapolated to patients with ESRD. It is critical to test cardiovascular therapies in these high-risk patients who are usually excluded from major cardiovascular trials. The study objective was to evaluate the effect of fosinopril on CVEs in patients with ESRD. Eligible patients were randomized to fosinopril 5 mg titrated to 20 mg daily (n=196) or placebo (n=201) plus conventional therapy for 24 months. The primary end point was combined fatal and nonfatal first major CVEs (cardiovascular death, resuscitated death, nonfatal stroke, heart failure, myocardial infarction, or revascularization). No significant benefit for fosinopril was observed in the intent to treat analysis (n=397) after adjusting for independent predictors of CVEs (RR=0.93, 95% confidence interval (CI) 0.68-1.26, P=0.35). The per protocol secondary supportive analysis (n=380) found a trend towards benefit for fosinopril (adjusted RR=0.79 (95% CI 0.59-1.1, P=0.099)). In the patients who were hypertensive at baseline, systolic and diastolic blood pressures were significantly decreased in the fosinopril as compared to the placebo group. After adjustment for risk factors, trends were observed suggesting fosinopril may be associated with a lower risk of CVEs. These trends may have become statistically significant had the sample size been larger, and these findings warrant further study.

Appendix B: Abstracts of potentially relevant new trials of ACE Inhibitors