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, August 30, 2012 1:00-4:00 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 coverage, PDL composition, or 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.

I. CALL TO ORDER
- a. Roll Call & Introductions — B. Origer (Chair)
- b. Conflict of Interest Declaration — R. Citron (OSU)
- c. Approval of Agenda and Minutes — B. Origer (Chair)

II. DUR ACTIVITIES
- a. CMS Annual Report — R. Magrish (DMAP)
- b. ProDUR Report — R. Holsapple (HP)
- c. RetroDUR Report — T. Williams (OSU)
- d. Quarterly Utilization Reports — R. Citron (OSU)
- e. Oregon State Drug Reviews — K. Sentena (OSU)
  1. Can The Diabetic War Be Fought By Aggressive Blood Pressure Control?

III. OLD BUSINESS
- a. Oral Direct Factor X Inhibitors: Rivaroxaban (Xarelto®)* — K. Sentena (OSU)
  1. Proposed PA criteria update
  2. Public Comment
  3. Discussion of clinical recommendations to OHA
- b. Targeted Immune Modulators* — M. Herink (OSU)
  1. Drug Use Evaluation
  2. Proposed PA criteria update
  3. Public Comment
  4. Discussion of clinical recommendations to OHA
- c. Antipsoriatics* — M. Herink (OSU)
  1. Proposed PA criteria update
  2. Public Comment
  3. Discussion of clinical recommendations to OHA
- d. Fingolimod (Gilenya®)* — M. Herink (OSU)
  1. Proposed PA criteria update
  2. Public Comment
  3. Discussion of clinical recommendations to OHA
- e. Erythropoiesis Stimulating Agents* — M. Herink (OSU)
  1. Proposed PA criteria update
  2. Public Comment
  3. Discussion of clinical recommendations to OHA

**Agenda items will be discussed by Committee members for the purpose of making recommendations to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9)*

IV. NEW BUSINESS

a. Inhaled Antibiotics and Dornase Alfa for Cystic Fibrosis* — B. Fouts (OSU)
   1. Abbreviated Class Review
   2. Public Comment
   3. Discussion of clinical recommendations to OHA

b. Ranolazine (Ranexa®)* — B. Liang (OSU)
   1. Abbreviated Drug Evaluation
   2. Public Comment
   3. Discussion of clinical recommendations to OHA

c. Diuretic Agents Class* — B. Liang (OSU)
   1. Abbreviated Class Review
   2. Public comment
   3. Discussion of clinical recommendations to OHA

d. Ophthalmics: Glaucoma Agents* — M. Herink (OSU)
   1. Abbreviated Class Update
   2. Tafluprost (Zioptan®) New Drug Evaluation
   3. Public Comment
   4. Discussion of clinical recommendations to OHA

e. Vascular Endothelial Growth Factors (VEGF) Inhibitors* — M. Herink (OSU)
   1. Abbreviated Class Review
   2. Public comment
   3. Discussion of clinical recommendations to OHA

V. EXECUTIVE SESSION

VI. RECONVENE for PUBLIC RECOMMENDATIONS

VII. ADJOURN

**Agenda items will be discussed by Committee members for the purpose of making recommendations to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9)*

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, June 28, 2012 1:00-4:00 PM
Hewlett-Packard Building
4070 27th Ct SE
Salem, OR 97302

MEETING MINUTES

Members Present: Tracy Klein, PhD, FNP; William Origer, MD; David Pass, MD; James Slater, PharmD
Members Present by Phone: Andris Antoniskis, MD; Joshua Bishop, PharmD
Staff Present: Roger Citron, RPh; Megan Herink, PharmD, BCPS; Kathy Ketchum, RPh, MPA: HA; Valerie Smith, Trevor Douglass, DC, MPH
Staff Present by Phone: Bing-Bing Liang, PharmD; Kathy Sentena, PharmD
Audience: Ann Neilson (Amgen); Vinson Lee (Amgen); Jamie Tobitt (Vertex); Paul Setlak (Abbott); Bob Snediker (Janssen); Jamie Damm (Vertex); Jeff Gold; Jeana Colabianchi; Anne Marie Licos (MedImmune); Bruce Smith; Cheryl Fletcher (Abbott); Mike Murphy (Abbott); Craig Black (Biogen Idec); Diann Matthews (J&J); Brad (Elan); Steve Faloon (Otsuka); Amy Burns (OSU); Lauren Armijo (OSU); Amanda Meeker (OSU); Chelsea Smith (OSU)

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I. CALL TO ORDER
a. The meeting was called to order at approximately 1:15pm.
b. Conflict of interest declarations were reviewed and no new conflicts were reported.
c. The June 28, 2012 meeting minutes were reviewed and it was noted that the minutes are correct; however the recommendations posted by Dr. Goldberg held a discrepancy. Lovaza was made non-preferred and the recommendation on fish oil was deferred.

ACTION: Minutes approved and directed staff to correct Lovaza recommendations with June posting..

II. OLD BUSINESS
a. Dr. Herink presented fidaxomicin (Dificid®) infectious disease consult from Dr. James Leggett and recommended continuation of previously recommended PA criteria.

***ACTION:** All in favor.
b. Dr. Sentena presented a new drug evaluation for ivacaftor (Kalydeco®). Jamie Tobill from Vertex presented public comment. Dr. Jeffrey Gold with OHSU Cystic Fibrosis Center presented public comment.

***ACTION:** All in favor after executive session with recommendations to implement PA with discussed updates and consult HERC for guidance on appropriate resource allocations.

III. NEW BUSINESS
a. Ms. Ketchum presented ESA class update and new drug review recommending peginesatide (Omontys®) non-preferred, limiting all to appropriate use per PA criteria and verify response at 8 weeks, and recommending the HERC update guideline note 7 with current FDA labeling. Robert Snediker with Janssen presented public comment. Vincent Lee from Amgen presented public comment.

**Agenda items will be discussed by Committee members for the purpose of making recommendations to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9)*

***ACTION:** All in favor after executive session with deferment of darbepoetin and epoetin status until September meeting to wait for supplemental rebate negotiations.

b. Dr. Liang presented nitrates abbreviated class review and new drug evaluation recommending PA criteria and the addition of nitrates to the PDL to include a short acting nitrate for angina prevention and treatment including sublingual tablets, isosorbid dinitrate tablets and sublingual tablets and isosorbide mononitrate tablets. Add a long acting nitrate for angina prophylaxis and treatment of angina and include isosorbide dinitrate ER for the management of heart failure including isosorbide mononitrate ER 24H tablets, isosorbide dinitrate ER capsules, nitroglycerin ER capsules and nitroglycerine patches. Make recommended making isosorbide dinitrate ER tablets, nitroglycerin spray and ointments, including nitroglycerin ointment 0.4% (Rectiv®) non-preferred and implement PA criteria to limit use to funded diagnoses.

***ACTION:** All in favor after executive session.

c. Dr. Herink presented targeted immune modulators (TIMS) drug class review recommending maintain the most recently approved TIMS golimumab, tocilizumab and ustekinumab as non-preferred TIMS, , consider additional clinical criteria for prior authorization of non-preferred TIMS including a step therapy requirement with a trial of methotrexate first for RA and limited to the appropriate FDA indications for each non-preferred drug and consider a DUE to evaluate preferred products for off-label use or use inconsistent with current clinical guidelines. Keep Humira and Enbrel as preferred, make ustekinumab and infliximab non-preferred and recommend closing natalizumab, infliximab, rituximab and tocilizumab to drug claims and require J-code billing.

***ACTION:** All in favor after executive session.

d. Dr. Willard presented the new drug review for deferiprone (Ferriprox®) recommending the addition of deferoxamine as preferred on the PDL and making the oral agents deferasirox and deferiprone non-preferred and use current PDL PA criteria to utilize them as second line agents.

***ACTION:** All in favor after executive session.

V. ADJOURN

The meeting adjourned at approximately 3:50pm. The next meeting will be in Wilsonville on August 30, 2012.

ProDUR Report for May 2012-July 2012

High Level Summary by DUR Alert

DUR Alert	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts
ER (Early Refill)	63,285	19,306	599	43,292	66.80%
HD (High Dose)	0	0	0	0	0.00%
PG (Pregnancy/Drug Interaction)	3,691	2,598	7	1,078	3.87%
ID (Ingredient Duplication)	15,257	5,748	63	9,355	16.03%
TD (Therapeutic Duplication)	6,450	2,659	19	3,720	6.73%

Summary of Override Codes by DUR Alert

DUR Alert	1A False Positive	1B Filled As Is	1C Different Dose	1D Different Directions	1E Different Drug	1F Different Quantity	1G Prescriber Approval	Totals
ER Total	**358**	**14,728**	**1,149**	**444**	**12**	**0**	**2,615**	**19,306**
ER (Prescriber Consulted)	236	5,568	321	246	9	0	2,177	8,557
ER (Patient Consulted)	24	554	7	16	1	0	12	614
ER (Other Consulted)	98	8,606	821	182	2	0	426	10,135
PG Total	**113**	**2,130**	**25**	**20**	**0**	**0**	**310**	**2,598**
PG (Prescriber Consulted)	49	810	10	11	0	0	282	1,162
PG (Patient Consulted)	37	315	1	2	0	0	9	364
PG (Other Consulted)	27	1,005	14	7	0	0	19	1,072
ID Total	**98**	**4,308**	**430**	**105**	**8**	**0**	**799**	**5,748**
ID (Prescriber Consulted)	54	1,567	108	57	7	0	656	2,449
ID (Patient Consulted)	18	158	1	4	1	0	5	187
ID (Other Consulted)	26	2,583	321	44	0	0	138	3,112
TD Total	**53**	**1,972**	**172**	**57**	**4**	**0**	**401**	**2,659**
TD (Prescriber Consulted)	30	769	59	32	4	0	323	1,217
TD (Patient Consulted)	7	61	0	1	0	0	1	70
TD (Other Consulted)	16	1,142	113	24	0	0	77	1,372

ProDUR Report for May 2012-July 2012							
Top Drugs in Enforced DUR Alerts							
DUR Alert	**Drug Name**	**# Alerts**	**# Overrides**	**# Cancellations & Non-Response**	**# Claims Screened**	**% Alerts/Total Claims in Therapeutic Category**	**% Alerts Overridden**
ER	Oxycodone HCl	318	159	156	4,684	6.8%	50.0%
	Hydrocodone Bit/APAP	621	230	391	10,352	6.0%	37.0%
	Gabapentin	497	175	322	3,692	13.5%	35.2%
	Clonazepam	834	293	538	7,299	11.4%	35.1%
	Lorazepam	2,968	1,025	1,937	33,378	8.9%	34.5%
	Geodon (Ziprasidone)	620	208	412	5,280	11.7%	33.5%
	Risperdal (Risperidone)	1,988	665	1,320	15,300	13.0%	33.5%
	Depakote (Divalproex Sodium)	1,257	417	832	11,797	10.7%	33.2%
	Seroquel (Quetiapine)	2,273	718	1,551	17,567	12.9%	31.6%
	Albuterol	490	151	339	7,643	6.4%	30.8%
	Zyprexa (Olanzapine)	1,147	351	791	9,188	12.5%	30.6%
	Lithium Carbonate	821	244	576	6,383	12.9%	29.7%
	Abilify (Aripiprazole)	1,883	548	1,334	15,324	12.3%	29.1%
	Buspar (Buspirone)	771	224	546	8,448	9.1%	29.1%
	Lamictal (Lamotrigine)	2,146	623	1,522	17,779	12.1%	29.0%
	Diazepam	1,124	326	798	14,219	7.9%	29.0%
	Effexor (Venlafaxine)	1,140	325	815	12,142	9.4%	28.5%
	Prilosec (Omeprazole)	593	166	427	6,692	8.9%	28.0%
	Lexapro (Escitaloprim)	1,169	325	844	12,137	9.6%	27.8%
	Paxil (Paroxetine)	870	238	630	9,403	9.3%	27.4%
	Cymbalta (Duloxetine)	1,789	483	1,306	18,190	9.8%	27.0%
	Zoloft (Sertraline)	2,724	729	1,995	25,339	10.8%	26.8%
	Alprazolam	1,940	516	1,423	22,382	8.7%	26.6%
	Amitriptyline	1,337	351	986	14,499	9.2%	26.3%
	Remeron (Mirtazapine)	742	190	552	5,697	13.0%	25.6%
	Trazodone	3,323	850	2,468	29,177	11.4%	25.6%
	Celexa (Citalopram)	2,686	678	2,008	26,432	10.2%	25.2%
	Prozac (Fluoxetine)	2,166	533	1,633	23,229	9.3%	24.6%
	Wellbutrin (Bupropion)	2,118	513	1,605	21,760	9.7%	24.2%
	Straterra (Atomoxetine)	682	148	534	6,654	10.2%	21.7%
PG	Lorazepam	414	344	70	33,378	1.2%	83.1%
	Ibuprofen	667	531	136	4,624	14.4%	79.6%
	Alprazolam	358	282	76	22,382	1.6%	78.8%
	Paroxetine	153	116	37	9,403	1.6%	75.8%
	Norethindrone	212	153	58	796	26.6%	72.2%

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Retro-DUR Intervention History by Quarter - FFY 2011-2012 — Letters Sent

	Profile Review-Based Lettering	Polypharmacy	Duplicate PPIs	Duplicate Statins	Change Form Follow-Up (mult. str.)	Lock-In	Psychotropics in Children	**Prescription Change Form Request**	Antidepressants	Atypical antipsychotics
Quarter 1 Oct-Dec										
Unique Patients	0	0	0	0	80	0		285	47	
Unique Patients Sent Interventions	0	0	0	0	28	0		285	47	
% Sent	-	-	-	-	35%	-		100%	100%	
Quarter 2 Jan-Mar										
Unique Patients	0	0	0	0	255	0		278	23	
Unique Patients Sent Interventions	0	0	0	0	53	0		278	23	
% Sent	-	-	-	-	21%	-		100%	100%	
Quarter 3 Apr-Jun										
Unique Patients	0	0	0	0	102	169		78	22	
Unique Patients Sent Interventions	0	0	0	0	44	0		78	22	
% Sent	-	-	-	-	43%	0%		100%	100%	
Quarter 4 Jul-Sep										
Unique Patients	0	0	0	0	0	0		0	0	
Unique Patients Sent Interventions	0	0	0	0	0	0		0	0	
% Sent	-	-	-	-	-	-		-	-	
Year to date summary										
Unique Patients	0	0	0	0	437	169		641	92	
Unique Patients Sent Interventions	0	0	0	0	125	0		641	92	
% Sent	-	-	-	-	29%	0%		100%	100%	
ROI per intervention	$51	NA	NA	NA	NA	NA		$49	$220	
Estimated program savings	$0	NA	NA	NA	NA	NA		$31,409	$20,240	

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Retro-DUR Intervention History by Quarter - FFY 2011-2012 Letters Sent

	Criteria-based lettering	LABA Monotherapy	High Dose Methadone
Quarter 1 Oct-Dec			
All Patients on Drug of Interest		49	345
Patients Hitting Criteria in Qtr		29	156
Patients Hitting Criteria / 100 Users		59	45
Unique Patients		14	44
Unique Patients Sent Interventions		8	35
% Sent		57%	80%
Quarter 2 Jan-Mar			
All Patients on Drug of Interest		46	329
Patients Hitting Criteria in Qtr		23	143
Patients Hitting Criteria / 100 Users		50	43
Unique Patients		14	38
Unique Patients Sent Interventions		4	19
% Sent		29%	50%
Quarter 3 Apr-Jun			
All Patients on Drug of Interest		39	252
Patients Hitting Criteria in Qtr		20	98
Patients Hitting Criteria / 100 Users		51	39
Unique Patients		11	14
Unique Patients Sent Interventions		8	10
% Sent		73%	71%
Quarter 4 Jul-Sep			
All Patients on Drug of Interest		0	0
Patients Hitting Criteria in Qtr		0	0
Patients Hitting Criteria / 100 Users		-	-
Unique Patients		0	0
Unique Patients Sent Interventions		0	0
% Sent		-	-
Year to date summary			
Unique Patients		39	96
Unique Patients Sent Interventions		20	64
% Sent		51%	67%
ROI per intervention		NA	NA
Estimated program savings		NA	NA

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Retro-DUR Intervention History by Quarter - FFY 2011-2012 — Responses Received

	Profile Review-Based Lettering	Polypharmacy	Duplicate PPIs	Duplicate Statins	Change Form Follow-Up (mult. str.)	Lock-In	Psychotropics in Children	**Criteria-based lettering**	LABA Monotherapy	High Dose Methadone
Quarter 1 Oct-Dec										
Unique Prescribers Sent Interventions	0	0	0	0	27	0		8	36	
Responses Received	0	0	0	0	5	0		2	13	
Response Rate	-	-	-	-	18%	-		25%	37%	
% Agree with message	-	-	-	-	100%	-		50%	69%	
% Consider in future prescribing	-	-	-	-	-	-		100%	38%	
Quarter 2 Jan-Mar										
Unique Prescribers Sent Interventions	0	0	0	0	45	0		4	19	
Responses Received	0	0	0	0	7	0		1	7	
Response Rate	-	-	-	-	13%	-		25%	37%	
% Agree with message	-	-	-	-	71%	-		100%	71%	
% Consider in future prescribing	-	-	-	-	14%	-		-	43%	
Quarter 3 Apr-Jun										
Unique Prescribers Sent Interventions	0	0	0	0	8	0		8	11	
Responses Received	0	0	0	0	0	0		2	2	
Response Rate	-	-	-	-	-	-		25%	20%	
% Agree with message	-	-	-	-	-	-		50%	50%	
% Consider in future prescribing	-	-	-	-	-	-		-	-	
Quarter 4 Jul-Sep										
Unique Prescribers Sent Interventions	0	0	0	0	0	0		0	0	
Responses Received	0	0	0	0	0	0		0	0	
Response Rate	-	-	-	-	-	-		-	-	
% Agree with message	-	-	-	-	-	-		-	-	
% Consider in future prescribing	-	-	-	-	-	-		-	-	
Year to date summary										
Unique Prescribers Sent Interventions	0	0	0	0	80	0		20	66	
Responses Received	0	0	0	0	12	0		5	22	
Response Rate	-	-	-	-	10%	-		25%	34%	
% Agree with message	-	-	-	-	83%	-		60%	68%	
% Consider in future prescribing	-	-	-	-	8%	-		40%	36%	

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OHP FFS Average Cost PMPM Top 40 Drugs (brand name) - Second Quarter 2012

previous year quarter is comparator (red = top 75th percentile of growth; yellow = top 50th percentile of growth)

			Cost PMPM			Rx Dispensed PMPM (x100)			Cost/Claim		
Rank	**Class Number**	**Brand Name**	**2012**	**2011**	**%**	**2012**	**2011**	**%**	**2012**	**2011**	**%**
1	7	ABILIFY	$3.73	$3.45	8.2%	0.56	0.59	-5.0%	$662	$581	13.9%
2	11	CYMBALTA	$1.61	$1.35	19.1%	0.72	0.67	8.5%	$222	$203	9.7%
3	10	METHYLPHENIDATE ER	$1.47	$0.88	68.1%	0.88	0.50	74.7%	$167	$174	-3.8%
4	71	REMODULIN	$1.29	$1.46	-11.2%	0.01	0.01	-21.5%	$23,404	$20,641	13.4%
5	15	SINGULAIR	$0.88	$0.77	14.2%	0.53	0.53	-0.2%	$167	$146	14.4%
6	40	OXYCONTIN	$0.85	$1.34	-36.7%	0.17	0.31	-47.4%	$512	$425	20.5%
7	33	ATRIPLA	$0.82	$1.10	-25.6%	0.05	0.07	-32.1%	$1,681	$1,534	9.6%
8	33	TRUVADA	$0.81	$0.93	-12.9%	0.08	0.10	-26.9%	$1,061	$890	19.2%
9	7	OLANZAPINE	$0.77			0.26			$299		
10	15	PROAIR HFA	$0.75	$0.54	39.6%	1.39	1.06	31.7%	$54	$51	6.0%
11	42	HUMIRA	$0.73	$0.47	55.1%	0.03	0.03	24.1%	$2,140.65	$1,711.03	25.1%
12	58	LANTUS	$0.67	$0.61	10.7%	0.31	0.32	-2.6%	$217.09	$190.91	13.7%
13	7	SEROQUEL XR	$0.62	$0.53	17.9%	0.14	0.14	1.6%	$434.57	$374.41	16.1%
14	7	GEODON	$0.59	$0.88	-33.1%	0.12	0.21	-40.2%	$476.91	$426.41	11.8%
15	11	STRATTERA	$0.58	$0.57	1.3%	0.26	0.28	-4.5%	$220	$207	6.1%
16	99	PULMOZYME	$0.57	$0.31	82.1%	0.02	0.02	49.2%	$2,499	$2,047	22.1%
17	51	FLOVENT HFA	$0.55	$0.48	14.6%	0.32	0.30	7.1%	$168.10	$157.10	7.0%
18	12	DEXTROAMPHETAMINE-AMPHETAMINE	$0.53	$0.34	52.6%	0.30	0.21	44.3%	$176.20	$166.51	5.8%
19	15	ADVAIR DISKUS	$0.47	$0.79	-41.2%	0.18	0.33	-46.0%	$261.37	$240.04	8.9%
20	23	TOBI	$0.44	$0.26	66.3%	0.01	0.01	36.4%	$5,064.39	$4,156.21	21.9%
21	11	LEXAPRO	$0.44	$0.60	-27.4%	0.31	0.52	-40.0%	$141.62	$117.13	20.9%
22	11	INTUNIV	$0.43	$0.26	66.4%	0.23	0.15	55.4%	$187.59	$175.11	7.1%
23	33	SYNAGIS	$0.43	$0.28	50.4%	0.02	0.02	8.9%	$2,432.03	$1,757.18	38.4%
24	40	HYDROCODONE-ACETAMINOPHEN	$0.41	$0.50	-17.0%	2.86	3.38	-15.6%	$14.47	$14.71	-1.7%
25	12	VYVANSE	$0.41	$0.34	21.4%	0.25	0.21	15.2%	$167.62	$159.11	5.3%
26	15	SPIRIVA	$0.41	$0.35	18.0%	0.16	0.16	1.3%	$253.44	$217.55	16.5%
27	15	COMBIVENT	$0.40	$0.36	9.2%	0.18	0.20	-12.7%	$226.17	$180.69	25.2%
28	33	REYATAZ	$0.40	$0.45	-11.2%	0.04	0.06	-25.8%	$918.67	$767.73	19.7%
29	65	LIPITOR	$0.39	$0.42	-6.1%	0.23	0.27	-15.2%	$168.27	$151.82	10.8%
30	30	REVLIMID	$0.38	$0.10	260.5%	0.00	0.00	299.1%	$8,942.82	$9,907.53	-9.7%
31	58	NOVOLOG	$0.37	$0.38	-3.4%	0.16	0.18	-12.4%	$236.72	$214.46	10.4%
32	77	LOVENOX	$0.36	$0.11	231.7%	0.04	0.01	263.0%	$1,013.84	$1,107.42	-8.4%
33	42	ENBREL	$0.36	$0.46	-22.2%	0.02	0.03	-31.1%	$1,854.64	$1,642.49	12.9%
34	99	COPAXONE	$0.33	$0.39	-14.5%	0.01	0.01	-22.9%	$3,828.10	$3,452.69	10.9%
35	33	PEGASYS	$0.33	$0.15	123.4%	0.01	0.01	75.2%	$2,997.18	$2,346.37	27.7%
36	58	HUMALOG	$0.33	$0.33	-0.9%	0.13	0.13	5.9%	$241.49	$258.17	-6.5%
37	1	OMEPRAZOLE	$0.32	$0.33	-2.8%	1.76	1.74	1.0%	$18.09	$18.80	-3.8%
38	7	INVEGA SUSTENNA	$0.29	$0.21	40.9%	0.03	0.02	36.6%	$1,158.80	$1,123.15	3.2%
39	40	FENTANYL	$0.29	$0.33	-10.4%	0.16	0.16	3.5%	$178.42	$206.26	-13.5%
40	33	ISENTRESS	$0.29	$0.29	0.5%	0.03	0.03	-7.9%	$988.17	$904.77	9.2%
		Aggregate	$57.96	$61.23	-5.3%	101.42	106.66	-4.9%	$69	$75	-8.7%
		75th Percentile			23.7%			16.1%			13.2%
		50th Percentile (Median)			-7.1%			-5.1%			0.0%

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OHP FFS Average Cost PMPM Top 30 Drug Class – Second Quarter 2012

previous year quarter is comparator (red = top 75th percentile of growth; yellow = top 50th percentile of growth)

			Cost PMPM			Rx Dispensed PMPM (x100)			Cost/Claim		
Rank	**Class Number**	**Class Description**	**2012**	**2011**	**%**	**2012**	**2011**	**%**	**2012**	**2011**	**%**
1	7	Ataractics, Tranquilizers	$8.28	$11.03	-24.9%	6.1	6.4	-4.5%	$135	$172	-21.4%
2	11	Psychostimulants, Antidepressants	$4.96	$4.98	-0.4%	9.3	9.3	-0.1%	$53	$53	-0.2%
3	33	Antivirals	$4.81	$4.72	1.9%	0.7	0.8	-13.2%	$660	$582	13.4%
4	15	Bronchial Dilators	$3.67	$3.77	-2.7%	3.6	3.9	-9.6%	$103	$96	7.7%
5	99	Miscellaneous	$3.41	$3.01	13.2%	1.5	1.5	2.4%	$211	$199	6.0%
6	40	Narcotic Analgesics	$2.63	$3.47	-24.1%	7.1	8.5	-16.3%	$37	$41	-9.5%
7	48	Anticonvulsants	$2.62	$2.66	-1.5%	5.4	5.7	-5.5%	$44	$42	3.8%
8	58	Diabetic Therapy	$2.48	$2.60	-4.6%	2.1	2.4	-10.9%	$116	$109	6.8%
9	10	CNS Stimulants	$2.44	$2.88	-15.2%	1.9	2.2	-9.6%	$126	$130	-3.7%
10	71	Other Hypotensives	$2.16	$2.15	0.5%	2.9	3.1	-6.8%	$74	$69	6.4%
11	30	Antineoplastic	$1.62	$1.01	59.7%	0.4	0.3	15.3%	$389	$257	51.1%
12	42	Antiarthritics	$1.52	$1.37	10.7%	2.2	2.3	-4.0%	$66	$59	13.1%
13	12	Amphetamine Preps	$1.39	$1.19	16.9%	1.0	0.9	6.5%	$138	$125	9.7%
14	51	Gluco Corticoids	$1.29	$1.16	11.9%	2.0	2.1	-3.7%	$63	$54	16.3%
15	63	Oral Contraceptives	$1.18	$1.19	-1.1%	2.5	2.5	-1.5%	$47	$47	-0.3%
16	1	Antacids	$1.12	$1.36	-17.8%	3.5	4.0	-12.5%	$32	$34	-7.1%
17	65	Lipotropics	$1.05	$1.16	-9.3%	2.1	2.3	-9.9%	$50	$50	0.3%
18	41	Non-narcotic Analgesics	$0.85	$0.85	0.1%	5.1	5.0	2.4%	$17	$17	-2.5%
19	64	Other Hormones	$0.75	$0.81	-6.3%	0.1	0.1	-15.7%	$699	$656	6.6%
20	77	Anticoagulants	$0.72	$0.96	-25.8%	0.5	0.6	-21.7%	$163	$165	-1.5%
21	6	Laxatives	$0.67	$0.66	0.8%	5.4	5.4	-1.1%	$12	$12	2.2%
22	87	Electrolytes and Misc Nutr	$0.65	$0.68	-4.0%	2.8	3.0	-5.7%	$23	$22	1.2%
23	23	Streptomycins	$0.57	$0.33	72.4%	0.0	0.0	29.8%	$1,379	$1,008	36.8%
24	27	Other Antibiotics	$0.48	$0.64	-25.2%	0.7	0.9	-15.8%	$57	$73	-20.9%
25	80	Fat Soluble Vitamins	$0.38	$0.39	-4.1%	3.7	3.5	5.5%	$10	$11	-9.2%
26	69	Enzymes	$0.37	$0.30	23.7%	0.1	0.0	21.7%	$708	$718	-1.4%
27	82	Multivitamins	$0.37	$0.37	-1.5%	3.5	3.6	-2.5%	$10	$10	0.4%
28	76	Other Cardiovascular Preps	$0.34	$0.39	-13.8%	1.9	2.1	-12.2%	$17	$19	-7.0%
29	14	Antihistamines	$0.34	$0.36	-6.8%	2.9	2.8	5.0%	$12	$13	-11.3%
30	88	Hematinics with/without Iron	$0.30	$0.35	-13.1%	1.4	1.4	-2.0%	$17	$24	-28.4%
		Aggregate	$57.96	$61.23	-5.3%	101.42	106.66	-4.9%	$69	$75	-8.7%
		75th Percentile			12.4%			5.5%			6.6%
		50th Percentile (Median)			-4.1%			-5.4%			-1.4%

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Pharmacy Utilization Summary Report: July 2011 - June 2012

	2011						2012						
	JULY	AUGUST	SEPTEMBER	OCTOBER	NOVEMBER	DECEMBER	JANUARY	FEBRUARY	MARCH	APRIL	MAY	JUNE	AVG/YTD
Eligibility													
Total Members	592,894	593,825	595,965	600,779	603,146	607,560	610,951	614,598	617,154	618,741	619,071	619,994	607,890
FFS Members	93,582	91,122	93,140	95,835	90,655	93,725	98,287	94,464	95,551	98,227	93,871	95,264	94,477
Standard	6,261	5,648	5,648	5,893	5,238	5,843	6,499	5,939	5,581	5,743	5,631	5,627	5,796
Plus	62,454	60,588	62,521	64,748	60,321	62,633	66,336	63,022	64,361	66,770	62,683	63,941	63,365
Medicare Wrap	24,867	24,886	24,971	25,194	25,096	25,249	25,452	25,503	25,609	25,714	25,557	25,696	25,316
Gross Figures													
Total Cost	$13,441,500	$14,406,998	$13,874,141	$13,696,222	$13,730,339	$14,022,722	$14,791,244	$14,418,495	$14,820,198	$13,121,847	$12,778,070	$11,935,044	$165,036,820
FFS Drugs	$4,152,647	$4,269,073	$4,234,164	$4,063,544	$4,091,975	$4,132,762	$4,333,277	$4,264,803	$4,418,704	$4,275,084	$4,177,873	$3,911,407	$50,325,313
Mental Health Carveout Drugs	$9,288,853	$10,137,924	$9,639,977	$9,632,678	$9,638,364	$9,889,960	$10,457,966	$10,153,693	$10,401,494	$8,846,763	$8,600,197	$8,023,637	$114,711,507
Total Rx	171,383	185,973	178,171	176,262	177,649	181,375	185,688	179,663	187,348	182,375	189,293	179,618	2,174,798
FFS Drugs	77,472	83,555	80,097	78,411	78,423	79,741	81,575	79,924	83,459	80,507	83,821	77,927	964,912
Mental Health Carveout Drugs	93,911	102,418	98,074	97,851	99,226	101,634	104,113	99,739	103,889	101,868	105,472	101,691	1,209,886
Cost/Rx	$78.43	$77.47	$77.87	$77.70	$77.29	$77.31	$79.66	$80.25	$79.11	$71.95	$67.50	$66.45	$75.92
FFS Drugs	$53.60	$51.09	$52.86	$51.82	$52.18	$51.83	$53.12	$53.36	$52.94	$53.10	$49.84	$50.19	$52.16
Mental Health Carveout Drugs	$98.91	$98.99	$98.29	$98.44	$97.14	$97.31	$100.45	$101.80	$100.12	$86.85	$81.54	$78.90	$94.89
Generic	$63.14	$62.68	$63.25	$63.10	$63.36	$64.21	$43.65	$43.94	$42.53	$34.52	$29.75	$27.40	$50.13
Brand	$5.13	$5.03	$5.10	$5.06	$4.95	$4.81	$338.13	$341.05	$341.17	$342.46	$336.19	$343.40	$172.71
PMPM Figures													
Cost PMPM	$60.04	$63.92	$61.64	$58.44	$61.12	$60.37	$61.21	$61.67	$63.10	$57.82	$58.40	$54.00	$60.14
Standard	$153.77	$168.38	$159.60	$144.12	$160.64	$161.45	$151.49	$151.63	$166.53	$151.91	$155.79	$147.60	$156.08
Plus	$61.57	$66.91	$64.08	$60.73	$64.23	$63.00	$63.00	$64.28	$66.14	$58.67	$62.20	$55.82	$62.55
Medicare Wrap	$14.95	$17.25	$15.94	$15.17	$16.81	$15.15	$15.95	$17.95	$14.66	$17.72	$14.39	$15.59	$15.96
FFS Drugs	$44.37	$46.85	$45.46	$42.40	$45.14	$44.09	$44.09	$45.15	$46.24	$43.52	$44.51	$41.06	$44.41
Mental Health Carveout Drugs	$15.67	$17.07	$16.18	$16.03	$15.98	$16.28	$17.12	$16.52	$16.85	$14.30	$13.89	$12.94	$15.74
Rx PMPM	0.99	1.09	1.02	0.98	1.03	1.02	1.00	1.01	1.04	0.98	1.06	0.98	1.02
Standard	1.98	2.31	2.16	2.00	2.21	2.07	1.95	2.04	2.21	2.10	2.22	2.10	2.11
Plus	0.86	0.95	0.91	0.84	0.90	0.88	0.86	0.88	0.90	0.85	0.93	0.85	0.88
Medicare Wrap	0.96	1.04	0.96	0.99	0.99	1.00	1.01	0.98	1.01	0.98	1.03	0.96	0.99
FFS Drugs	0.83	0.92	0.86	0.82	0.87	0.85	0.83	0.85	0.87	0.82	0.89	0.82	0.85
Mental Health Carveout Drugs	0.16	0.17	0.16	0.16	0.16	0.17	0.17	0.16	0.17	0.16	0.17	0.16	0.17
Utilization Percentages													
Generic %	83.4%	83.5%	83.3%	83.3%	83.4%	83.4%	87.8%	87.8%	87.8%	87.8%	87.7%	87.6%	85.6%
FFS Drugs	88.1%	88.2%	88.0%	88.1%	88.4%	88.5%	89.4%	89.6%	89.6%	89.7%	89.8%	89.8%	88.9%
Mental Health Carveout Drugs	79.6%	79.6%	79.5%	79.5%	79.5%	79.4%	86.5%	86.3%	86.3%	86.4%	86.0%	86.0%	82.9%
PDL %	80.0%	79.9%	79.8%	79.7%	80.7%	80.8%	80.7%	80.8%	80.5%	80.0%	80.6%	80.5%	80.3%

PMPM calculated as sum of physical health and mental health carve-outs
Data from DSSURS and DMAP FCHP first of month reports
Dates are service dates
All eligibility groups included except for CAWEM, QS, QB
Drug Cost = Amt Paid +Copay + Other Insurance Paid

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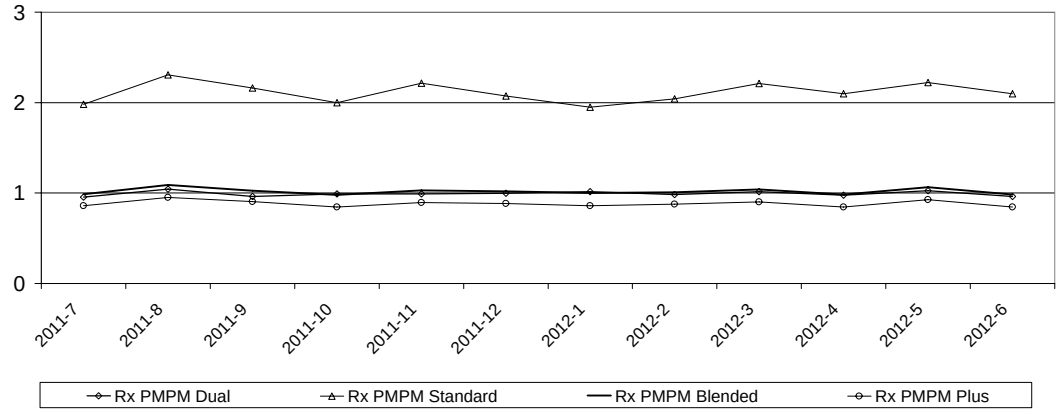
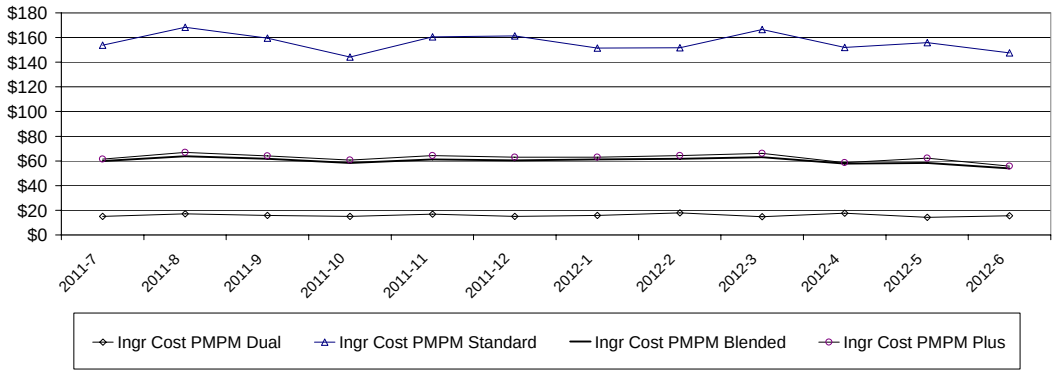
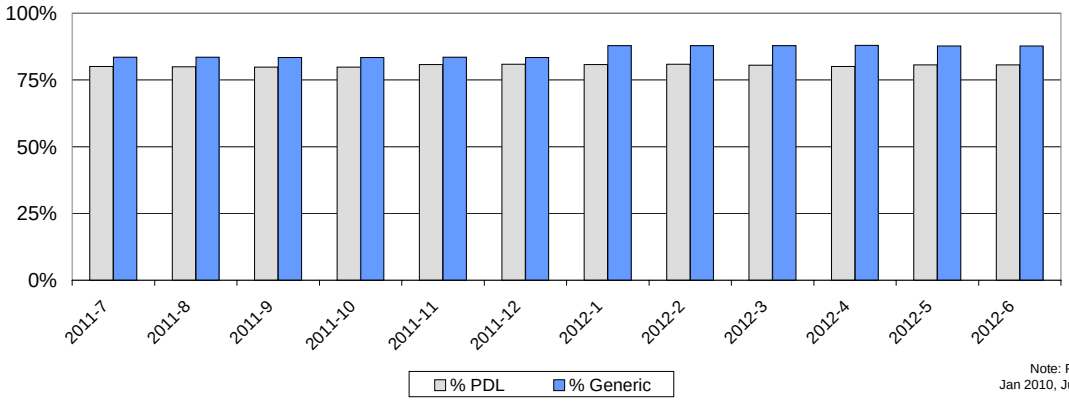
RX Dispensed PMPM



Ingredient Cost PMPM



Percent Generic and PDL



Note: PDL updated
Jan 2010, Jul 2010, Jan 2011

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Can The Diabetic War Be Fought By Aggressive Blood Pressure Control?

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Current epidemiologic evidence indicates that the risk of cardiovascular disease (CVD) is increased two to four-fold among patients with diabetes mellitus (DM), and that having hypertension (HTN) with DM confers a greater risk of microvascular and macrovascular complications than either condition alone.[1] Therefore, the current American Diabetes Association (ADA) guidelines recommend a blood pressure (BP) goal of <130/80 mmHg in patients with DM.[2] Specifically, a systolic blood pressure (SBP) of <130 mmHg is recommended for most patients and a diastolic blood pressure (DBP) <80 mmHg is recommended for all patients with DM. However, this recommendation was mainly driven by expert consensus and data on microvascular complications rather than cardiovascular (CV) events. Recent clinical data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial re-ignited questions regarding the appropriateness of the SBP goal for patients with DM and whether attaining this goal leads to better CV outcomes.

United Kingdom Prospective Diabetes Study

One early landmark trial that provided strong evidence of CVD risk reduction by lowering BP in patients with DM was the United Kingdom Prospective Diabetes Study (UKPDS).[3] The UKPDS trial investigated DM-related endpoints in 1148 patients with type 2 DM randomized to either "tight" (<150/85 mmHg) or "less tight" (<180/105 mmHg) BP control. The study showed a significant reduction in deaths related to DM (11% vs. 16%; RR 0.68, 95% CI 0.49 to 0.94; p=0.019), and a significant reduction in stroke (5% vs. 8.7%, RR 0.56, 95% CI 0.35 to 0.89; p=0.013) in the tighter control group versus the less tight. There was not a statistically significant difference in all-cause mortality. The UKPDS trial concluded that tight BP control (achieved SBP of 144 mmHg compared to 154 mmHg) in patients with type 2 DM was associated with significant reductions in CV and other DM-related events. Observational cohort studies from UKPDS suggest a linear correlation between lowerSBP and myocardial infarction (MI), stroke, and microvascular disease.[4,5] These results were seen as SBP fell from >160 mmHg to <120 mmHg.[5]

Hypertension Optimal Treatment Trial

Another landmark trial that supported the link between aggressive BP lowering and decreased CVD risk was the Hypertension Optimal Treatment (HOT) trial.[6] The HOT trial investigated the effects of DBP targets of <80 mmHg, <85 mmHg and <90 mmHg on major CV events. In the cohort of subjects with DM (n= 1501), an absolute risk reduction of 4.6% in major CV events in the DBP <80 mmHg target group vs. DBP <90 mmHg target group (4.4% vs. 9.0%; RR 2.06, CI 1.24 to 3.44; p=0.005) was demonstrated. The HOT trial concluded that intensive SBP lowering in patients with DM and HTN is associated with a significant reduction in major CV events. However, one limitation is that this was a subgroup analysis and consisted of only 8% of the entire population studied.

Action to Control Cardiovascular Risk in Diabetes Trial

Although both UKPDS and HOT trials provided evidence that lowering BP is associated with reduced CVD, neither of the trials was designed to achieve a goal of SBP <130 mmHg. Actual CV benefits in these trials were observed at higher SBP than what is currently recommended (SBP <130mmHg).[3,6] The mean BP achieved in the tight BP control group of the UKPDS trial was 144/82 mmHg, whereas the mean SBP achieved in all subjects included in the HOT trial, for patients in the <80 DBP group, was 139.7 mmHg. More recent trials have challenged the established SBP goal <130 mmHg.[7,8,9,10,11] The ACCORD trial randomized 4733 hypertensive patients with type 2 DM to either "intensive" therapy with a SBP goal <120 mmHg or "standard" therapy with a SBP goal of <140 mmHg to investigate effects on CV events. There were no significant differences between the two groups with respect to the primary endpoint (1.87% vs. 2.09%; HR 0.88, 95% CI 0.73 to 1.06; p=0.20), a composite of nonfatal MI, nonfatal stroke, and death from CV causes. However, the intensive BP control group had a significantly lower risk of both any and nonfatal stroke (HR 0.59, 95% CI 0.39 to 0.89; p=0.01 and HR 0.63, 95% CI 0.41 to 0.96; p=0.03, respectively), which were secondary outcomes.[7] The average SBP achieved in the intensive control group was 119.3 mmHg compared to 133.5 mmHg in the standard control group. In addition, the ACCORD trial reported significantly higher rates of hypotension (7 fold increase), bradycardia, and hyperkalemia (10 fold increase) in the intensive therapy group.[7]

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation Trial

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial studied both the effects of intensive glycemic control and BP lowering in diabetic patients.[9] The BP lowering arm investigated the effects of a fixed combination of perindopril and indapamide on major vascular events. The primary end points were composites of major macrovascular events (death from CV causes, nonfatal MI, or nonfatal stroke) and major microvascular events (new or worsening nephropathy or retinopathy). The mean change in BP over the duration of the trial was significantly decreased in the active BP treatment group compared to placebo (SBP -5.6mmHg, 95% CI 5.2 to 6.0; p<0.0001 and DBP -2.2 mmHg, 95% CI 2.0 to 2.4; p<0.0001), which resulted in a significant reduction in major macrovascular or microvascular events (HR 0.91, 95% CI 0.83 to 1.00; p=0.04). However, the individual microvascular and macrovascular endpoints were only statistically significant when combined, not when separated (macrovascular HR 0.92, 95% CI 0.81 to1.04; p=0.16 and microvascular HR 0.91, 0.80 to1.04; p=0.16). The baseline BP was 145/81 mmHg. At the conclusion of the trial, BP was 136/73 mmHg in the treatment group (which was where subjects in the ACCORD trial started) compared to 140/73 mmHg in the control group.

The lack of linear correlation observed between BP and CV outcomes could be argued based on the differences in patient characteristics between earlier and later studies, as well as the lower target BP values in the newer studies. In the ACCORD trial, subjects were older and 10 years post-diagnosis with DM while the UKPDS study subjects had newly diagnosed DM.[3,7] Also, patients in the ACCORD trial had lower SBP at baseline compared to patients in the UKPDS study (139 mmHg vs. 160 mmHg).[3,7]

Other Trial Data

Similarly, other recent trials showed no difference between intensive SBP control verses moderate control in reducing microvascular and macrovascular complications.[10-12] A subgroup analysis of patients from the International Verapamil SR-Trandolapril (INVEST) study compared the effects of "tight" SBP control (<130 mmHg), "normal" SBP (130-140 mmHg) and "uncontrolled" SBP (>140 mmHg) on CV outcomes in 6400 patients with DM and CAD.[10] The primary endpoint was the first occurrence of all-cause death, nonfatal MI, or nonfatal stroke. The study concluded that tight SBP control did not result in decreased risk of CV events compared to normal SBP control. The event rate was 12.7% in the tight SBP group versus 12.6% in the normal SBP group (HR 1.11, 95% CI 0.93 to 1.11; p=NS).[10] With extended follow-up, the tight control group had a higher mortality rate of 22.8% versus 21.8% in the normal control group (HR 1.05, 95% CI 1.01 to 1.32; p=0.04). These results need to be interpreted carefully because this was a post-hoc analysis based on achieved BP, and mortality was

assessed using the National Death Index. Nevertheless, SBP goals in patients with DM and CAD may need to be re-evaluated. .

The Appropriate Blood Pressure Control in diabetes (ABCD) trial randomized patients to intensive diastolic blood pressure (DBP of 75 mm Hg) vs. moderate DBP control (80-89 mm Hg). The mean BP achieved was 132/78 mm Hg in the intensive group and 138/86 mm Hg in the moderate control group. This trial reported a significant decrease in all cause mortality with intensive BP control (5.5% vs. 10.7%; RR 0.5, 95% CI 0.25 to 1.0; p=0.037). However, there were no significant reductions in the various CV events studied and progression of diabetic retinopathy or neuropathy over a 5 year period.[11] The inconsistencies across the trials may be due to the differences in the baseline CV risk profile of the study subjects enrolled.

The Irbesartan Diabetic Nephropathy (IDNT) trial compared effects of SBP targets of <120 mmHg and ≥120 mmHg on the primary endpoints of all-cause and CV mortality in 1590 patients with type 2 DM. This trial showed an increase in all-cause mortality (28% vs. 12%; RR 3.05, 95% CI 1.80 to 5.17; p<0.0001), and CV mortality (19% vs. 6%; RR 4.06, 95% CI 2.11 to 7.80; p<0.0001) in patients who achieved a SBP <120 mmHg compared to those with a SBP ≥120 mmHg.[12] The results of these studies further support that more intensive SBP control among patients with DM is not associated with improved CV outcomes.

To further determine the optimal target SBP in patients with DM, a recent meta-analysis was conducted.[13] This meta-analysis included randomized controlled trials investigating antihypertensive therapy in patients with type 2 DM or impaired fasting glucose/impaired glucose tolerance with achieved SBP of ≤135 mmHg in the "intensive" BP control group and ≤140 mmHg in the "standard" BP control group. Each trial also had to include a follow-up of at least 1 year and evaluation of macrovascular and microvascular outcomes. A total of 13 randomized controlled trials with a total of 37,736 patients were included in the meta-analysis. The authors assessed trial eligibility and trial bias risk as recommended by the Cochrane Collaboration; of the 13 trials, 9 were considered trials with low risk of bias. Results of the meta-analysis showed a reduction in all-cause mortality in the <135 SBP group (OR 0.87; 95% CI 0.79 to 0.95) but not in the more intensive group of <130 SBP (OR 1.04; 95% CI 0.86 to 1.25). There was also a demonstrated 0.4% absolute risk reduction in stroke (OR 0.83; 95% CI 0.73 to 0.95) with the intensive SBP (≤135 mmHg) versus standard control with the risk continuing to fall with more aggressive control of <130 mmHg. There was no difference between the two groups in CV mortality, MI, and heart failure. In the few studies that reported serious side effects, intensive SBP control was associated with an increased incidence versus standard control (OR 1.20; 95% CI 1.08 to 1.32).[13] There was a greater magnitude of effect in risk reduction of stroke and increase in serious side effects in trials in which the SBP was <130 mmHg, without any additional benefits for other CV outcomes.[13]

Treatment Guidelines

Current guidelines continue to reflect the <130/80 mmHg BP goal for patients with DM based on microvascular benefit despite a lack of evidence for macrovascular events for SBP <130 mmHg. While the upcoming 8th edition of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8) guidelines has not yet been published, other guidelines have been updated more recently. The 2011 Canadian Hypertension Education Program (CHEP) guidelines continue to recommend using the <130/80 mmHg BP treatment goal in patients with DM. The authors of the CHEP guidelines are waiting for a more detailed analysis of the ACCORD trial before reconsidering the current BP recommendation. The CHEP guidelines also emphasize that the BP goal used in the ACCORD trial (<120 mmHg) is lower than the current recommendation (<130 mmHg), and that this excessive lowering of BP can lead to increased risk of hypotension and hyperkalemia.[14]

Summary

In conclusion, lowering SBP to the ADA goal of <130 mmHg in patients with DM is associated with a reduction in stroke but not other CV outcomes. Caution should be taken in patients when aggressive therapy to lower SBP to <130 mmHg is likely to cause more harm than benefit. At this time, emphasis should be placed on a multifactorial approach to HTN management in DM which includes: maintaining SBP between 130-139 mmHg while focusing on behavioral modifications (exercise and smoking cessation) and nutritional counseling to reduce long term cardiovascular risks.

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Oral Direct Factor Xa Inhibitors (Rivaroxaban)

Goal(s):

- Promote safe and effective therapies for oral direct factor Xa inhibitors.

Length of Authorization: 1 year

Covered Alternatives: Listed at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
What is the diagnosis that rivaroxaban is being prescribed for?	Record the ICD9 code:	
1. Does the patient have a diagnosis requiring short-term (<45 days) anticoagulation (i.e. total knee replacement: ICD9 - 81.54 or 81.55) or total hip replacement: ICD9 – 81.51 or 81.52)?	**Yes:** Approve for 12 days for TKR. Approve for 35 days for THR.	**No:** Go to #2
2. Does the patient have a diagnosis of nonvalvular atrial fibrillation (ICD9 – 427.3x)?	**Yes:** Go to #3	**No:** Deny (Medical Appropriateness)
3. Will the prescriber consider a change to the preferred oral anticoagulant, warfarin?	**Yes:** Approve. Additional information can be found at: http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html	**No:** Go to #4
4. Is the patient unable to tolerate the preferred oral anticoagulant due to one of the following: - unstable INR - allergy - contraindications to therapy - drug-drug interactions - intolerable side effects	**Yes:** Go to #5	**No:** Deny with the allowance of a 14 days of rivaroxaban (or until patient is deemed adequately anticoagulated)*. Recommend warfarin trial.
5. Is patient unable to tolerate the second line agent, dabigatran (Pradaxa)?	**Yes:** Approve for up to 1 year.	**No:** Deny with the allowance of a 14 days of rivaroxaban (or until patient is deemed adequately anticoagulated)*. Recommend dabigatran trial.
* Patients switching from rivaroxaban to other anticoagulants have been shown to have an increased risk of thrombotic events. Adequate anticoagulation is recommended during the switch from rivaroxaban to another anticoagulant. Rivaroxaban effects INR measurements, therefore, the appropriate dose of warfarin based on INR can not be used. Adding a parenteral anticoagulant in addition to warfarin at the time the next dose of rivaroxaban is due is recommended.		

~~DUR Board~~P&T Action: 8/30/12 (KS), 1/26/12(KS)
Revision(s):
Initiated: ~~1/26/12 (KS)~~

Drug Use Evaluation: Preferred Targeted Immune Modulators (TIMs)

A drug class review on Targeted Immune Modulators (TIMs) was conducted and discussed during the June P&T committee.[1] The goal of this evaluation is to assess the off-label use, recommended dosage and safety concerns of the preferred drugs, which include adalimumab, etanercept, and infliximab.

Background:

Adalimumab, administered by subcutaneous injection, is Food and Drug Administration (FDA) approved for rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), and plaque psoriasis (Ps).[2] In addition, it is used for the treatment of ulcerative colitis (UC) off-label.[3,4] Table 1 lists the FDA recommended doses for adalimumab. The use of adalimumab beyond one- year for the treatment of CD and PP has not been evaluated in clinical trials, therefore long-term safety and efficacy for these indications is not known. The FDA recommends careful monitoring of patients taking adalimumab with a history of congestive heart failure (CHF), previous diagnoses with hepatitis B, tuberculosis, and Central Nervous System (CNS) demyelinating disease (multiple sclerosis, optic neuritis, Guillain-Barre syndrome). Higher incidences of infection and malignancy have been reported in the elderly taking adalimumab compared to younger adults.

Table 1-FDA approved indications and dosages for adalimumab

Indication	Recommended Dose Range	Maximum Recommended Dose
RA - Rheumatoid arthritis	40mg every other week	40mg every week (without concurrent MTX)
JIA - Juvenile idiopathic arthritis (age 4-17)	15kg (33lbs) to <30kg (66 lbs): 20 mg every other week ≥30kg (66lbs): 40mg every other week	
PsA - Psoriatic arthritis	40mg every other week	40mg every week (without concurrent MTX)
AS - Ankylosing spondylitis	40mg every other week	40mg every week (without concurrent MTX)
CD - Crohn's disease	Initial dose (Day 1)160mg; On Day 15 80mg; Maintenance begins on Day 29 at 40mg every other week	
Ps - Plaque psoriasis	80mg initial dose, then 40mg every other week starting one week after initial dose	

MTX = methotrexate

Etanercept is FDA approved for the treatment of RA, polyarticular JIA in patients age ≥2 years, PsA, and Ps.[5] Etanercept has also been used to treat scleroderma, Alzheimer's disease, and Wegener's granulomatosis off-label.[6–8] The FDA does not recommend the use of etanercept in patients with Wegener's granulomatosis who are also receiving immunosuppressive treatment. Table 2 lists the FDA approved doses for etanercept. Caution should be taken in patients with a history of hepatitis B virus, tuberculosis, congested heart failure (CHF), demyelinating CNS disease, and moderate to severe alcoholic hepatitis. In addition, hypoglycemia following initiation of etanercept in patients receiving diabetic medications has been reported, therefore patients taking diabetic medications should be monitored and dose adjusted if needed. No overall difference in safety or effectiveness among geriatrics was observed in comparison to younger patients.

Table 2-FDA approved indications and dosages for etanercept

Indication	**Recommended Dose Range**	**Maximum Recommended Dose**
RA	50mg once weekly with or without MTX	
Polyarticular JIA (≥2 years of age)	0.8mg/kg weekly	50mg/week
PsA	50mg once weekly with or without MTX	
AS	50mg once weekly	
Ps	50mg twice weekly for 3 months, followed by 50mg once weekly	

The FDA approved indications for infliximab include pediatric and adult Wegener's granulomatosis, CD, pediatric and adult UC, RA in combination with MTX, AS, PsA, and Ps.[9] Infliximab is used off-label in the treatment of Behcet's Disease and age-related macular degeneration.[10–12] Table 3 lists the FDA approved doses for infliximab. Pediatric CD and UC are only indicated for children older than six years old due to the lack of studies in younger children. Like the other TIMs, infliximab should be used with caution in patients with demyelinating disease, hepatitis B, tuberculosis, seizure disorders, and heart failure. Patients with moderate to severe heart failure (NYHA Class III/IV) should not be dosed with >5mg/kg of infliximab due to risk of heart failure exacerbation. Geriatrics may have a higher incidence of infection.[9]

All of the preferred medications have an FDA warning for severe and possibly fatal infections related to their use. Due to these findings, their use is contraindicated in patients with active acute hepatitis B or C, tuberculosis, herpes zoster, fungal or bacterial infections.

Table 3-FDA approved indications and dosages for infliximab

Indication	Recommended Dose/Dose Range	Maximum Recommended Dose
CD	5mg/kg at 0, 2, 6 weeks, then every 8 weeks	10mg/kg if they later lose response
Pediatric CD	5mg/kg at 0, 2, 6 weeks, then every 8 weeks	
UC	5mg/kg at 0, 2, 6 weeks, then every 8 weeks	
Pediatric UC	5mg/kg at 0, 2, 6 weeks, then every 8 weeks	
RA (with MTX)	3mg/kg at 0, 2, 6 weeks, then every 8 weeks	10mg/kg or treat every 4 weeks if needed
AS	5mg/kg at 0, 2, 6 weeks, then every 6 weeks	
PsA	5mg/kg at 0,2, 6 weeks, then every 8 weeks	
Ps	5mg/kg at 0,2, 6 weeks, then every 8 weeks	

In 2012, the American College of Rheumatology published revised treatment guidelines.[13] This update separates recommendations for early (<6 months) and established (> 6 months) RA. For early RA, the guidelines recommend DMARD monotherapy initially and the use of TIMs with or without MTX only in patients who have high disease activity and with poor prognostic features.[13] The use of infliximab in combination with MTX was designated a level of evidence A, and use of etanercept, adalimumab, golimumab, and certolizumab with or without MTX were given a level of evidence B. In established RA, the guidelines recommend DMARD monotherapy and combination therapy before switching to a TIM.[13] Patients must undergo a 3 month trial with MTX monotherapy or DMARD combination therapy. If moderate or high disease activity persists after 3 months, an alternative is switching to a TIM. This included level of evidence A for etanercept, infliximab, adalimumab, golimumab, certolizumab, abatacept, and rituximab all in combination with MTX. These same agents are given a level of evidence C when given without MTX.[13]

The 2011 national clinical guidelines on the management of early RA from the Scottish Intercollegiate Guidelines Network (SIGN) state that the use of the TIMs for the treatment of severe, active and progressive RA in adults not previously treated with MTX or other DMARDs is not recommended.[14] Clinical guidelines from the National Institute for Clinical Excellence (NICE) in 2009 recommend that adalimumab, etanercept, and infliximab are options for adults with active RA and for those who have undergone trials of two DMARDs, including MTX (for 6 months).[15]

The American College of Rheumatology recommends the initiation of TIMs in patients with JIA who have received glucocorticoid joint injections and 3 months of MTX at the maximum tolerated dose (level of evidence C).[16] For systematic arthritis, level C evidence supports the initiation of anakinra in all patents with active fever and features of poor prognosis.

The SIGN guidelines for psoriasis and PsA recommend NSAIDs for short term symptom relief.[17] The use of DMARDs (leflunomide, sulfasalazine, or MTX) for the treatment of PsA is recommended first line. TIMs are only recommended after failed responses to two different DMARD therapies, each treated for at least a 3 month period.

The guidelines of care for the management of psoriasis and PsA from the Journal of the American Academy of Dermatology were updated in 2009.[18] They recommend that topical agents such as corticosteroids and vitamin D analogues or systemic agents such as MTX and cyclosporine should be used as first line depending on severity of the Ps. Only when trial periods with these agents have failed can patients be recommended to use TIMs.

In 2008, NICE guidelines issued recommendations for biologic therapy use in AS. The recommendations state that adalimumab and etanercept may be considered as possible treatments for people with severe AS who have tried at least two non-steroidal anti-inflammatory drugs (NSAIDs) but failed to work. [19]

The American College of Gastroenterology (ACG) and the Gut Guidelines both recommend that patients with CD or UC first be unsuccessfully treated with aminosalicylates, corticosteroids and immunomodulators before a TIM is administered.[20-22]

Treatment Guidelines are summarized in Table 4.

Table 4 – Treatment Guidelines

Disease	Guidelines	Recommendations
RA	American College of Rheumatology (2012)[13] Scottish Intercollegiate Guidelines Network (2011)[14] National Institute for Clinical Excellence (2009)[15]	Early RA (<6 mo)=DMARD monotherapy initially, then biologics with or without MTX Established RA (>6 mo)=DMARD monotherapy and combination therapy before starting biologics (DMARD for 3-6 months depending on guidelines)
JIA	American College of Rheumatology (2011)[16]	Glucocorticoid joint injections and 3 months of MTX before initiating biologics
PsA	Scottish Intercollegiate Guidelines Network (2010)[17]	NSAIDS for short term relief; DMARD therapy for 3 months before starting biologics
Ps	Journal of the American Academy of Dermatology (2009)[18]	Corticosteroids, vitamin D analogues or systemic agents (MTX and cyclosporine) should be used as first line depending on severity; if failed, biologics can be used
AS	National Institute for Clinical Excellence (2008)[19]	Adalimumab and etanercept may be considered after trying at least two non-steroidal anti-inflammatory drugs (NSAIDs)
CD	The American College of Gastroenterology (2010)[20,21] Gut Guidelines (2004)[22]	Unsuccessfully treated with aminosalicylates, corticosteroids and immunomodulators before biologics can be started
UC	The American College of Gastroenterology (2010)[20,21] Gut Guidelines (2004)[22]	Unsuccessfully treated with aminosalicylates, corticosteroids and immunomodulators before biologics can be started

Methods

Patients were selected for inclusion if they had a new fee-for-service (FFS) pharmacy or professional claim for any of the preferred drugs during 2011. See appendix A for a list of codes used to identify the preferred drugs. The definition of "new" was a patient with no prior history of any TIMs use (FFS or managed care) in the year prior to the index claim. See Appendix B for list of codes to identify TIMs drugs. Patients needed to be continuously eligible for at least 75% of the year prior and 100% eligible 90 days before and after the index claim. Only patients with valid demographic data and without Medicare Part D coverage were included. Recommended and maximum doses are defined in Appendix A. The "Days Supply" field was used for pharmacy

claims to calculate a daily dose (Quantity Dispensed x Strength per Unit divided by the Days Supply). For professional claims the days between fills were determined as a proxy for Days Supply and calculated similarly. Concurrent DMARD therapy was determined for all patients on a preferred product for a minimum of 60 day spans (7 day gap allowed). A minimum of 30 days of overlap was considered concurrent therapy. Codes to identify DMARDs are in Appendix C. Finally, International Classification of Diseases, 9th Revision (ICD-9) diagnostic codes was identified in the year prior to the index fill to associate potential uses for the TIMs and co-morbid conditions. These are listed in Appendix D.

Results

There were a total of 42 new patients identified using a preferred TIMs (Table 5). A majority of the patients were adult white females between the ages of 19-65 years. None of the patients were below the age restriction for the specific TIM used.

Table 5-Demographics of all users

	All Users	
Total	42	(%)
Age		
Mean	47.3	
Range	7-93	
<6	0	0.0%
6-12	2	4.8%
13-18	1	2.4%
19-65	31	73.8%
>65	8	19.0%
Female	26	61.9%
Race		
White	37	88.1%
Hispanic	0	0.0%
American Indian	2	4.8%
Black	2	4.8%
Asian	0	0.0%
Other	1	2.4%

Table 6 lists the preferred drugs and numbers of patients taking each of them. The most commonly used TIM was infliximab followed by adalimumab and then etanercept.

Table 6-Distribution of all users

Drug	N= 42	(%)
ADALIMUMAB	12	28.57%
ETANERCEPT	6	14.29%
INFLIXIMAB	24	57.14%

The average daily doses prescribed for each drug were reviewed. The results show that infliximab had the highest occurrence of patients exceeding the maximum recommended dose per day (Table 7 and 8) at a rate of 50% of the included patients on infliximab. All of the prescribed TIMs had incidences of doses exceeding the maximum recommendation.

Table 7 - Dose Analysis of users (pharmacy users only)

Drug	N=	Avg Daily Dose (mg)	Patients exceeding maximum recommended dose/ day	(%) of patients on drug
ADALIMUMAB	12	3.3	3	25%
ETANERCEPT	6	6.7	2	33%
INFLIXIMAB	0	-	0	-

Table 8 - Dose Analysis of Users (professional claims only)

Drug	N=	Avg Daily Dose (mg)	Patients exceeding maximum recommended dose/ day	(%) of patients on drug
INFLIXIMAB (J1745)	18	11.4	9	50%

Note: The "N" is the count of patients with adequate dosage information to determine an average for that patient. It is not a comprehensive count of all patients on that drug.

Data was queried for the prevalence of concurrent DMARD use in patients taking TIMs, but no concurrent use of medications was found.

Table 9 categorizes each of the TIMs using the FDA approved indications to determine the most commonly used disease state in which they are prescribed. The preferred TIMs are most commonly associated with RA, though infliximab is also highly associated with CD. There were eight (16.3%) patients with no history of an FDA approved diagnosis for the TIMs.

Table 9 - FDA approved diagnostic information for users by drug in year prior to index drug (patients may be in >1 diagnostic group)

Drug	N=	RA	JIA	PsA	Ps	AS	CD	UC	No FDA Dx	Any FDA Dx
ADALIMUMAB	12	3		4	1	1			4	8
ETANERCEPT	6	1		2	2				3	3
INFLIXIMAB	24	8		1	1	4	8	3	1	23

Off-label uses for the preferred TIMs were evaluated and none of the patients had a diagnosis of the specified off-label indications. Cautionary diagnostic information was also queried from the year prior to the use of the drugs and four of 42 patients (9.5%) were identified. Adalimumab had one patient with a diagnosis of seizure and one with an infection diagnosis. Etanercept had one diagnosis of heart failure and infliximab had one diagnosis of multiple

sclerosis. Incidence of infection 90 days after the start of TIMs was evaluated and only one occurrence of infection was documented which included a diagnosis hepatitis C in a patient taking adalimumab.

DMARDs, which are the first line therapy for RA, PsA and an optional first line for Ps, were used in seven patients 1 year prior to the initiation of TIMs (Table 10).

Table 10-Users with DMARD in 1 year previously

Drug	N= 42	%
ADALIMUMAB	5	11.9%
ETANERCEPT	2	4.8%
INFLIXIMAB	0	0.0%

Discussion

This analysis is limited because it uses retrospective administrative data and thus suffers from the possibility of missing diagnostic information. Diagnostic information cannot be directly linked to drug use but is associated by patient and time period only. This evaluation is not controlled and merely descriptive. Finally, the sample size is very small with only 42 new patients identified. Thus conclusions should be cautiously drawn and applied to the larger population.

There was no evidence of use for identified off-label indications or for children under the recommended age. The recommended dose was exceeded in 25-50% of patients. Four patients (9.5%) with a past history of seizure, MS, or infection were identified which are contraindicated conditions in the use of some TIMs. Of most concern is the low number of patients where previous DMARD therapy was detected in the year before the index TIMs claim. It appears TIMs are not used in accordance with treatment guidelines.

Recommendations

1. Consider prior authorization to ensure DMARDs are used first line
2. Initiate a quantity limit to prevent doses from exceeding recommendations

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Appendix A – Codes identifying preferred drugs in fee-for-service pharmacy and professional claims

GSN	Drug	Drug Strength per Billing Unit	Maximum recommended billing units per day	Corresponding Recommended Dose
51599	ADALIMUMAB	40	0.071	40 mg every other week
61205	ADALIMUMAB	40	0.071	40 mg every other week
63724	ADALIMUMAB	20	0.143	40 mg every other week
40869	ETANERCEPT	25	0.286	50mg once weekly
58214	ETANERCEPT	50	0.143	50mg once weekly
61938	ETANERCEPT	50	0.143	50mg once weekly
62624	ETANERCEPT	50	0.143	50mg once weekly
40650	INFLIXIMAB	100	0.119	100kg (at 5mg/kg) every 6 weeks
J0135	ADALIMUMAB	20	0.143	40 mg every other week
J1438	ETANERCEPT	25	0.286	50mg once weekly
J1745	INFLIXIMAB	10	1.190	100kg (at 5mg/kg) every 6 weeks

Appendix B – Codes identifying TIMs drugs in fee-for-service or managed care pharmacy or professional claims

GSN/ J-code	Drug
67681	ABATACEPT
J0129	Abatacept injection
60226	ABATACEPT/MALTOSE
51599	ADALIMUMAB
61205	ADALIMUMAB
63724	ADALIMUMAB
J0135	ADALIMUMAB
51694	ALEFACEPT
51695	ALEFACEPT
J0215	Alefacept
48899	ANAKINRA
63903	CERTOLIZUMAB PEGOL
65189	CERTOLIZUMAB PEGOL
J0718	Certolizumab pegol inj
40869	ETANERCEPT
58214	ETANERCEPT
61938	ETANERCEPT
62624	ETANERCEPT
J1438	ETANERCEPT
65113	GOLIMUMAB
65114	GOLIMUMAB
40650	INFLIXIMAB
J1745	INFLIXIMAB
58384	NATALIZUMAB
J2323	Natalizumab injection
65775	OFATUMUMAB
67553	OFATUMUMAB
J9302	Ofatumumab injection
63759	RILONACEPT
36870	RITUXIMAB
J9310	Rituximab injection
65409	TOCILIZUMAB
65410	TOCILIZUMAB
65411	TOCILIZUMAB
J3262	Tocilizumab injection
65993	USTEKINUMAB
65994	USTEKINUMAB
J3357	Ustekinumab injection

Appendix C – Codes identifying DMARD drugs in fee-for-service or managed care pharmacy or professional claims

GSN/Jcode	GroupByCategory*	Strength
9580	HYDROXYCHLOROQUINE SULFATE	200 mg
40549	LEFLUNOMIDE	10 mg
40550	LEFLUNOMIDE	20 mg
45266	METHOTREXATE SODIUM	2.5 mg
35928	METHOTREXATE SODIUM	10 mg
36872	METHOTREXATE SODIUM	2.5 mg
36874	METHOTREXATE SODIUM	7.5 mg
47823	METHOTREXATE SODIUM	5 mg
47824	METHOTREXATE SODIUM	15 mg
42778	MINOCYCLINE HCL	75 mg
52057	MINOCYCLINE HCL	75 mg
60730	MINOCYCLINE HCL	45 mg
60731	MINOCYCLINE HCL	90 mg
60732	MINOCYCLINE HCL	135 mg
65433	MINOCYCLINE HCL	65 mg
65434	MINOCYCLINE HCL	115 mg
66683	MINOCYCLINE HCL	55 mg
66684	MINOCYCLINE HCL	80 mg
66685	MINOCYCLINE HCL	105 mg
9226	MINOCYCLINE HCL	100 mg
9227	MINOCYCLINE HCL	50 mg
9230	MINOCYCLINE HCL	100 mg
9231	MINOCYCLINE HCL	50 mg
9402	SULFASALAZINE	500 mg
9403	SULFASALAZINE	500 mg
J9250	Methotrexate sodium inj	5 MG
J9260	Methotrexate sodium inj	50 MG
J8610	Methotrexate oral 2.5 MG	2.5 MG

Appendix D – International Classification of Diseases, 9th Revision (ICD-9) diagnostic codes identified in FFS and managed care professional claims the year prior to index fill.

FDA Indications	FDA codes
Rheumatoid Arthritis (RA)	714.0
juvenile idiopathic arthritis (JIA)	714.3
Psoriatic arthritis (PsA)	696.0
Plaque Psoriasis (Ps)	696.1
Ankylosing Spondylitis (AS)	720.0
Chrohn's Disease (CD)	555.x
Ulcerative Colitis (UC)	556.x

Off-Label Indications	Off-Label Codes
Circumscribed scleroderma	701
Wegener's granulomatosis	446.4
Alzheimer's disease	331
Behcet's disease	136.1
Behcet's disease	711.2x
age-related macular degeneration	362.5

Other Infection Indications	Infection Codes
Endemic Mycoses	114.xx - 116.xx
Septic Arthritis	711.0
Listeriosis	027.0
Legionella pneumonia	482.8, 482.84
herpes zoster infection	053.xx
Cryptococcosis	117.5
Aspergillosis	117.3
Pneumocystis pneumonia	136.3
Non-healed infected skin ulcers	707.xx
Hepatitis C	070.70
Hepatitis C	070.4
Hepatitis C	070.5

Cautionary Indications	Cautionary Codes
Heart Failure	428.xx
Multiple Sclerosis	340.xx
Optic neuritis	377.3x
Guillain-Barre	357.0x
Hepatitis B	070.2x
Tuberculosis	010.xx - 018.xx
Seizure	345.xx

Targeted Immune Modulators (TIMS)

Goal(s):

- *Cover TIMs according to OHP list guidelines.*
- *Promote use that is consistent with National Guidelines and medical evidence.*
- *Promote use of high value products.*

Requires PA: Non-preferred products
Preferred products for non-approved indications

Preferred Products: Adalimumab (Humira®), Etanercept (Enbrel®)

Length of Authorization: 12 months

Generic Name	Trade Name	Indication
Abatacept	Orencia	RA, Juvenile RA, Juvenile idiopathic arthritis
Adalimumab	Humira	RA, Psoriatic arthritis, ankylosing spondylitis, Juvenile idiopathic arthritis, Crohn's disease, Plaque psoriasis
Anakinra	Kineret	RA
Certolizumab	Cimzia	RA, Crohn's disease
Etanercept	Enbrel	RA, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, plaque psoriasis
Golimumab	Simponi	RA, psoriatic arthritis, ankylosing spondylitis
Infliximab*	Remicade	RA, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, plaque psoriasis
Natalizumab*	Tysabri	Crohn's disease
Rituximab*	Rituxan	RA
Tocilizumab*	Actemra	RA, juvenile idiopathic arthritis
Ustekinumab	Stelara	Plaque psoriasis

Abbreviations: RA, rheumatoid arthritis
* Must be billed via J-code and payment requires trial of preferred self-administered drug first.

Approval Criteria : TIMS		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the diagnosis covered by OHP?	**Yes:** Go to #3	**No:** Pass to RPH; Deny (medical appropriateness)
3. Is the product requested preferred?	**Yes:** Go to #5	**No:** Go to #4
4. Will the provider change to a preferred product?	**Yes:** Go to #5.	**No:** Go to #6
5. Is the diagnosis a FDA-approved indication for the product requested (see table above)?	**Yes:** Approve treatment for up to 1 year	**No:** Pass to RPH; Deny (medical appropriateness)
6. Is the diagnosis psoriasis (ICD-9: 696.1-696.2, 696.8) and the product requested FDA approved for psoriasis (see table above)? * Moderate/Severe psoriasis treatments are covered on the OHP.	**Yes:** Refer to anti-psoriatics PA criteria at http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/OR%20Medicaid%20PA%20Criteria/	**No:** Go to #7

	PA%200711.pdf	
7. Is the diagnosis ankylosing spondylitis (ICD-9 720) and the product requested is FDA approved for ankylosing spondylitis?	**Yes:** Approve treatment for up to 1 year	**No:** Go to #8
8. Is the diagnosis rheumatoid arthritis (ICD-9 714.xx) or psoriatic arthropathy (ICD-9 696.0) and the product requested FDA approved for rheumatoid arthritis (see table above)?	**Yes:** Go to #9	**No:** Go to #10
9. Has the patient had a trial and inadequate response to methotrexate or other first line DMARDs (leflunomide, sulfasalazine, hydroxychloroquine, penicillamine) and a disease duration of ≥6 months? Or, An intolerance or contraindication to oral DMARDs?	**Yes:** Approve treatment for up to 1 year	**No:** Pass to RPH; Deny (medical appropriateness)
10. Is the diagnosis Crohn's disease (ICD-9 555) and the product requested FDA approved for Crohn's (see table above)?	**Yes:** Go to #11	**No:** Pass to RPH; Deny (medical appropriateness)
11. Has the patient had a trial and inadequate response to conventional therapy including immunosuppressive therapy (mercaptopurine, azathioprine) and/or corticosteroid treatments? Or, Has an intolerance or contraindications to conventional therapy?	**Yes:** Approve treatment for up to 1 year	**No:** Pass to RPH; Deny (medical appropriateness)

P&T Action: 8-30-12 (MH)
Revision(s):
Initiated:

Antipsoriatics

Goal(s): Cover topical antipsoriatics only for covered OHP diagnoses. Moderate/Severe psoriasis treatments are covered on the OHP. Treatments for mild psoriasis (696.1-696.2, 696.8), seborrheic dermatitis (690.XX), keroderma (701.1-701.3) and other hypertrophic and atrophic conditions of skin (701.8, 701.9) are not covered.

Length of Authorization: 1 year

Alternatives with no PA:
Topical corticosteroids, methotrexate, cyclosporine See: http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Requires PA for OHP coverage: TC = 92 and HIC = L1A, L5F, L9D, T0A

After OHP coverage verified these products are preferred:

ANTHRALIN	CREAM(GM)
CALCIPOTRIENE	SOLUTION
DOVONEX	CREAM(GM)
TACLONEX	OINT.(GM)
TAZORAC	CREAM(GM)

Approval Criteria		
1. What is the diagnosis being treated?	Record ICD9 code	
2. Is the diagnosis for seborrheic dermatitis (690.XX), keroderma (701.1-701.3) or other hypertrophic and atrophic conditions of skin (701.8, 701.9)?	**Yes:** PASS TO RPH - Deny (Not Covered by the OHP).	**No:** Go to **#3.**
3. Is the diagnosis Psoriasis? (ICD-9: 696.1-696.2, 696.8)	**Yes:** Go to **#4.**	**No:** Go to #6.
4. Is the Psoriasis Moderate/Severe? *Defined as:* At least 10% body surface area involved or with functional impairment?	**Yes:** Go to 5.	**No:** PASS TO RPH Deny (Not Covered by the OHP).
5. Is the product requested a non-preferred biologic agent approved for plaque psoriasis?	**Yes:** Go to #6	**No:** Got to 7
6. Has the patient tried and not had an adequate response to standard systemic therapies, including cyclosporine or methotrexate or acitretin, or the person is intolerant of or has a contraindication to these treatments?	**Yes:** Approve for length of treatment; maximum 1 year.	No: Pass to RPH; Deny (medical appropriateness)
7~~5~~. Is the product requested preferred?	**Yes**: Approve for length of treatment ; maximum 1 year	**No:** Go to #~~8~~6
8~~6~~. Will the prescriber consider a change to a preferred product? Message: • Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Pharmacy and Therapeutics (P&T) Committee. ~~Health Resources Commission (HRC).~~ Reports are available at: http://pharmacy.oregonstate.edu/drug_policy/index.php ~~http://www.oregon.gov/OHPPR/HRC/Evidence_Based_~~	**Yes**: Inform provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml. .Approve for length of treatment or 1year.	**No:** Approve for length of treatment; maximum 1 year.

~~Reports.shtml.~~		
~~9~~6. RPH only All other indications need to be evaluated as to whether they are above the line or below the line diagnosis.	**If above the line or clinic provides supporting literature:** approve for length of treatment.	**If below the line:** Deny, (Not Covered by the OHP).

DUR Board/P&T Action: *09/16/2010 (DO),9/24/09 (klk), 3/19/09(klk), 2/26/06, 5/24/07*
Revision(s): *09/16/2010 (DO),1/1/10, 7/1/09, 6/1/07, 6/28/12 (MH).*
Initiated: *9-1-06*

fingolimod (Gilenya)

Goal(s):

- To ensure appropriate and safe drug use of fingolimod
- Promote preferred drugs

Length of Authorization: One year

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Does the patient have a diagnosis of relapsing Multiple Sclerosis (ICD-9 340)?	**Yes:** Go to #3.	**No:** Pass to RPH; Deny (medical appropriateness)
3. Will the prescriber consider a change to a Preferred MS product? Message: • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics Committee.	**Yes:** Inform Provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml	**No:** Go to #4
4. Has the patient failed or cannot tolerate a full course of interferon beta 1a or interferon beta 1b, and glatiramer?	**Yes:** Go to #5.	**No:** Pass to RPH; Deny (medical appropriateness)
5. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #6.	**No:** Pass to RPH; Deny (medical appropriateness)
6. Is the patient on concurrent treatment with a disease modifying drug (i.e. interferon beta-1B, glatiramer acetate, interferon beta 1A, natalizumab, mitoxantrone)?	**Yes:** Pass to RPH; Deny (medical appropriateness)	**No:** Go to #7
7. Does the patient have evidence of macular edema (ICD-9 362.07)?	**Yes:** Pass to RPH; Deny (medical appropriateness)	**No:** Go to #8
8. Does the patient have ~~as~~ preexisting or recent (within last 6 months) MI, unstable angina, TIA, stroke, decompensated heart failure requiring hospitalization or Class III/IV heart failure, or taking Class Ia or Class III anti-arrhythmic drugs (see list below)? ~~cardiac disease, risk factors for bradycardia, or is on antiarrhythmics, beta-blockers, or calcium channel blockers?~~	**Yes:** Pass to RPH; Deny (medical appropriateness~~Go to #9.~~	**No:** Go to #9~~Approve up to one year~~
9. Is the patient on beta-blockers, digoxin or calcium channel blockers?	**Yes:** Go to #10	**No:** Approve up to one year
10~~9~~. Has the patient had a cardiology consultation before initiation?	**Yes:** Approve up to one year	**No:** Pass to RPH; Deny (medical appropriateness)

Clinical Notes:

- Class Ia anti-arrhythmics: quinidine, procainamide, disopyramide.
- Class III anti-arrhythmics: amiodarone, dofetilide, sotalol, dronedarone, ibutilide.

- Because of bradycardia and atrioventricular conduction, patients must be observed for six hours after initial dose in a clinically appropriate area. The time of cardiovascular monitoring should be extended past 6 hours if patients are at higher risk (prolonged QTc interval, severe bradycardia post-administration, HR lowering medications) or may not tolerate bradycardia, which includes continuous ECG monitoring.
- Patients on antiarrhythmics, beta-blockers or calcium channel blockers or with bradycardia risk factors (h/o MI, age >70 yrs, electrolyte disorder, hypothyroidism) may be more prone to development of symptomatic bradycardia and should be initiated on fingolimod with caution and cardiology evaluation should be done before considering treatment in addition to extended monitoring. Posibility of switching to drugs that do not slow heart rate is an option.
- Additional contraindications include baseline QTc interval >500 ms or a history or presence of Mobitz Type II second-degree or third-degree AV block or sick sinus syndrome unless patient has a functioning pacemaker.
- Injectable disease modifying treatments remain first line agents in MS therapy.
- ~~Injectable disease modifying treatments remain first line agents in MS therapy.~~
- An ophthalmology evaluation should be repeated 3- 4 months after fingolimod initiation with subsequent evaluations based on clinical symptoms.

DUR Board Action: 3-29-2012 (MH)
Revision(s): 8-30-12 (MH)
Initiated:

Erythropoiesis Stimulating Agents (ESAs)

Goals:

- Cover ESAs according to OHP guidelines and current medical literature.
- Promote evidence based preferred drug list (PDL) options for covered diagnoses

Length of Authorization :

- 8 weeks initially; then up to 12 months
- Quantity limit of 30 day per dispense

Requires PA: All ESAs require PA for clinical appropriateness

Covered Alternatives:
Preferred alternatives listed at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. What anemia diagnosis is being treated?	recode ICD9 code:	
2. Is the diagnosis covered by OHP?	Yes: Go to #3	No: Pass to RPh; Deny (Not covered by OHP)
3. Is this continuation therapy?	Yes: Go to #12	No: Go to #4
4. Is product requested preferred?	Yes: Go to #6	No: Go to #5
5. Will provider change to a preferred product?	Yes: Inform provider of preferred products and go to #6	No: Go to #6
6. Is the diagnosis anemia due to chronic renal failure or chemotherapy?	Yes: Go to #7	No: Go to #8
7. Is Hb < 10g/dl ~~or Hct < 30%~~ AND Transferrin saturation >20% and/or ferritin >100ng/ml?	Yes: Approve for 8 weeks with additional approval based upon adequate response.	No: Pass to RPh; Deny (Not Medically Appropriate)
8. Is the diagnosis anemia due to HIV?	Yes: Go to #9	No: Go to #10

9. Is the Hb < 10g/dL ~~or Hct < 30%~~ AND Transferrin saturation >20% and/or ferritin >100ng/ml? AND Endogenous erythropoietin < 500 iu/L AND If on Zidovudine, dose is < 4200mg/week?	Yes: Approve for length of Rx or 1 year, whichever is less.	No: Pass to RPh; Deny (Not Medically Appropriate)
10. Is the diagnosis anemia due to ribavirin treatment?	Yes: Go to #11	No: Pass to RPh; Deny (Not Medically Appropriate)
11. Is the Hb < 10g/dL ~~or Hct < 30%~~ AND Is the transferrin saturation >20% and/or ferritin >100ng/ml AND Has the dose of ribavirin been reduced by 200mg/day and anemia persisted ≥ 2 weeks or to 600mg / day for patients on triple antiviral therapy?	Yes: Approve up to the length of ribavirin treatment.	No: Pass to RPh; Deny (Not Medically Appropriate)
#12. Has patient responded to initial therapy?	Yes, approve for length of prescription or 1 year, whichever is less.	No: Go to #13.
#13. Does the patient have factors where a slower response to ESA is expected? For example: Inadequate Fe repletion: minimum ferritin of 100 ng/ml with suggested trial of 200-500ng/ml Inadequate ESA dosing: Darbepoetin: 1.5mcg/kg/wk Epoetin: 300iu/kg/wk SQ or 450iu/kg/wk IV	Yes, Document factors approve for 4-8 additional weeks.	No: Pass to RPh; Deny (Not Medically Appropriate)

Abbreviated Class Review: Inhaled Antibiotics and Dornase Alfa for Cystic Fibrosis

Month/Year of Review: August 2012 **End of literature search:** May 2012
Drugs Included: Tobramycin (Tobi®), Aztreonam (Cayston®), Dornase alfa (Pulmozyme®)

Issues:

- What evidence is available for the efficacy and safety of inhaled tobramycin, aztreonam, and dornase alfa for cystic fibrosis (CF)?
- Is there comparative evidence that either inhaled tobramycin or aztreonam is superior in efficacy or safety?
- Are there specific subpopulations or clinical situations in which one inhaled antibiotic provides clear benefit over another?

Conclusions:

- There is insufficient long-term evidence available for all drugs in the class. The longest study for dornase alfa (DA) is 2 years and tobramycin inhalation solution (TIS) is 33 months. There is no evidence for aztreonam lysine for inhalation (AZLI) beyond a 28-day course.
- Efficacy and safety has not been established for use of AZLI in patients <7 years old, TIS < 6 years old, and DA <5 years old.
- There is insufficient comparative evidence for efficacy and safety of TIS and AZLI.
- There is moderate quality evidence that overall, the frequencies of pulmonary exacerbations, hospitalizations, and parenteral antipseudomonal antibiotic use are improved with chronic suppressive therapy with TIS in patients with mild to severe CF.
- There is low to moderate quality short term evidence that AZLI modestly improves lung function as measured by FEV1, improves patient-reported respiratory symptoms, and lengthens the time to use of additional antipseudomonal antibiotics compared to placebo.
- A Cochrane review showed demonstrated low quality evidence that inhaled antibiotics improved lung function in patients with CF and that TIS, specifically, significantly decreased hospitalization among patients.
- AZLI and TIS were well tolerated throughout all clinical trials, with cough being the most frequently reported adverse event. There have been post-marketing reports of hearing loss in patients using TIS.
- The Cystic Fibrosis Foundation evaluated 19 trials of DA in a total of 3140 patients. Long-term studies show a significant improvement over placebo in lung function and improvement in quality of life, while there is conflicting evidence on the effect of DA on the incidence of pulmonary exacerbations. A Cochrane review of DA, including 2469 participants, found no statistical difference in mortality compared to placebo or hypertonic saline. Spirometric lung function was improved in the treatment groups at multiple time frames up to two years.
- The only significant adverse effects found in clinical trials of DA compared to placebo were voice alteration and rash.

Recommendations:

1) Due to more published efficacy and safety data and a demonstrated continued benefit over 2 years and decrease in hospitalizations, make TIS a preferred agent on the PDL with a quantity limit of 56 vials/56 days (for cycles of 28 days on followed by 28 days off therapy)
2) Make AZLI a non-preferred agent due to a lack of comparative evidence or demonstrated clinical benefit in efficacy or safety over TIS, and limit to patients with cystic fibrosis with a quantity limit of 84 vials/56 days (for cycles of 28 days on followed by 28 days off therapy)
3) Make DA a preferred agent on the PDL with a quantity limit of 30 vials/30 days

Drug Products[1-3]	FDA approval [1-3]	FDA approved indications[1-3]	Usual Dose/Duration[1-3]	Potential Off-label Uses	Other Considerations
Tobramycin inhalation solution (Tobi)	1997	Management of cystic fibrosis patients with *Pseudomonas aeruginosa*	300mg inhaled twice daily (as close to 12 hours apart and not less than 6 hours apart). Tobi should be administered in repeated cycles of 28 days on drug followed by 28 days off drug.	Bronchiectasis for patients without cystic fibrosis and chronic bronchial infection with *Pseudomonas aeruginosa*	Inhaled tobramycin is administered using a hand-held PAR LC PLUS Reusable Nebulizer with a DeVilbiss Pulmo-Aide compressor.
Aztreonam inhalation solution (Cayston)	2010	Improve respiratory symptoms in cystic fibrosis (CF) patients with *Pseudomonas aeruginosa*	75mg administered 3 times a day for a 28-day course, followed by 28 days off therapy	Bronchiectasis for patients without cystic fibrosis and chronic bronchial infection with *Pseudomonas aeruginosa*	Patients should use bronchodilator prior to administration of aztreonam. Aztreonam must be administered using an Altera nebulizer system.
Dornase alfa (Pulmozyme)	1993	Management of cystic fibrosis patients to reduce the frequency of respiratory infections that require parenteral antibiotics in patients with forced vital capacity (FVC) >40% of predicted; in conjunction with standard therapies, to improve pulmonary function in patients with cystic fibrosis.	2.5 mg daily using a recommended nebulizer	Non-cystic fibrosis pre-term infants suffering from atelectasis	Patients should use a recommended nebulizer/compressor system.

Methods:
A Medline literature search ending May 2012 for meta-analyses or randomized active-controlled trials (RCT's) comparing all included drugs to each other or to other drugs for the treatment of cystic fibrosis was performed. The Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs (VA), Clinical Evidence, UpToDate, Dynamed and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for relevant systematic reviews. The FDA website was searched for background information from advisory committees, new indications, and safety alerts. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. Randomized controlled trials will be emphasized only if evidence is lacking or insufficient from those preferred sources. Results of this search included two RCT's for tobramycin, 3 RCT's for aztreonam, two Cochrane systematic reviews, and one evidence based treatment guideline.

Background:
CF is an inherited chronic disease that affects about 30,000 children and adults in the U.S. and about 70,000 people worldwide. It is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, a complex chloride channel and regulatory protein found in exocrine tissues.[4] Transport of chloride, sodium, and bicarbonate are disrupted, which may lead to thick, viscous secretions in the lungs, pancreas, liver, intestine, and reproductive tract, and to increased salt content in sweat gland secretions.[4]

Although multiple organ systems are affected in CF patients, pulmonary disease is the leading cause of morbidity and mortality in patients with CF. The thickened, viscous airway secretions obstruct the airway, resulting in endobronchial infection, and an exaggerated inflammatory response that may lead to development of bronchiectasis and progressive obstructive airways disease.[4,5] There are a number of treatment options for the maintenance of lung health in CF patients, including aerosolized antibiotics, recombinant human deoxyribonuclease (rhDNase), hypertonic saline, and anti-inflammatory agents. Although some of these treatments may be administered by multiple routes (intravenous, oral, inhaled), administration by inhalation is preferred, as this method of delivery promotes high concentrations of the drug in airways and lower concentrations in plasma, minimizing the system toxicity.[6]

Bacterial colonization of the airway secretions with *Pseudomonas aeruginosa, Haemophilus influenza, Staphylococcus aureus or Burkholderia cepacia* may occur in patients with CF. *P. aeruginosa* is the most common pathogen in CF patients, and chronic colonization may cause respiratory insufficiency and eventual respiratory failure.[7] Consequences in this patient population include increased morbidity and mortality. Therefore, therapies that may decrease or eliminate colonization in addition to treating exacerbations are essential to improving outcomes. The CF foundation defines clinically meaningful endpoints as time to need for additional antipseudomonal antibiotics and hospitalization. The Cystic Fibrosis Questionnaire-Revised (CFQR) has been validated as a subjective measure to assess multiple domains of patient quality of life and is approved by the FDA as a patient reported outcome measure. The clinical importance is uncertain due to no known correlation to other clinically meaningful endpoints.

There are two inhaled antibiotic agents approved for the management of patients with CF that is complicated by *Pseudomonas aeruginosa,* TIS and AZLI. AZLI is a monobactam antibiotic that was FDA approved in 2010. It is administered via nebulizer at a dose of 75mg three times daily for 28 days, followed by 28 days off therapy. TIS is an aminoglycoside antibiotic that was FDA approved in 1997 and is administered at a dose of 300mg twice daily for 28 days, followed by 28 days off therapy.[1,2] Inhaled antibiotics help reduce exacerbations and improve lung function by reducing *P.aeruginosa* concentrations. Guidelines published by the Cystic Fibrosis Foundation in 2007 (prior to approval AZLI) recommend the routine use of TIS in patients with chronic *P. aeruginosa* infections for asymptomatic and symptomatic CF patients ≥ 6 years old cultures to improve lung function and/or reduce exacerbations. Data from their registry suggests that almost 70% of eligible patients use inhaled tobramycin.[5] AZLI is the only other inhaled antibiotic approved for use in CF patients.[2]

DA is a purified solution of recombinant human deoxyribonuclease I (rhDNase), an enzyme that assists in the breakdown of DNA which accumulates in cystic fibrosis patients. It treats the thickened secretions in the lungs that facilitate bacterial infection and airway obstruction in CF patients. It works by degrading the excess DNA that accumulates with CF mucus, and promoting airway clearance. DA was approved in 1993 for the management of cystic fibrosis patients to reduce the frequency of respiratory infections that require parenteral antibiotics in patients with forced vital capacity (FVC) >40% of predicted; in conjunction with standard therapies, to improve pulmonary function in patients with CF.[3] The Cystic Fibrosis Guidelines recommend use of DA in patients with asymptomatic, mild, moderate, or severe lung disease to improve lung function and reduce exacerbation.[5]

Hypertonic saline (HS) inhalation increases hydration of airways surface liquid in patients with CF, which helps improve mucociliary clearance. For patients 6 years of age and older with C , the Cystic Fibrosis Foundation recommends the chronic use of inhaled hypertonic saline to improve lung function and to reduce exacerbations (fair level of evidence, grade of recommendation B).[5]

Systematic Reviews:

CF GUIDELINES

The Cystic Fibrosis Foundation published treatment guidelines on chronic medications for maintenance of lung health in 2007, prior to the FDA approval of AZLI. The guidelines strongly recommend TIS to improve lung function and reduce exacerbations in patients ≥6 years old, who have moderate to severe lung disease and with *P. aeruginosa* persistently present in cultures of the airways. The guidelines also recommend chronic use of TIS to reduce exacerbations in patients ≥6 years old that are asymptomatic or with mild lung disease, and with *P. aeruginosa* persistently present in cultures of the airways.[5]

The recommendations are based on results from a systematic review of 6 trials, with a total of 679 participants. Three of the studies showed that patients taking TIS had a significantly improved forced expiratory volume at one second (FEV_1), with a net benefit in lung function of 7.8 to 12%. The largest study (n=520), reported a 26% reduction in hospitalizations and a 36% reduction in the use of IV anti-pseudomonal antibiotics for those using tobramycin compared to placebo.[5]

The Cystic Fibrosis Foundation recommends the use of DA for CF patients with mild lung disease, and they strongly recommend its use for CF patients with moderate to severe lung disease. DA was studied in 19 trials (n=3140) of varying lengths. Most short-term studies showed a significant improvement in FEV_1 by 11.2-15.4%, and long-term studies uniformly demonstrated improvement in lung function. One study (n=968) found that FEV_1 increased by 5.8% compared to placebo after 24 weeks of treatment with dornase alfa, and another study (n=320), saw a similar improvement in FEV_1 (net benefit 7.3%) in patients with severe CF lung disease who were treated for 12 weeks. DA was well tolerated as there were few adverse events that were increased by DA compared to placebo. The most common adverse event was voice alteration.[5]

INHALED ANTIBIOTIC COCHRANE REVIEW

A 2009 Cochrane review found 19 trials, including 1724 patients from a literature search ending January 2011, which evaluated the effect of any inhaled antibiotic treatment as long-term therapy in people with CF, compared to placebo or usual treatment. Investigators found that inhaled antibiotics improved lung function and reduced the frequency of exacerbations during the study and that the best evidence is for inhaled tobramycin. Further research is necessary to show maintenance of benefits, and to establish a preferred antibiotic therapy and dosage regimen. There was significant heterogeneity among the trials, in terms of design, drug type, dose and delivery, duration of treatment and outcome measures, which complicated interpretation of the results and reduces the validity of pooling the data.[14]

Eight trials, including 1152 patients, compared TIS to usual treatment from 1 to 33 months, with the majority of participants (45%) included in one high quality trial. Three trials reported the mean change in % predicted FEV_1, which was greater for inhaled antibiotics compared to placebo [mean difference: 9.48 (95% CI 5.92, 13.04)]. Two of these trials (81.9% of the evaluable population) studied the effectiveness of TIS. Three trials reported the change in % predicted FVC, which was greater for inhaled antibiotics compared to placebo [mean difference 8.04 (95% CI 4.24, 11.85)]. Two of these trials (81.9% of the evaluable population) studied the effectiveness of TIS. The largest trial included in the Cochrane review, with 520 participants, reported a mean increase in FEV_1 of 10% in the TIS treated group, compared to a 2% decrease in mean FEV_1 in the control group after 20 weeks ($P<0.001$). The same trial reported a mean increase in FVC of 8% in the TIS treated group, compared to a mean of a 1% decrease in the mean FVC in the control group.[14]

Two trials with a duration of three to 12 months had outcomes for hospital admissions available for analysis. There was a significant risk reduction for one or more hospital admissions [RR 0.72 (95% CI 0.60, 0.86)]. One trial of more than 12 months had a nonsignificant risk reduction for at least

one hospital admission [RR 0.59 (95% CI 0.34, 1.05)]. The longest trial was 32 months and found no significant difference for hospital admissions [RR 0.80 (95% CI 0.39, 1.65)]. All four of these trials were conducted using TIS as the study drug.[14]

Two trials included AZLI. In one trial, Participants were treated with aztreonam lysine for 28 days and followed after this period to measure the time to a pulmonary exacerbation treatment; estimated as 92 days in the aztreonam lysine group and 71 days in the control group (P = 0.007). This study did not utilize intent to treat analysis, had a moderate rate of patient discontinuation, and was of short duration. The second study evaluated CFQR as the primary endpoint but was not included in the analysis because it was classified as "awaiting classification" until more information available.[14]

There was no evidence of clinically important adverse effects during the trials. Overall, patients who used inhaled antibiotics experienced more resistance to antibiotics, tinnitus and change in voice than those in placebo groups. Five trials measured renal function and found no significant evidence of renal impairment. However, one trial found that nine people in the TIS group and the placebo group saw transient increases of 50% or more in the creatinine level. Five trials measured audiometry and found that four stated that no abnormality was found.[14]

DORNASE ALFA COCHRANE REVIEW

A 2010 Cochrane review on DA in CF set out to determine whether DA improved mortality and morbidity compared to placebo or other mucolytics (hypertonic saline, acetylcysteine, and mesna) and to identify adverse effects. The last data search occurred on July 17, 2009. A total of 43 trials were identified, but only trials that were randomized or quasi-randomized which compared DA to placebo, standard therapy, or another mucolytic were included in the analysis. Fifteen trials remained after exclusion criteria were applied, which contained 2469 participants. Of these studies, 12 compared DA to placebo or no DA treatment; one compared daily DA with hypertonic saline and alternate day DA; and two compared daily DA to hypertonic saline. The timeframe of these studies ranged from six days to two years and included patients of all ages.[13]

Outcomes of the review were grouped into the following timeframes: one, three, six, and twelve months and annually thereafter. The primary outcomes were changes in lung function (FEV_1 and FVC) from baseline, change from baseline in quality of life, mean number of exacerbations, and number of deaths. Secondary outcomes were number of days treatment with IV antibiotics, number of days treatment with oral antibiotics, number of days in hospital due to respiratory exacerbations, change in weight from baseline, number of adverse events such as alteration in voice, hemoptysis, bronchospasm, and cost.[13]

Dornase alfa versus placebo or no dornase alfa treatment.
Overall there was no statistical difference in mortality between treatment groups at any time period. For the mean percentage change of FVC in DA treated group versus placebo there was improvement at one month [mean difference 7.52 (95% CI 1.34, 13.69)], three months [mean difference 5.10 (95% CI 1.23, 8.97)], six months [mean difference 3.80 (95% CI 2.62, 4.98)], but not at two years [mean difference 0.70 (95% CI -1.24, 2.64)]. The only identified increased adverse effect was voice alteration and rash. No differences were seen in mean number of days of IV antibiotics at three months [mean difference 2.96 (95% CI -7.29, 1.37), or mean number of inpatient treatment at 3 months [mean difference 0.92 (95% CI -2.19, 4.05)]. For safety outcomes there was no difference in hemoptysis, dyspnea, or pneumothrax. There was an increase in voice alteration at one month in the treatment group [mean difference 4.03 (95% CI 1.29, 12.62), three months [RR 2.87 (95% CI 1.44, 5.71), but not at six months [RR 1.73 (95% CI 0.69, 4.34). There was increase in the incidence of rash at two years [RR 4.63 (95% CI 1.35, 15.89)].[13]

Dornase alfa versus mucolytic
There was a reported 8% (95% CI 2, 14%) increase in FEV1 from baseline in the DA group compared to hypertonic saline. There were no deaths reported in any of the trials. There was no difference in number of inpatient days of treatment when DA was compared to hypertonic saline [mean difference -0.4 (95% CI -2.32, 1.52). The most frequently reported adverse events were increased cough, coryza, throat infection, allergic reaction to antibiotic, wheeze, breathlessness, hemoptysis, chest pain, and oral thrush.[13,15]

Randomized Controlled Trials (Evidence table in Appendix 1).
There are no published head to head trials comparing TIS to AZLI. An open-label, randomized, phase 3 trial, sponsored by Gilead Sciences, has been conducted comparing AZLI to TIS. Preliminary results have been published only in abstract form. 268 patients received 28-day, intermittent, repeating courses of either treatment over 24 weeks. The co-primary endpoints were non-inferiority of AZLI for mean percent change in FEV1 percent predicted at Day 28 compared to baseline and superiority of AZLI for mean actual change in FEV1 percent predicted across three treatment cycles (six months).

<u>TOBRAMYCIN</u>
Pivotal studies evaluating the use of tobramycin have been included in the Cystic Fibrosis Foundation Pulmonary Guidelines published in 2007, as well as a 2009 Cochrane Review of inhaled antibiotics. Since the publication of these reviews, one additional study has been published evaluating the safety and efficacy of TIS.[8]

In the Early Inhaled Tobramycin for Eradication (ELITE) trial, the short and long term efficacy of tobramycin inhalation solution (TIS) 300mg/5ml twice daily was evaluated in CF patients with early onset *P. aeruginosa* infection (n=88). All patients received TIS twice daily for 28 days, at which

point they were randomized to either discontinue TIS (28-day group) or receive an additional 28 days of therapy (56-day group). Patients were excluded from the efficacy analysis if there was no eradication at 1 month after their last dose of TIS, protocol deviation or use of prohibited medications. This trial was rated of poor quality because it was not blinded which may have increased the risk of bias and included a high attrition rate.[8] Of the 88 patients randomized, only 65 were included in the efficacy analysis (74%). [8]

AZTREONAM

The efficacy and safety of AZLI, dosed 75mg two or three times daily, has been studied in two phase III, randomized, placebo-controlled trials (AIR-CF1 and AIR-CF2), and a phase IIIb published study (AIR-CF4). Efficacy endpoints and inclusion/exclusion criteria varied across studies.[6,18]

AIR-CF1 was a fair quality, randomized, double-blind, placebo-controlled, international study (n=164) which evaluated the short-term efficacy and safety of AZLI in patients with cystic fibrosis, *P. aeruginosa* infection, and moderate-to-severe lung function [FEV_1 25%-75% predicted].[9] Patients ≥6 years old with no recent use of anti-pseudomonal antibiotics or azithromycin were treated with 75mg AZLI three times a day for 28 days or placebo and monitored for 14 days after study completion.[9] The primary endpoint was the change in patient-reported respiratory symptoms using the CF-Questionnaire-Revised (CFQ-R) Respiratory Scale. The CFQ-R scale is a validated, disease-specific, health related quality-of-life instrument that meets most of the US FDA guidelines on patient reported outcomes.[6] After 28 days, patients treated with AZLI saw an improved mean CFQ-R respiratory score compared to placebo [9.7 points (95%CI 4.3, 15.1), p<0.001]. Although the scores of both groups declined after treatment, at day 42, the treatment difference was still significant [6.3 points (95% CI 1.2, 11.4), p=0.15). The minimum clinically important difference for clinically stable patients is 5 points for the CFQR. The increase in disease scores was independent of disease severity, although patients treated with AZLI also saw a significant improvement in all secondary endpoints of FEV_1 (10.3% predicted, p<0.001), sputum *P. aeruginosa* density (-1.453 log 10 cfu/g, p<0.001), and non-respiratory CFQ-R scales (e.g. eating, emotional functioning, health perceptions), compared to placebo.[9]

AIR-CF2 was a fair quality, randomized, double-blind, placebo-controlled, multicenter study (n=211) which evaluated maintenance treatment for a *P. aeruginosa* infection in patients with CF. This study included patients ≥6 years old who had a pulmonary *P. aeruginosa* infection requiring ≥3 courses of TIS within the previous year.[6,10] Patients were randomized into one of three treatment groups (placebo, AZLI twice daily or AZLI three times daily) and treated for 28 days and followed up with for an additional 56 days (day 84). The primary efficacy endpoint was the time to need for inhaled or intravenous anti-pseudomonal antibacterials to treat symptoms of pulmonary exacerbations. The median time to need additional inhaled antibiotics in patients treated with AZLI was 21 days longer compared to the placebo group (92 vs 71 days, measured from baseline; p=0.007). Pulmonary function was also improved in AZLI patients compared to placebo. Pooled data for AZLI showed a mean change in FEV_1 of 6.3% [95% CI 2.5, 10.1); p=0.001], and a significant improvement in mean change in CFQ-R score [5.01 points (95% CI 0.81, 9.21); p=0.02].[10] The prespecified statistical plan compared subjects in each treatment regimen to the corresponding placebo regimen, however there was not sufficient power to compare dosage regimens and the data was pooled.[6]

AIR-CF4 is a fair quality phase IIIb trial with a similar study design to AIR-CF1, but extends the efficacy and safety evaluation of AZLI to include patients with CF, *P. aeruginosa* airway infection, and milder impairment of lung function (FEV_1 >75% predicted).[11] Patients were randomized to a 28-day course of AZLI or placebo, administered three times daily. The primary endpoint was the change from baseline at day 28 on the CFQ-R Respiratory Scale. Patients treated with AZLI saw a non-statistically significant improvement in CFQ-R score of 1.80 versus placebo [(95% CI: -2.83, 6.44); p=0.443)]. Statistically significant treatment effects were seen in AZLI-treated patients for several secondary endpoints: change from baseline at day 28 for adjusted mean log 10 PA CFUs in sputum (AZLI -1.4, placebo -0.14; p=0.016), and relative change in FEV_1% predicted (AZLI 0.29%, Placebo -2.5%; p=0.21). This study did not meet its primary endpoint, and authors suggest that the sensitivity of the CFQ-R is not sufficient for patients with modest symptoms at baseline, or the study may not have been adequately powered to detect a change.[11]

Safety/tolerability:

AZTREONAM:

Overall, in clinical trials, AZLI was well tolerated. Most adverse events were mild to moderate in severity, and the most commonly reported adverse events were associated with respiratory symptoms, such as cough, productive cough, nasal congestion, respiratory tract congestion, wheezing and pharyngolaryngeal pain.[6,11] The observed respiratory symptoms are consistent with those generally seen in patients with cystic fibrosis lung disease, and there were no statistically significant differences between treatment groups in drug-related adverse events or serious adverse events.[6]

In AIR-CF1, the only adverse event with a statistically significant difference in incidence between treatment groups was productive cough (12% in AZLI-treated patients vs. 25% in placebo-treated patients; p=0.047).[9] During the study, 5% of AZLI-treated patients were hospitalized, compared to 14% of placebo-treated patients; the difference was not statistically significant (p=0.064).[6] Six AZLI-treated patients and 13 placebo-treated patients discontinued the study due to an adverse event. Sixteen of these patients required treatment with non-study anti-pseudomonal antibiotics and had symptoms indicative of pulmonary exacerbation. There were no deaths or reports of anaphylaxis reported in this study.[9] In AIR-CF2, there were no statistically significant differences between treatment groups in the type and incidence of adverse events. Overall, seven patients were hospitalized during the treatment period for pulmonary exacerbations (AZLI-BID:2, AZLI-TID:4, placebo-1). No deaths were reported during this study period.[10]

The safety profile of AZLI was similar in AIR-CF4. The most common adverse events seen in both treatment groups were cough, productive cough, respiratory tract congestion, fatigue, pulmonary function test decreased, and abdominal pain. Abdominal pain is the only adverse effect that occurred at a higher rate in one group than the other (12.3% placebo, 1.3% AZLI, p=0.01). Serious adverse events occurred in 11.8% of AZLI-treated patients and 3.7% of placebo-treated patients (p=0.073), and all of these adverse events resulted in hospitalizations, but none were considered to be treatment related. There were no deaths in this study.[11]

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Appendix 1:
Evidence Table

Ref./ Study Design[1]	Drug Regimens	Patient Population	Efficacy Results[2] (CI, p-values)	ARR / NNT	Safety Results^ (CI, p-values)	ARR / NNH[3]	Quality Rating[4]; Comments
1. Ratjen et al. 2010[8]. RCT, OL, MC	1. TIS 300mg/5ml x 28 days n=45 2. TIS 300mg/5ml x 56 days n=43	• ≥ 6 months old • Confirmed CF • First/early PA infection (new detection of PA after negative cultures for ≥ 1 yr and ≥ 4 negative cultures available or up to 2 yrs with 4 negative cultures in the absence of anti-pseudomonal treatment	Median time to recurrence of any strain of PA: 28 day group: 26.12 months 56 day group: 25.82 months HR 0.81; 95% CI 0.37 to 1.75 Difference: 0.3 months 95% CI (0.37,2.75) P=0.593	N/A	Treatment emergent adverse events: 28 day group: 73% 56 day group: 58% Serious adverse events: 28 day group: 14% 56 day group: 12% P-values not reported	N/A	Quality Rating: Poor **Internal Validity: RoB** Selection: The number of subjects analyzed was lower than investigators initially planned. Unclear on generation of randomization sequence. Performance: This was an open-label study, increasing the risk of bias. Good adherence in both groups. The comparato used of TIS for 56 days is not standard treatment or an indicated length of therapy in CF. Detection: Patient's selected in routine clinic visits with positive P. aeruginosa diagnostic test causing possible increased diagnostic interventions. Attrition: Patients who received at least one dose of the study medication were included in the analysis, however, if there was no PA eradication at 1 month after their last dose of TIS, protocol deviation or use of prohibited medications, patients were excluded from analysis. Although 88 patients were randomized, only 65 were included in the efficacy analysis. **External Validity:** Recruitment: Only included patients who regularly attended outpatient clinic appointments. Patient Characteristics: Appropriate Setting: Clinic Setting Outcomes: Microbiological outcome and not clinical outcome used as primary endpoint

2. Retsch-Bogart et al.[9] 2009 (AIR-CF1) Phase 3, RCT, DB, MC	1. AZLI 75mg TID x 28 days n=80 2. Placebo (PBO) n=84	• ≥6 yrs old • Cystic fibrosis • Positive for PA on throat swab or sputum culture • FEV_1 ≥25% to ≤75% of predicted • No antipseudomonals within 4 weeks	Δ in CFQ-R score: Day 28 treatment difference: 9.7 points 95% CI (4.3, 5.1) P<0.001 Day 28 mean FEV_1 (% change from baseline) AZLI: 7.9% PBO: -2.4% Diff: 10.3%; 95% CI (6.3-14.3) P<0.001 Hospitalizations AZLI: 5% PBO: 14% P=0.064	N/A N/A N/A	Productive cough: AZLI: 10 (12.5%) PBO: 21 (25%) P=0.047 Incidence of all other adverse events was similar between treatment groups.	ARR: 12.5% NNT: 8	Quality Rating: Fair **Internal Validity: RoB** Selection: Computer generation central randomization schedule, unclear concealment of allocation. Slightly older mean age in placebo group. Performance: Short term efficacy measured (1 cycle of treatment), double-blinded Detection: Unclear blinding of evaluators. Attrition: Efficacy and safety analyses included all randomly assigned patients receiving one or more doses of AZLI/placebo. FEV1 and CFQ-R analyses used the last-observation-carried-forward convention. 84% of patients completed treatment and only 75% of patients completed follow-up **External Validity:** Recruitment: N/A Patient Characteristics: Patients included in this trial were receiving lower doses of maintenance therapy than recommended in clinical guidelines. They had received fewer courses of TIS during the previous year (mean 1.8 compared to 5.3 in previous clinical trials), and fewer patients were using dornase alfa (65% vs 85% in other trials), and none had received azithromycin. This may have impacted patient intolerance to available therapies, lack of clinical response to specific therapies, clinician and patient preferences, or difficulty of obtaining drugs. Setting: International sites; 63% in the US and Canada Outcomes: Treatment difference was larger than the 5 point minimal clinically important difference previously determined, but used primary endpoint that is subjective based on patient ratings.

McCoy et al.[10] 2008 (AIR-CF2) Phase 3, RCT, DB, MC	1. AZLI 75mg BID x 28 days n=69 2. AZLI 75mg TID x 28 days n=66 3. Matching PBO n=76	• ≥6 yrs old • Cystic fibrosis • PA infection requiring ≥3 courses of TIS within the previous year	<u>Median time to need antipseudomonal antibacterials:</u> AZLI: 92 days PBO: 71 days Diff: 21 days P=0.007	NA	Treatment-emergent adverse events were comparable; differences were not statistically significant.	NA	Quality rating: Fair **Internal Validity: RoB** <u>Selection:</u> The proportion of patients younger than 18 years in the placebo group (15.8%) was smaller than that in the AZLI-pooled group (25.2%), adding potential bias as a higher percentage of patients >18 y/o are pseudomonas positive.. Unclear information regarding randomization sequence generation and allocation concealment. <u>Performance:</u> High dosing compliance, double blinded <u>Detection:</u> Unclear blinding of evaluators. <u>Attrition:</u> Efficacy and safety analyses included all randomly assigned patients receiving one or more 1 doses of AZLI/placebo. CFQ-R and FEV1 efficacy analyses used the last observation carried forward convention. **External Validity:** <u>Recruitment: N/A</u> <u>Patient Characteristics:</u> Only patients who had 3 or more courses of tobramycin inhalation solution within the previous year <u>Setting:</u> All study patients completed a course of tobramycin inhalation prior to starting aztreonam inhalation <u>Outcomes:</u> Primary endpoint depended on clinician judgment/patient report of symptoms. The prespecified statistical plan compared subjects who received AZLI with those who didn't, but there was not sufficient power to compare dosage regimens. (DRUGS) Results from treatment and placebo groups were pooled.

4.Wainwright et al.[11] 2011 (AIR-CF4) RCT, DB, MC	1. AZLI 75mg TID n=76 2. PBO n=81 x28 days	• ≥6 yrs old • Cystic fibrosis • Positive for PA on throat swab or sputum culture • FEV_1 ≥75% of predicted • No symptoms of pulmonary exacerbation w/in 7 days of baseline	<u>Δ in CFQ-R score:</u> AZLI: 3.22 PBO: 1.41 Diff: 1.8 points, 95% CI(-2.83,6.44) P=0.443	NA	<u>Serious adverse events:</u> AZLI: 11.8% PBO: 3.7% Difference: 8.1% P=0.073 None were considered treatment-related	NA	Quality rating: Fair **Internal Validity: RoB** <u>Selection:</u> Unclear information regarding randomization sequence generation and allocation concealment. <u>Performance:</u> Double-blinded <u>Detection:</u> Unclear blinding of evaluators. <u>Attrition:</u> low attrition rate, ITT analysis using all patients receiving at least 1 dose of drug **External Validity:** <u>Recruitment:</u> N/A <u>Patient Characteristics</u>: Included patients with milder impairment of lung function than previous trials (FEV1 > 75%). <u>Setting:</u> Appropriate <u>Outcomes:</u> This study did not meet its primary endpoint. Authors suggest that the sensitivity of the CFQ-RSS is not sufficient for patients with modest symptoms at baseline, or the study may not have been adequately powered to detect a change.

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover, MC=mulitcentre, OL=open label.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid), RoB=risk of bias

Appendix 2: Drug Information

Pharmacology:

Tobramycin[1]	Aztreonam[2]	Dornase alfa[3]
An aminoglycoside antibiotic produced by *Streptomyces tenebrarius*. It acts primarily by disrupting protein synthesis, leading to altered cell membrane permeability, progressive disruption of the cell envelop, and eventual cell death.	A beta-lactam antibiotic that exhibits activity *in vitro* against Gram-negative pathogens including *P. aeruginosa*. Aztreonam binds to penicillin-binding proteins of susceptible bacteria, which leads to inhibition of bacterial cell wall synthesis and death of the cell.	A deoxyribonuclease (DNA) enzyme genetically engineered from Chinese Hamster Ovary cells which selectively cleaves DNA of the viscous mucous in cystic fibrosis patients. This reduces viscosity and improves airflow, potentially decreasing the risk of bacterial infection.

Pharmacokinetics:

Table 1. Pharmacokinetic comparison

Parameters	Tobramycin[1]	Aztreonam[2]	Dornase alpha[3,16]
Protein Binding		56%	
Half-life (h)	2 hrs (for IV administration)	2.1 hrs	Unknown
Metabolism		Hepatic (IM administration, minor)	Unknown
Elimination	Renal/expectorated sputum	Renal (10%)	Unknown
Renal Dose Adjustment	None listed	None	None listed
Hepatic Dose Adjustment	None listed	None	None listed
Food effect on pharmacokinetics	None listed	None	None listed
Mean Sputum Concentration	1237 mcg/g 10 minutes after dose	726mcg/g 10 minutes after dose	3 µg/mL
Mean Plasma Concentration	0.95mcg/mL 1 hour after dose	0.59 mcg/mL 1 hour after dose	
Mean sputum concentration 2 hours following inhalation			0.6 µg/mL
Concentration following bronchoalveolar lavage fluid obtained within 90 minutes of first dose in patient 3 months to 10 years			0.007 to 1.8 µg/mL
Over an average of 14 days of doses, serum DNase concentrations (mean ± SD) increase			Patients 3 months to <5 years: 1.3 ± 1.3 ng/mL Patients 5 to ≤ 10 years 0.8 ±

			1.2 ng/mL

Contraindications/warnings

Tobramycin[1]

- **Contraindication:** Patients with a known hypersensitivity to any aminoglycoside.
- **Warnings:**
  - **General:** Caution should be exercised when prescribing tobramycin to patients with known or suspected renal, auditory, vestibular, or neuromuscular dysfunction. Patients receiving concomitant parenteral aminoglycoside therapy should be monitored as clinically appropriate.
  - **Ototoxicity:** Ototoxicity, as measured by complaints of hearing loss or by audimetric evaluations, did not occur with tobramycin therapy during clinical studies. However, transient tinnitus occurred in eight tobramycin-treated patients versus no placebo patients in the clinical studies. Onset of tinnitus warrants caution. In post-marketing experience, patients receiving tobramycin have reported hearing loss.
  - **Nephrotoxicity:** Nephrotoxicity was not seen in clinical trials with tobramycin but has been associated with aminoglycosides as a class. If nephrotoxicity occurs, tobramycin should be discontinued until serum concentrations fall below 2 mcg/mL.
  - **Muscular Disorders:** Aminoglycosides may aggravate muscle weakness because of a potential curare-like effect on neuromuscular function.
  - **Bronchospasm:** Bronchospasm can occur with inhalation of tobramycin. In clinical studies, changes in FEV_1 measured after the inhaled dose were similar in the tobramycin and placebo groups.

Aztreonam[2]

- **Contraindication:** Patients with a known allergy to aztreonam.
- **Warnings:**
  - **Allergic reactions:** Severe allergic reactions have been reported following administration of aztreonam for injection in patients with no known history of exposure to aztreonam. If an allergic reaction occurs, stop administration and initiate treatment as appropriate. Caution is advised when administering aztreonam to patients if they have a history of beta-lactam allergy, although patients with a known beta-lactam allergy have received aztreonam in clinical trials and no severe allergic reactions were reported.
  - **Bronchospasm:** Bronchospasm is a complication associated with nebulized therapies. Reduction of 15% or more in FEV_1 immediately following administration of study medication after pretreatment with a bronchodilator was observed in 3% of patients treated with aztreonam.
  - **Decreases in FEV_1 after 28-day treatment cycle:** In clinical trials, patients with increases in FEV_1 during a 28-day course of aztreonam were sometimes treated for pulmonary exacerbations when FEV_1 declined after the treatment period. Consider a patient's baseline FEV_1 measured prior to aztreonam therapy and the presence of other symptoms when evaluating whether post-treatment changes in FEV_1 are caused by a pulmonary exacerbation.

- **Development of drug-resistant bacteria:** Prescribing aztreonam in the absence of known *Pseudomonas aeruginosa* infection in patients with CF is unlikely to provide benefit and increases the risk of development of drug-resistant bacteria.

Dornase alpha[3]

- **Contraindication:** Patients with known hypersensitivity to dornase alfa, Chinese Hamster Ovary cell products, or any component of the product.
- **Warnings:**
  - **Decreased pulmonary function** of less than 40% of normal. It does not significantly reduce the risk of respiratory infections that require intravenous antibiotics. Safety and efficacy studies have not been conducted for daily administration for greater than 1 year.

Abbreviated New Drug Evaluation: Ranolazine

Month/Year of Review: August 2012
Generic Name: Ranolazine

End date of literature search: May 2012
Brand Name (Manufacturer): Ranexa® (CV Therapeutics)
Comparator Therapies: Long acting Nitrates, beta blocker and Calcium channel blockers

FDA Approved Indications: Treatment of chronic angina in combination with amlodipine, β-blockers or nitrates in patients who have not achieved an adequate response with other antianginal drugs.[1]

Research Questions:

- Is ranolazine more effective than other antianginal agents?
- Is ranolazine safer than other antianginal agents?
- Are there subpopulations that will benefit from ranolazine in terms of effectiveness or harms compared to other antianginal agents?

Conclusions:

- There is low to moderate level of evidence that ranolazine shows improved exercise duration, time to onset of angina, and time to 1 mm ST-segment depression when used with other antianginal agents such as β blockers, calcium channel blockers (CCBs) and long-acting nitrates, compared to placebo.[2–4]
- There is no data to show ranolazine improves clinical outcomes, such as reduce mortality or cardiovascular events.
- A significant concern with ranolazine is its potential for QT prolongation.
- Currently there is limited data comparing ranolazine to other currently available antianginal agents.[5] One fair quality cross over study showed immediate release ranolazine is comparable to atenolol on time to onset of angina.[6]

Recommendations

- Make non-preferred due to the lack of comparative effectiveness data that ranolazine is more effective or safer than other antianginal agents for managing the risk of cardiovascular events or death.

Background/Current landscape

Angina is a symptom of coronary artery disease, commonly known as chest pain. It is discomfort that occurs when the heart muscle is not getting enough oxygen-rich blood. There are two forms of angina – stable or unstable. Stable angina happens during physical activity or under mental or emotional stress. Unstable angina (UA) is chest pain that occurs even at rest, without apparent reason. The currently available treatment options for chronic angina include long acting nitrates, β blockers and calcium channel blockers (CCBs). These agents either decrease oxygen demand and/or increase oxygen supply. Long acting nitrates reduce cardiac oxygen demand by decreasing left ventricular pressure and systemic vascular resistance and dilating coronary arteries. However, the use of nitrates as first-line agents has been limited because of tolerance that develops with chronic use.[7] β-blockers reduce heart rate and contractility by competitively blocking the response to β-adrenergic stimulation in the heart. β-blockers are recommended as first-line agents in patients with stable angina since they have been shown to reduce mortality following myocardial infarction.[8] CCBs increase oxygen supply by producing coronary and peripheral vasodilatation, decreasing atrioventricular conduction and reducing contractility. CCBs also decrease cardiac oxygen demand by reducing systemic vascular resistance and arterial pressure.[5] CCBs are often used because they are presumed to have similar efficacy and fewer side effects when compared to β-blockers. However, short-acting CCBs have been shown to increase the risk of cardiac events in patients with hypertension and nifedipine has been shown to increase mortality following acute ischemic syndromes.[8] Differences in long-term rates of survival or myocardial infarction between classes of antianginal agents have not been studied.

The exact mechanism of ranolazine is unknown. According to the manufacturer, it has a different mechanism of action than other agents and does not cause hemodynamic changes such as reduction in blood pressure and heart rate.[1] The American College of Cardiology/American Heart Association guideline on unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI), states that when used in accordance with its FDA-approved indication, ranolazine may be safely administered for symptom relief after UA/NSTEMI but it does not appear to significantly improve underlying disease.[8] NICE Treatment Guidelines on Stable Angina recommend for patients who cannot tolerate β-blockers and CCBs or both are contraindicated, consider ranolazine as one of the monotherapy treatment options and for patients who are on β-blocker or CCB monotherapy whose symptoms are not controlled and the other option (CCB or β-blocker) is contraindicated or not tolerated, ranolazine can be added as one of the treatment options.[9]

Clinical Efficacy

Ranolazine was developed in 1985 as an immediate-release and intravenous product. CV Therapeutics submitted CARISA[3] and MARISA[2], two pivotal efficacy trials evaluating ranolazine sustained release in patients with stable exertional angina. The primary endpoint for both studies was the change from baseline, compared to placebo, in treadmill exercise test duration.

CARISA[3] was a good quality study that included 823 chronic stable angina patients, and was a randomized placebo-controlled parallel-group trial including 12 weeks of active treatment and a rebound assessment. Patients were stratified according to sub-maximal doses of background therapy with amlodipine, atenolol, or diltiazem. The primary endpoint of exercise duration at trough showed a significant improvement in ranolazine 750mg twice daily ($p = 0.03$) and 1000 mg twice daily ($p = 0.03$) compared to placebo beginning after 2 weeks, However, the effect was modest (23.7 and 24 seconds compared to 750mg and 1000mg, respectively) and was not consistently significantly different when analyzed by subgroups. The improvement in exercise tolerance test for women was about 33% of that in men. Ranolazine reduced the mean (SE) angina attacks per week from 3.3 (0.3) for placebo to 2.5 (0.2) for ranolazine 750mg ($p=0.006$) to 2.1 (0.2) for ranolazine 1000mg ($p<0.001$).

MARISA[2] was a 4-period placebo-controlled poor quality, crossover study of 191 patients with chronic stable exertional angina responding to antianginal therapy. 175 patients were included in the near/all completer population and 185 patients in the intention to treat (ITT) population. Pooling data from all

periods, the trial reported improvements for exercise duration (p<0.001), time to angina (p<0.001), and time to onset of 1mm ST depression (p<0.001), with all doses of ranolazine compared to placebo. The trial has poor quality rating due to major study flaws such as lack of interim washout between treatment periods, lack of baseline measurements for each period, presence of treatment-by-period interaction and possible carryover effect. In addition, the analysis population only included the patients who completed at least 3 of their 4 double blinded study periods, hence the analysis was not true ITT as it was reported.

ERICA[4] was a fair quality clinical trial studying the efficacy of the SR formulation of ranolazine. It was a placebo control, randomized in patients with persisting symptoms despite maximum recommended dose of amlodipine. A total of 565 patients were randomized: 281 patients to ranolazine and 284 patients to placebo. The average weekly rate of angina attacks in ranolazine – versus placebo-treated patients was significantly lower (trimmed mean2.88 ± 0.19 on ranolazine vs. 3.31 ± 0.22 on placebo; p = 0.028) and weekly nitroglycerin consumption was also significant less in ranolazine group (2.03 ± 0.20 on ranolazine vs. 2.68 ± 0.22; p = 0.014). The treatment effect appeared consistent across subgroups.

RAN 80[6] was a double-blind crossover of 158 patients with chronic stable angina responding to therapy. Patients were randomized to ranolazine IR 400mg three times a day, atenolol 100mg once daily, and placebo three times a day. There was no washout between treatment periods. Significant improvements in peak exercise duration by treadmill or bicycle testing was seen with ranolazine (51.0 sec; 95% CI 34.2 – 67.8, p< 0.001) and atenolol (39.5 sec; 95% CI 22.7 -56.3, P < 0.001) compared to placebo, but not between the active-treatments (11.4 sec; 95% CI -5.4 to 28.2;p= NS). The study used immediate release formulation of ranolazineand the duration was short term at 4 weeks.

Comparative Clinical Efficacy

Relevant Endpoints: 1) All cause Mortality

2) MI

3) Tolerability

Study Endpoints: 1) Exercise duration

2) Time to onset of angina

3) Time to 1mm ST depression

4) Number of angina attacks per week

5) Number of NTG consumption

Evidence Table

Ref./ Study Design[1]	Drug Regimens	Patient Population	N	Duration	Efficacy Results[2] (CI, p-values)	ARR / NNT[3]	Safety Results^ (CI, p-values)	ARR / NNH	Quality Rating[4]; Comments
CARISA[3] (Combination Assessment of Ranolazine in Stable Angina)									
Chaitman et al DB, PC, RCT; PG	R1: 750mg ranolazine BID R2: 1,000mg ranolazine BID P: placebo	Mean age (P/R1/R2): 63.7/64.3/63.9 Male (P/R1/R2): 75.1%/77.8%/79.6 Background antiangina Drug (P/R1/R2): Atenolol – 43.9%/42.7%/42.6% Amlodipine – 30.1%/30.8%/32.4% Diltiazem – 26%/26.5%/25.1% Angina frequency (attacks/wk; P/R1/R2): 4.6/4.3/4.7 NTG use (tablet/wk; P/R1/R2): 4.0/4.0/3.7	N= 823 P: 269 R1: 279 R2: 275	12 weeks followed b long term open-label study up to 39 months	<u>Exercise duration at trough ranolazine level on treadmill - 1° end point (P/R1/R2 in seconds):</u> Change from baseline – 91.7/115.4/140.3 Difference from placebo: R1: 23.7 (p = 0.03) R2: 24.0 (p = 0.03) <u>Time to onset of angina at trough ranolazine level - 2° end point (P/R1/R2 in seconds):</u> Change from baseline – 114.3/144.0/140.3 Difference from placebo: R1: 29.7 (P = 0.01) R2: 26.0 (p = 0.03) <u>Time to ECG ischemia at trough ranolazine level - 2° end point (P/R1/R2 in seconds):</u> Change from baseline – 125.1/145.1/146.2 Difference from placebo: R1: 19.9 (p = 0.10) R2: 21.1 (p = 0.09) <u>Angina attack frequency (2° end point):</u> Difference from placebo: R1: 0.8 attacks/wk (p = 0.006) R2: 1.2 attacks/wk (p < 0.001)	NA	Any events (P/R1/R2): 26.4%/31.2%/32.7% (CI , p not reported) The most common dose-related ADEs: dizziness, constipation, nausea and asthenia. QT prolongation: P: 421.5 mSec. R1: 427.6 mSec. R2: 430.7 mSec. (p<0.001) Mortality: P: 1.1% (3/269) R1: 0.7% (2/279) R2: 0.4% (1/275)	**NA**	Good Internal Validity Review of Bias: <u>Selection:</u> Low bias; the randomizatio and allocation concealment was clear <u>Performance:</u> Low bias; blinding of patients and study monitors <u>Attrition:</u> Relatively low attrition at 10.4% from all study groups. The reasons for drop out were not explained. ITT analysis. External Validity Review of Bias: <u>Patient characteristics:</u> There were smaller number of patients in placebo group who had CABG, but not statistically significant. <u>Setting:</u> The method of recording angina attacks was not reported. <u>Outcomes:</u> The study was not designed to show the clinical outcomes such as MI, mortality as primary endpoint.

ERICA[4] (Efficacy of Ranolazine In Chronic Angina trial)									
Stone et al DB, PC, PG; RCT	R: 1,000mg ranolazine with amlodipine 10mg daily P: Placebo with amlodipine 10mg daily	Stable patients with CAD and ≥ 3 anginal attacks/wk despite of max. dose of amlodipine at 10mg/day. Mean age: (P/R): 62.0/61.3 Gender Male% (P/R): 73%/72% Baseline weekly angina attacks (P/R): 5.68/5.59 Previous CABG (P/R): 12%/10% Previous PCI (P/R): 9%/12%	N = 565 R: 281 P: 284	6 weeks	<u># of Angina attacks per week trimmed mean ± SE (1° end point):</u> R: 2.88 ± 0.19 Placebo: 3.31 ± 0.22 P = 0.028 <u>Weekly NTG consumption trimmed mean ± SE (2° end point) :</u> R: 2.03 ± 0.20 Placebo: 2.68 ± 0.22 P = 0.01 <u>Seattle Angina Questionnaire (SAQ) scores on in 5 dimensions: angina frequency, physical limitations, angina stability, disease perception, and treatment satisfaction (2° end point) :</u> Out of 5 dimensions, only scores in angina frequency dimension is statically significant: R: 18.5 ±18.8 Placebo: 22.5 ± 19.0 P = 0.008	<u>NA</u> NA	Any ADEs: (CI and p value not reported R: 39.9% P: 35.3% Other common ADEs (R/P): Constipation: 8.9%/ 1.8% Peripheral edema: 5.7%/2.8% Dizziness: 3.9%/2.5% Nausea: 2.8%/0.7% Headache: 2.8%/2.5% Discontinuation due to ADEs R: #3 pts Placebo: #4 pts	NA	Fair Internal Validity Review of Bias: <u>Selection:</u> Low bias; the randomizatio and allocation concealment was clear <u>Performance:</u> Low bias; blinding of patients and study monitors. <u>Attrition:</u> Low attrition at 2% from all study groups. It appears to be ITT analysis. • Subgroup analysis performed for baseline characteristics and treatment results. • External Validity Review of Bias: <u>Setting:</u> • Study design is multi-national. SAQ was not culturally and linguistically validated in the locations where th trial took place. • Level of activities were not controlled or tested, the weekly angina attacks could be due to activity levels vs. drug effect. <u>Outcomes:</u> • The use of patient anginal diaries rather than ambulatory Holter monitors to detect episodes of ischemia added a subjective component to the design. • Short term study for a chronic disease. Ranolazine long term benefit remains unclear.

Rousseau et al[6] DB, MC, PC, XO	R: 400mg ranolazine IR 3 times a day AT: atenolol 100mg daily Placebo	Patients with well documented CAD and chronic angina who were on standard doses of atenolol Mean age: 59 ± 8 Male: 89%	N = 158	21 – 30 days	Time increase to onset of angina (1° end point): R vs. Placebo: 51.0 sec. (34.2 – 67.8 p< 0.001 AT vs. placebo: 39.5 sec. (22.7 -56.3 P < 0.001 R vs. AT: 11.4 (-5.4 to 28.2); NS Time increase to 1 mm ST-segment depression (2° end point): R vs. Placebo: 52.6 sec. (34.8 – 70.5 p < 0.001 AT vs. placebo: 51.0 sec. (33.1 – 68.9) p < 0.001 R vs. AT: 1.6 sec. (-16.3 to 19.6) NS Increase in exercise duration (2° end point): R vs. Placebo: 37.1sec. (22.2 – 52.0 P< 0.001 AT vs. Placebo: 16.0 sec. (1.1 – 30.9) p < 0.04 R vs. AT: 21.1 sec. (6.2 – 36.0), p = 0.006	NA	Any ADEs (R/AT/Placebo): 29%/25%/17% (CI and p value not reported) Common ADEs (R/AT/Placebo): Asthenia: 12.3/16.9%/2.6% Dizziness: 1.3%/5.8/2.6% Nausea: 3.9%/0/3.2% Constipation: 3.2%/0/0.6% Discontinuation due to ADEs R: #2 patients AT: None Placebo: #2 patients	NA	Fair Internal Validity Review of Bias: Selection: potential bias; the randomization and allocation concealment were not reported among 6 possible treatment sequences. Performance: potential bias; despite of the reported blinding of patients and study monitors, ranolazine, atenolol and placebo were dosed at different frequency. Attrition: Low attrition External Validity Review of Bias: Setting: • Study used immediate release form of ranolazine with 3 times daily dose vs. atenolol and placebo once daily dose. • Two exercise protocols were used among study centers. • There was no washout between treatment periods. Outcomes: • Short term study for a chronic disease. Ranolazine long term benefit remains unclear.

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

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Appendix A: Specific Drug Information

CLINICAL PHARMACOLOGY [1]

The mechanism of action of ranolazine's antianginal effects has not been determined. Ranolazine has anti-ischemic and antianginal effects that do not depend upon reductions in heart rate or blood pressure. It does not affect the rate-pressure product, a measure of myocardial work, at maximal exercise. Ranolazine at therapeutic levels can inhibit the cardiac late sodium current (INa). However, the relationship of this inhibition to angina symptoms is uncertain.

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications): No listed BBW. Ranolazine is contraindicated in patients 1) taking strong inhibitors of cytochrome P450 3A (CYP3a); 2) taking inducers of CYP3A; and 3) with liver cirrhosis. Ranolazine has been shown to prolong the QT interval in a dose-dependent manner. However, clinical experience in patients with acute coronary syndrome did not show an increased risk of proarrhythmia or sudden death. In controlled clinical trials of angina patients, the most frequently reported treatment-emergent adverse reactions (> 4% and more common on ranolazine than on placebo) were dizziness (6.2%), headache (5.5%), constipation (4.5%), and nausea (4.4%). Dizziness may be dose-related. Ranolazine has precautions on QT prolongation.

Tolerability: At recommended doses, about 6% of patients discontinued treatment with Ranexa because of an adverse event in controlled studies in angina patients compared to about 3% on placebo. The most common adverse events that led to discontinuation more frequently on ranolazine than placebo were dizziness (1.3% versus 0.1%), nausea (1% versus 0%), asthenia, constipation, and headache (each about 0.5% versus 0%). Doses above 1000 mg twice daily are poorly tolerated.

Pregnancy/Lactation rating: C. There are no adequate well-controlled studies in pregnant women. Ranolazine should be used during pregnancy only when the potential benefit to the patient justifies the potential risk to the fetus.

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

LA/SA names are assessed during the PDL selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexi-Comp	USP Online	First DataBank	ISMP	Clinical Judgment
LA/SA for ranolazine [generic]	None	None	None	None	Ranitidine, ranibizumab
LA/SA for Ranexa®[brand]	None	None	None	None	Pradexa®, Krystexxa®

ADVERSE REACTIONS (incidence > 0.5%)[1]

Adverse Events	Incidence %
Cardiaovascular	
Bradycardia	0.5 – 2.0
Hypotension/orthrostatic hypotension	0.5 – 2.0
Palpitations	0.5 – 2.0
QT prolongation	NR
Central Nervous System	
Dizziness	6.2
Headache	5.5
Vertigo	0.5 – 2.0
Gastrointestinal Disorders	
Abdominal pain	0.5 – 2.0
Constipation	4.5
Dry mouth	0.5 – 2.0
Nausea	4.4
Vomiting	0.5 – 2.0
Respiratory	
Dyspnea	0.5 – 2.0
Other	
Peripheral edema	0.5 – 2.0
Tinitus	0.5 – 2.0

DOSE & AVAILABILITY:[1]

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
500mg, 1,000mg	Tablet, Extended release	Oral	Twice daily	Not defined.	Contraindicated in patients with liver cirrhosis	Not been established.	Same as adult dose, start at the low end of the dosing range.	• The tablet should not cut/crushed/chew.

PHARMACOKINETICS:[1]

Parameter	Result
Oral Bioavailability	76%
Tmax	2-5 hours
Protein Binding	Approximately 62%
Elimination	Approximately 75% of dose is excreted in urine and 25% in feces
Half-Life	Ranging from 6 to 22 hours
Metabolism	Metabolized rapidly and extensively in the liver and intestine; less than 5% is excreted unchanged in urine and feces. The pharmacologic activity of the metabolites has not been well characterized.

ALLERGIES/INTERACTIONS:[1]

Drug-Drug: Ranolazine is almost completely metabolized by the cytochrome P450 (CYP) isoenzyme system. Therefore the potential for numerous drug interactions does exist. As such, other strong CYP3A inhibitors should not be coadministered.

Food-Drug: Grapefruit juice or grapefruit containing products.

Diuretic Agents: Abbreviated Class Review

Month/Year of Review: August 2012
Classes Included: Loop, thiazide/thiazide-like, aldosterone antagonists, and potassium-sparing diuretics.
End date of literature search: May 2012

Issues:

- What is the evidence regarding the role of diuretics in the management of hypertension and chronic heart failure?
- What is the comparative evidence for effectiveness and harms for different diuretics?
- What is the comparative evidence for diuretics for benefits and harms within subgroups of patients?

Conclusions:

- Thiazide diuretics improve mortality and stroke in hypertensive patients. Thiazides are recommended as first line blood pressure lowering agents by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of high Blood Pressure (JNC 7) treatment guidelines in adults[5] and by other national treatment guidelines in children[6], adolescents[6] and the elderly[7].
- There is insufficient evidence demonstrating efficacy and safety differences among different thiazide diuretics.
- Loop diuretics lower blood pressure modestly but play a role in heart failure patients with reduced left ventricular ejection fraction (LVEF) who are symptomatic with fluid retention. They are recommended over thiazide diuretics in severe heart failure. In this patient population, the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) gives them a class I recommendation for treatment. (Level of evidence: C)
- There is insufficient evidence comparing efficacy and safety of different loop diuretics. One small study provided low strength evidence to suggest a lower mortality with torsemide compared to furosemide/other diuretics.
- Potassium sparing diuretics, specifically aldosterone antagonists, reduce heart failure hospitalization and decrease mortality in patients with LVEF < 35%. ACCF/AHA heart failure treatment guidelines include a class I recommendation for aldosterone antagonists in this subset of heart failure patients (Level of evidence: B). There is insufficient evidence comparing efficacy and safety of spironolactone and eplerenone. Spironolactone is recommended over eplerenone in the Institute for Clinical Systems Improvement ICSI guideline due to fewer outcome studies in heart failure, although both agents have high grade evidence on reduction of mortality.
- Both spironolactone and eplerenone should only be used in patients whose serum creatinine is 2.5 mg per dL or less in men or 2.0 mg per dL or less in women and potassium should be less than 5.0 mEq per liter. Under circumstances where monitoring for hyperkalemia or renal dysfunction is not anticipated to be feasible, the risks may outweigh the benefits of aldosterone antagonists. (Level of evidence: B)

Recommendations:

- Add loop, thiazide/thiazide like and potassium sparing diuretics to PDL.
- Evaluate price comparisons of individual agents for each class due to lack of clinical distinction in efficacy or harms and include agents from each class on preferred PDL.
- Include aldosterone antagonists due to mortality benefit in select patients with heart failure and include agents based upon cost.

Reason for Review:

Diuretics commonly used for hypertension, heart failure and edema and are not currently on the Preferred Drug List (PDL). This review will examine their place in therapy for PDL placement, and identify any relevant comparative effectiveness evidence, high-quality systematic reviews, or evidence-based guidelines for consideration.

Background:

High blood pressure is the most common chronic medical problem prompting visits to primary health care providers in the USA. Hypertension increases the risk for heart disease and stroke, the first and third leading causes of death. Nearly 68 million people in the U.S. have hypertension. Another 28% of American adults have pre-hypertension (Internal analysis from National Health and Nutrition Examination Survey).[1] Reduction of the blood pressure by 5 mmHg can decrease the risk of stroke by 34%, of ischemic heart disease by 21%, and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular disease.[2] A recent meta-analysis by the Center for Reviews and Dissemination reviewed 25 randomized control trials (RTCs) in 64,162 patients with pre-existing cardiovascular disease or cardiovascular disease equivalents (such as diabetes) to compare antihypertensive treatment versus control for the prevention of cardiovascular events (fatal or nonfatal stroke, fatal or nonfatal myocardial infarction, congestive heart failure and mortality) with blood pressure less than 140 mmHg systolic or less than 90 mmHg diastolic.[3] The results showed antihypertensive treatment reduced the risk of stroke (RR 0.77, 95% CI 0.61 to 0.98; seven RCTs, I^2=61.9%), myocardial infarction (RR 0.80, 95% CI 0.69 to 0.93; six RCTs, I^2=26.5%), congestive heart failure (RR 0.71, 95% CI 0.65 to 0.77; eight RCTs, I2=0.0%), cardiovascular disease events (RR 0.85, 95% CI 0.80 to 0.90; 13 RCTs, I^2=35.4%), cardiovascular disease mortality (RR 0.83, 95% CI 0.69 to 0.99; six RCTs, I^2=43.6%) and all-cause mortality (RR 0.87, 95% CI 0.80 to 0.95; 15 RCTs, I^2=46.1%).

Heart failure is generally defined as the inability of the heart to supply sufficient blood flow to meet the needs of the body. Fluid overload is a common problem for people with heart failure. Heart failure is caused by any condition which reduces the efficiency of the myocardium, or heart muscle, through damage or overloading. Around 5.8 million people in the United States have heart failure. About 670,000 people are diagnosed with it each year.

Diuretics help excrete sodium and water, which, in turn decrease the amount of fluid in the blood vessels to reduce blood pressure. There are three types of diuretics: loop, thiazide/thiazide like and potassium sparing. Each type of diuretic works at a different part of the kidneys. A diuretic provides a means of forced diuresis which elevates the rate of urination. Loop diuretics inhibit the body's ability to reabsorb sodium at loop of Henle, proximal and distal convoluted tubule, which leads to an excretion of water in the urine whereas water normally follows sodium back into the extracellular fluid. Thiazide type

diuretics act on the distal convoluted tubule and inhibit the sodium-chloride resorption. The short-term anti-hypertensive action is based on the fact that thiazide diuretics decrease preload, and result in decreased blood pressure. Potassium sparing diuretics inhibit distal convoluted tubule aldosterone-induced sodium resorption.[4]

Methods:
A MEDLINE Ovid search was conducted using all diuretics including: cardiovascular disease, hypertension, heart failure, diuretics. The search was limited to meta-analysis, English language, and to studies conducted in humans in the last 10 years. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, Oregon Evidence-based Practice Center, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs (VA) 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.

Drugs Included in This Review

Drug	Generic Availability
Loop diuretics	
Bumetanide (Bumex®)	Yes
Ethacrynic acid (Edecrin®)	Yes
Furosemide (Lasix®)	Yes
Torsemide (Demadex®)	Yes
Thiazide/thiazide-like diuretics	
Chlorothiazide (Diuril®)	Yes
Chlorthalidone	Yes
Hydrochlorothiazide(HCTZ) (Micronize®, Esidrix®)	Yes
Indapamide (Lozol®)	Yes
Metolazone (Zaroxolyn®)	Yes
Potassium sparing diuretics	
Amiloride (Midamor®); Amiloride/HCTZ	Yes
Eplerenone (Inspra®)	Yes
Spironolactone (Aldactone®), spironolactone/HCTZ (Aldactizide®)	Yes
Triamterene (Dyrenium); triamterene/HCTZ(Maxzide®, Dyazide®)	Yes

Hypertension Treatment Guidelines:

The Seventh Report of the Joint National Committee (JNC 7) Report (August, 2004)[5]

The JNC7 report on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure is a landmark report developed by the U.S Department of Health and Services and supported by the National Heart, Lung, and Blood Institute. In patients without compelling indications, thiazide diuretics are recommended as first line therapy with no specific distinction between agents; in patients with compelling indications, thiazide diuretics are recommended as one of the initial options for patients with heart failure, high cardiovascular disease (CVD) risk , diabetes and patients who need recurrent stroke prevention. The potassium sparing diuretics are recommended as one of the initial options for patients with heart failure and post MI. The key pharmacologic treatment recommendations are summarized in Appendix A.

The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents by National High Blood Pressure Education Program (NHBPEP) working group (August, 2004) recommendations on drug therapy[6]:

- According to the NHBPEP guidelines, indications for antihypertensive drug therapy in children include secondary hypertension and insufficient response to lifestyle modifications and recent clinical trials have expanded the number of drugs that have pediatric dosing information. Pharmacologic therapy, when indicated, should be initiated with a single drug. Acceptable drug classes for use in children include ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, and diuretics. The goal for antihypertensive treatment in children should be reduction of BP to <95th percentile, unless concurrent conditions are present. In that case, BP should be lowered to <90th percentile.

Expert Consensus Document on Hypertension in the Elderly (April, 2011) by American College of Cardiology Foundation (ACCF) and American Heart Association (AHA)[7]:

This consensus report recommended general principles on initiation of antihypertensives in the elderly. With similar approach to JNC 7 report, the recommendations also targeted initial treatment options in patients with compelling indication. Thiazide diuretics are recommended in patients with heart failure, CAD or high CAD risk, airtopathy/aortic aneurysm, diabetes or for recurrent stroke prevention. See Appendix A for the summary of the key recommendations.

Heart Failure (HF) Treatment Guidelines:

In March 2009, the ACCF/AHA released a focused guideline update on the diagnosis and management of heart failure in adults.[8] The guidelines give a class I recommendation for the initiation of diuretics in patients with current or prior symptoms of HF and reduced LVEF who have evidence of fluid retention; the class I recommendation also includes the addition of an aldosterone antagonist in selected patients with moderately severe to severe symptoms of HF and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration. Creatinine should be 2.5 mg per dL or less in men or 2.0 mg per dL or less in women and potassium should be less than 5.0 mEq per liter prior to initiation. Under circumstances where monitoring for hyperkalemia or renal dysfunction is not anticipated to be feasible, the risks may outweigh the benefits of aldosterone antagonists. (See Appendix A for summary of key drug therapy recommendations.)

ICSI guideline on heart failure in adults recommends loop diuretics over thiazide diuretics in severe heart failure and in refractory cases of volume overload[9]. They could not recommend a single, ideal diuretic for heart failure patients other than to use the lowest possible dose. One small study provided low strength evidence to suggest a lower mortality with torsemide compared to furosemide/other diuretics.[16] Aldosterone antagonists have been shown to

reduce mortality in HF are recommended in selected patients with moderately severe to severe symptoms and reduced LVEF. Spironolactone is recommended over eplerenone in the ICSI guideline due to fewer outcome studies in heart failure, although both have been shown to reduce mortality in studies. (See Appendix A for key clinical highlights.)

The Veterans Affairs (VA) Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel Clinical Practice Guideline for the Pharmacologic Management of Chronic Heart Failure in Primary Care Practice (September, 2007)[10] also has similar recommendations regarding the position of diuretics and aldosterone antagonists in management of heart failure in adults. (See Appendix A for summary of key drug therapy recommendations.)

Systematic Reviews

Sciarretta et al. [11]
This published systematic review compared different antihypertensive strategies (as first-line treatment) in the prevention of heart failure in patients with hypertension or populations with high cardiovascular risk (> 65% with hypertension). The analysis included 26 randomized controlled trials (RCTs) including 223,313 patients. The authors reported that angiotensin-converting enzyme inhibitors (OR 0.78, 95% CI 0.69 to 0.98; one RCT), angiotensin II receptor blockers (OR 0.85, 95% CI 0.55 to 1.31; two RCTs), calcium-channel blockers (OR 0.67, 95% CI 0.48 to 0.94; three RCTs) and diuretics (OR 0.37, 95% CI 0.23 to 0.61; one RCT) were more effective than placebo in preventing heart failure. Diuretics were statistically significantly more effective than α-blockers (OR 0.49, 95% CI 0.43 to 0.55; one RCT), angiotensin-converting enzyme inhibitors (OR 0.86, 95% CI 0.78 to 0.95; two RCTs) and calcium-channel blockers (OR 0.71, 95% CI 0.64 to 0.79; five RCTs) in preventing heart failure. The authors reported that conventional treatment, which differed slightly between trials, (OR 0.84, CI 0.72 to 0.98; three RCTs), angiotensin-converting enzyme inhibitors (OR 0.84, 95% CI 0.76 to 0.93; three RCTs) and angiotensin II receptor blockers (OR 0.88, 95% CI 0.76 to 1.01; one RCT) were significantly more effective than calcium-channel blockers in preventing heart failure. There was no evidence of statistical heterogeneity or publication bias based on authors' assessment. The authors concluded diuretics and angiotensin-converting enzyme inhibitors (or angiotensin receptor blockers) should be used as first-line treatment for the prevention of heart failure in hypertensive patients. These treatments should be used in preference to calcium-channel blockers and beta blockers. Given the potential for bias in the review, possible limitations with the included studies and uncertainties around the use of multiple treatment comparisons, caution should be applied when interpreting the authors' conclusions.

Cochrane Collaboration Reviews
In 2009, Wright et al. performed a systematic review that compared the evidence of first-line drugs for hypertension versus placebo and no treatment.[12] Of 57 trials identified, 24 trials with 28 arms, including 58,040 patients met the inclusion criteria. In comparison to untreated control group, thiazides (19 RCTs) demonstrated a significantly reduced mortality (RR 0.89, 95% CI 0.83, 0.96), stroke (RR 0.63, 95% CI 0.57, 0.71), coronary heart disease (CHD) (RR 0.84, 95% CI 0.75, 0.95) and total cardiovascular events (RR 0.70, 95% CI 0.66, 0.76). Low-dose thiazides (8 RCTs) significantly reduced all outcomes, including CHD (RR 0.72, 95% CI 0.61, 0.84), but high-dose thiazides (11 RCTs) did not reduce CHD(RR 1.01, 95% CI 0.85, 1.20) or mortality. Five RCTs allowed for a comparison of beta-blockers to thiazides and suggests less benefit for beta-blockers in reducing total stroke and total cardiovascular events than all thiazide trials (RR 0.70 [0.64-0.76] versus RR 0.89 [0.81-0.98] for beta blockers). Based on these results, authors concluded first-line low-dose thiazides reduce all morbidity and

mortality outcomes; first-line ACE inhibitors and calcium channel blockers may be similarly effective but the evidence is less robust; first-line high-dose thiazides and first-line beta-blockers are inferior to first-line low-dose thiazides.

There were two Cochrane reviews[13, 14] that investigated the loop diuretics and potassium sparing diuretics with regards to blood pressure lowering ability. Based on the limited number of published RCTs, the SBP/DBP lowering effect of loop diuretics is modest at -8/-4 mmHg and is likely an overestimate due to the high risk of bias in the included studies. There is no clinically meaningful BP lowering differences between different drugs within the loop diuretic class. The dose ranging effects of loop diuretics could not be evaluated. The review did not provide a good estimate of the incidence of harms associated with use because of the short duration of the trials and the lack of reporting of adverse effects in many of the trials. Similar conclusions were also reported that potassium sparing diuretics do not have a statistically or clinically significant BP lowering effect at low doses but trials at higher doses are not available. The review did not provide a good estimate of the incidence of harms associated with potassium sparing diuretics.

In February 2012, Faris et al. published a Cochrane review to assess the harms and benefits of diuretics for chronic heart failure.[15] The review includes 14 trials (525 participants), seven were placebo-controlled, and seven compared diuretics against other agents such as ACE inhibitors or digoxin. The authors analyzed the data for mortality and for worsening heart failure. Mortality data were available in three of the placebo-controlled trials (202 participants). Mortality was lower for participants treated with diuretics than for placebo (odds ratio (OR) 0.24, 95% CI 0.07 to 0.83; P = 0.02). Admission for worsening heart failure was reduced in those taking diuretics compared to placebo in two trials including 169 participants (OR 0.07, 95% CI 0.01 to 0.52; P = 0.01). In four trials (91 participants) comparing diuretics to a other active agent (three with captopril, one with digoxin), diuretics improved exercise capacity in participants with CHF (difference in means 0.72, 95% CI 0.40 to 1.04; P < 0.0001). The authors concluded that the available data from several small trials show that in patients with chronic heart failure, conventional diuretics appear to reduce the risk of death and worsening heart failure compared to placebo. Compared to active control, diuretics appear to improve exercise capacity. However, the authors also noted most of the trials had small numbers and lasted from 4 to 24 weeks, a short time for a chronic disease. The age of the participants was 59 years, which is relatively young, and the use of diuretic drug was not standardized across the studies. More research would be needed to further confirm the long term benefits of diuretic treatment for CHF patients because these studies were small. The authors assessed the risk of bias for individual studies included in the analysis. Although there is considerably heterogeneity among these studies, no statistical heterogeneity test was conducted by authors. Due to study limitations, the conclusions of this analysis should be interpreted with caution.

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Appendix A

1. **The Seventh Report of the Joint National Committee (JNC 7) Report (August, 2004) key recommendations:**

Patients without Compelling Indications:

- Stage I hypertension (Systolic Blood pressure 140-159 (SBP) or diastolic blood pressure (DBP) 90-99 mmHg): Thiazide-type (THIAZ) diuretics for most. May consider angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), beta blocker (BB), calcium channel blocker (CCB), or combination.
- Stage II hypertension (SBP ≥ 160 or DBP ≥ 100): two drug combination for most (usually THIAZ and ACEI or ARB, or BB, or CCB.

Patients with Compelling Indications:

- Heart failure: THIAZ, BB, ACEI, ARB, aldosterone antagonist (ALDO ANT) as initial therapy options.
- Post myocardial infarction (MI): BB, ACEI, ALDO ANT as initial therapy options.
- High cardiovascular disease (CVD) risk: THIAZ, BB, ACEI, CCB as initial therapy options.
- Diabetes: THIAZ, BB, ACEI, ARB, CCB as initial therapy options.
- Chronic kidney disease (CKD): ACEI, ARB as initial therapy options.
- Recurrent stroke prevention: THIAZ, ACEI as initial therapy options.

In addition to these general recommendations, JNC 7 also made treatment recommendations on subpopulations:

- Pregnant women: methyldopa is preferred first line therapy. Other agents include BBs, which is generally safe. There were reports of intrauterine growth retardation for atenolol. Labetolol is increasingly preferred to methyldopa due to reduced side effects. There were limited data on use of clonidine and CCB during pregnancy.
- Older people: Weight loss and reduced sodium intake are particularly beneficial in older people. Use of specific drug class in older people is largely similar to that recommended in the general algorithm and for individual compelling indication. Combination therapy with two or more drugs is generally needed to achieve optimal BP control.

2. **Expert Consensus Document on Hypertension in the Elderly (April, 2011) by American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) key recommendations:**

General principle on initiation of therapy: The initial antihypertensive drug should be started at the lowest dose and gradually increased depending on the BP response to the maximum tolerated dose. If the antihypertensive response to the initial drug is inadequate after reaching full dose (not necessarily maximum recommended dose), a second drug from another class should be added, provided the initial drug is tolerated. If the person is having no therapeutic response or significant adverse effects, a drug from another class should be substituted. If a diuretic is not the initial drug, it is usually indicated as the second drug. If the antihypertensive response is inadequate after reaching the full dose of 2 classes of drugs, a third drug from another class should

be added. When the BP is > 20/10 mm Hg above goal, drug therapy should generally be initiated with 2 antihypertensive drugs, 1 of which should be a thiazide diuretic; however, in the elderly, treatment must be individualized.

Patients with Compelling Indications:

- Heart failure: THIAZ, BB, ACEI, ARB, CCB, ALDO ANT
- Post MI: BB, ACEI, ALDO ANT, ARB
- CAD or high CVD risk: THIAZ, BB, ACEI, CCB
- Angina Pectoris: BB, CCB
- Aortopathy/Aortic Aneurysm: BB, ARB, ACEI, THIAZ, CCB
- Diabetes: ACEI, ARB, CCB, THIAZ, BB
- CKD: ACEI, ARB
- Recurrent stroke prevention: THIAZ, ACEI, ARB, CCB

3. **ACCF/AHA Focused update: Guidelines for the diagnosis and management of HF in adults key recommendations on drug therapy:**

Class I Recommendations:

- Diuretics and salt restriction are indicated in patients with current or prior symptoms of HF and reduced LVEF who have evidence of fluid retention. *(Level of Evidence: C)*
- Angiotensin-converting enzyme inhibitors are recommended for all patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated. *(Level of Evidence: A)*
- Beta blockers (using 1 of the 3 proven to reduce mortality, i.e., bisoprolol, carvedilol, and sustained release metoprolol succinate) are recommended for all stable patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated. *(Level of Evidence: A)*
- Angiotensin II receptor blockers are recommended in patients with current or prior symptoms of HF and reduced LVEF who are ACE inhibitor-intolerant. *(Level of Evidence: A)*
- Drugs known to adversely affect the clinical status of patients with current or prior symptoms of HF and reduced LVEF should be avoided or withdrawn whenever possible (e.g., nonsteroidal anti-inflammatory drugs, most antiarrhythmic drugs, and most calcium channel blocking drugs. *(Level of Evidence: B)*
- Addition of an aldosterone antagonist is recommended in selected patients with moderately severe to severe symptoms of HF and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration. Creatinine should be 2.5 mg per dL or less in men or 2.0 mg per dL or less in women and potassium should be less than 5.0 mEq per liter. Under circumstances where monitoring for hyperkalemia or renal dysfunction is not anticipated to be feasible, the risks may outweigh the benefits of aldosterone antagonists. *(Level of Evidence: B)*
- The combination of hydralazine and nitrates is recommended to improve outcomes for patients self-described as African-Americans, with moderate-severe symptoms on optimal therapy with ACE inhibitors, beta blockers, and diuretics. *(Level of Evidence: B)*

Class IIa Recommendations:

- Angiotensin II receptor blockers are reasonable to use as alternatives to ACE inhibitors as first-line therapy for patients with mild to moderate HF and reduced LVEF, especially for patients already taking ARBs for other indications. *(Level of Evidence: A)*
- Digitalis can be beneficial in patients with current or prior symptoms of HF and reduced LVEF to decrease hospitalizations for HF. *(Level of Evidence: B)*
- The addition of a combination of hydralazine and a nitrate is reasonable for patients with reduced LVEF who are already taking an ACE inhibitor and beta blocker for symptomatic HF and who have persistent symptoms. *(Level of Evidence: B)*

Class IIb Recommendations:

- A combination of hydralazine and a nitrate might be reasonable in patients with current or prior symptoms of HF and reduced LVEF who cannot be given an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency. *(Level of Evidence: C)*
- The addition of an ARB may be considered in persistently symptomatic patients with reduced LVEF who are already being treated with conventional therapy. *(Level of Evidence: B)*

4. **Institute for Clinical systems Improvement health Care Guideline: Heart Failure in Adults clinical highlights:**

- Evaluate patients presenting with heart failure for exacerbating and underlying causes, including coronary artery disease, hypertension, valvular disease and other cardiac and non-cardiac causes.
- Studies show that the distinction between systolic dysfunction and preserved systolic function is important, because the choice of therapy may be quite different and some therapies for systolic dysfunction may be detrimental if used to treat preserved systolic function.
- Daily weights are critical for managing heart failure and early detection of increases in fluid retention. Patients should call their provider about a two-pound or greater weight gain overnight or a five-pound or greater weight gain in a week. Patients can expect the provider to assess symptoms, adjust diuretics if appropriate, discuss dietary sodium compliance/restriction, review treatment plan, and recommend appropriate level of care (office visit, ER, etc.)
- Unless specific contraindications exist, treat all patients, including Class IV patients, with beta-blockers, starting with a low dose and titrating upward.
- Treat all patients with left ventricular systolic dysfunction with ACE inhibitors (or ARBs if intolerant) unless specific contraindications exist.
- Consider early specialty referral for patients with ischemia or those who are refractory despite optimal medical therapy.
- Brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NTproBNP) are useful in the diagnosis and prognosis of heart failure in patients with dyspnea of unknown etiology.
- For patients self-described as African Americans who have moderate-to-severe symptoms on optimal therapy with ACE inhibitors, beta-blockers and diuretics, the combination of hydralazine and nitrates is recommended because the combination has resulted in significant benefit to the group in randomized controlled trials.

5. **VA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel Clinical Practice Guideline for the Pharmacologic Management of Chronic Heart Failure in Primary Care Practice key drug recommendations:**
    - In addition to risk factor modification, patients in Stage B should receive post-myocardial infarction (MI) treatment with an angiotensin-converting enzyme inhibitor (ACEI) and beta-adrenergic blocker, regardless of the presence of left ventricular systolic dysfunction, to prevent future development of HF and improve overall survival (Grade A Recommendation, Good Overall Quality of Evidence). It is also recommended that patients with evidence of left ventricular systolic dysfunction who are without symptoms should be treated with an ACEI (Grade A Recommendation, Good Overall Quality of Evidence) and beta-adrenergic blocker (Grade B Recommendation, Fair Overall Quality of Evidence). An angiotensin II receptor antagonist may be prescribed in patients with a history of MI who have a reduced left ventricular ejection fraction without symptoms of HF if they are ACEI intolerant (Grade A Recommendation, Good Overall Quality of Evidence).

    - Patients with HF in Stage C should also be educated on risk factor modification. Pharmacotherapy recommendations for these patients include:

        - A diuretic should be used in the treatment of patients with signs of fluid overload (Grade B Recommendation, Fair Overall Quality of Evidence).
        - All patients should be treated with an ACEI unless contraindicated or not tolerated (Grade A Recommendation, Good Overall Quality of Evidence). These agents improve HF symptoms, functional status, and quality of life, while decreasing frequency of hospitalization and mortality. An angiotensin II receptor antagonist may be considered as an alternative to an ACEI (in patients who are on standard therapy for HF) and are unable to tolerate an ACEI (Grade A Recommendation, Good Overall Quality of Evidence).
        - A beta-adrenergic blocker that has proven to reduce mortality (i.e., bisoprolol, carvedilol, sustained release metoprolol succinate) should be used in conjunction with an ACEI in all patients who are considered stable (i.e., minimal or no signs of fluid overload or volume depletion and not in an intensive care unit), unless contraindicated or not tolerated. These agents have been shown to reduce mortality and decrease the symptoms of HF (Grade A Recommendation, Good Overall Quality of Evidence).
        - Low dose of an aldosterone antagonist should be considered in patients with recent New York Heart Association (NYHA) Class IV HF and current Class III or IV symptoms and left ventricular ejection fraction (LVEF) < 35%, provided the patient has preserved renal function and normal potassium levels. This therapy improves symptoms (as assessed by change in NYHA functional class), decreases hospitalizations for worsening HF, and decreases mortality (Grade A Recommendation, Good Overall Quality of Evidence). An aldosterone antagonist may also be considered in patients with LVEF < 40% in patients early post-MI on standard therapy for HF.
        - The combination of hydralazine and a nitrate should be considered, especially in African American patients with NYHA Class III or IV HF, who continue to have symptoms despite therapy with an ACEI and beta-adrenergic blocker (Grade B Recommendation, Good Overall Quality of Evidence). The combination of hydralazine and a nitrate may be considered as an alternative to an ACEI in patients who are unable to tolerate an ACEI (or angiotensin II receptor antagonist) due to hypotension, renal insufficiency, hyperkalemia, or possibly, angioedema (Grade C Recommendation, Fair Overall Quality of Evidence).

- Addition of an angiotensin II receptor antagonist to standard therapy (i.e., an ACEI and beta-adrenergic blocker) in patients with systolic HF may be considered to decrease cardiovascular death or HF hospitalizations (Grade B Recommendation, Fair Overall Quality of Evidence); although routine use of an angiotensin II receptor antagonist, ACEI, and aldosterone antagonist is not recommended.
- Digoxin can be used in patients whose symptoms persist despite treatment with an ACEI (or an angiotensin II receptor antagonist if an ACEI is not tolerated), a beta-blocker, and a diuretic. Digoxin reduces symptoms associated with HF and decreases the risk for hospitalizations due to HF but does not improve mortality (Grade B Recommendation, Fair Overall Quality of Evidence).
- Patients should receive regular follow-up in order to provide the most effective care. At each encounter, an inquiry should be made as to the patient's adherence to the medication regimen, nonpharmacologic measures, and adverse effects to therapy. Patients should be scheduled for routine laboratory monitoring. The patient should also be assessed for any change in functional status or frequency of hospitalizations, and medication therapy should be optimized.

Oregon State University
College of Pharmacy

Abbreviated Class Update: Ophthalmics, Glaucoma agents

Month/Year of Review: August 2012
New Drug: Tafluprost
Dossier received: Yes

End date of literature search: June 2012
Brand Name (Manufacturer): Zioptan™ (Merck)
Comparator Therapies: timolol, latanoprost

Current Status of PDL Class:

- Preferred Agents: APRACLONIDINE HCL (IOPIDINE®), BETAXOLOL HCL, BRIMONIDINE TARTRATE, BRINZOLAMIDE (AZOPT®), CARTEOLOL HCL, DORZOLAMIDE HCL/TIMOLOL MALEATE, PILOCARPINE (ISOPTO CARPINE®), PILOCARPINE HCL (PILOPINE HS®) GEL, TIMOLOL MALEATE, TRAVOPROST (TRAVATAN Z®)
- Non Preferred Agents: BRIMONIDINE/TIMOLOL (COMBIGAN®), APRACLONIDINE (IOPIDINE®), LATANOPROST, DORZOLAMIDE HCL, METIPRANOLOL, LEVOBUNOLOL, BIMATOPROST (LUMIGAN®), TRAVAPROST (TRAVATAN®)

Research Questions:

- Does any of the new information change previous conclusions regarding effectiveness and safety of glaucoma agents?
- Is tafluprost more effective or safer for the treatment of glaucoma than currently available agents?
- Are there unique patients or situations where the new agent may be more effective or safer than currently available agents?

Conclusions:

- There is moderate strength evidence that all currently used medications lower intraocular pressure (IOP) and as single agents, prostaglandins are the most effective at lowering IOP and have been shown to be better than timolol, brimonidine, and dorzolamide.
- There is low quality evidence that prostaglandins are similar in efficacy and in the extent at which they lower IOP.
- There is insufficient evidence to establish a link between the intermediate outcomes of IOP reduction, prevention of optic nerve damage, or prevention of visual field loss to the ultimate outcomes of visual impairment and vision-related quality of life.
- There is low quality evidence that the combination of dorzolamide/timolol has similar effects as prostaglandins on lowering IOP and that fixed combination therapies are equally safe and effective at lowering IOP as their non-fixed components administered concomitantly, with no statistically significant differences in reported convenience or satisfaction.
- There is low-moderate quality evidence that tafluprost is noninferior to timolol in reducing IOP and failed to demonstrate noninferiority to latanoprost in reducing IOP.
- There is insufficient direct clinical evidence to recommend a preservative-free (PF) preparation over a preservative-containing (PC) preparation except when there is evidence that the patient is allergic to the preservative, and therefore tafluprost may provide value in those patients.

Recommendations:

- Recommend continuing to include a medication from each category including miotics, sympathomimetics, beta blockers, carbonic anhydrase inhibitors, and prostaglandin analogues as preferred on the preferred drug list (PDL).
- Recommend no changes to current PDL status based on new clinical evidence or differences in efficacy/effectiveness or harms between members within each class; recommend price comparisons in executive session for any further changes.
- Due to lack of evidence for a benefit in efficacy or safety of tafluprost over currently available prostaglandins, evaluate comparative costs with other agents.

Reason for Review:

In September 2010, the Oregon Health Resources Commission (HRC) evaluated the comparative effectiveness evidence of the drugs used for glaucoma. A Provider Synergies Review from September 2009 was the evidence source.[1] Since this review a comparative effectiveness review for the treatment of glaucoma was produced by the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program[2] and tafluprost, another prostaglandin analog, was FDA approved in February 2012.[3]

Previous HRC Conclusions (September 2010)[1]:

- Evidence does not support a difference in efficacy/effectiveness between members of this class.
- Evidence does not support a difference in harms between members of this class.
- Consider including one medication from each category (miotics, sympathomimetics, beta blockers, carbonic anhydrase inhibitors, combination products, prostaglandin analogues).
- Consider prior authorization of prostaglandin analogues for diagnostic verification (glaucoma) to eliminate cosmetic use.

Background

Primary open-angle glaucoma (OAG) is the most prevalent type of glaucoma in the U.S. population and worldwide it is the second most common cause of blindness.[4,5] In the U.S. there is estimated that 2.2 million people in 2004 have been diagnosed with open angle glaucoma.[6] Primary open-angle glaucoma is a chronic, progressive disease that often presents with characteristic optic nerve damage, retinal nerve fiber layer defects, and subsequent visual field loss. [6] African Americans have a 4-fold higher incidence and prevalence of primary open-angle glaucoma than whites.[5]

Elevated IOP is a surrogate marker known to be a risk factor for glaucoma as well as is correlated with the worsening of glaucoma once present. Studies have shown that the reduction of IOP slows the progression of damage to the optic nerve and slows visual field loss. The ultimate outcome of treating OAG is the prevention of visual impairment and the maintenance or improvement of patient-reported outcomes like quality of life. The direct link that lowering IOP leads to preservation of vision-related quality of life and reduction in visual impairment has not been demonstrated.[3] However, glaucoma is a slowly progressive disease and publications indicate that the average untreated glaucoma patient would require more than 20 years to lower most of his/her visual field.[2] Current evidence includes studies that are of too short in duration and not enough subjects to evaluate these outcomes. Lowering the pretreatment IOP by 25% or more has been shown to inhibit progression of open angle glaucoma.[3,7] The importance of fluctuations in IOP throughout the 24-hour period on long-term outcomes for glaucoma patients is not known.[2]

National guidelines recommend treatment to maintain IOP in a range at which the patient is likely to remain stable or at which worsening of glaucoma will be slow enough that the risk of additional intervention is not justified.[6–8] Prostanglandin analogues and beta blockers are most frequently recommended as initial therapy and if a single medication is effective in lowering IOP but the target pressure is not reached, combination therapy or switching to an alternative therapy may be appropriate.[7,8] Therapy relies on the reduction of IOP and prostaglandin analogues have been proven to be the most potent in lowering IOP (25%-33%) with very few systemic side effects.[4] Prostaglandins have minimal systemic side effects but local side effects are more common, whereas β-blockers have a number of possible systemic side effects including bronchoconstriction, bradycardia, and central nervous system effects such as depression, fatigue and loss of libido.[7]

In February 2012, the FDA approved tafluprost for the treatment of open angle glaucoma or ocular hypertension. Tafluprost is a new antiglaucoma agent that is a prostaglandin analogue that is indicated to reduce IOP in those with glaucoma or ocular hypertension. It has been studied in both PC and PF formulations, although only the PF preparation is available in the United States. An epidemiological survey was carried out from 1997 to 2003 on 9658 patients using beta-blocking eye drops.[9] This study demonstrated that the most commonly reported symptoms of foreign body sensation, dry eye sensations, tearing, and eyelid itching occurred with a significantly lower prevalence in those receiving a preservative free drop compared to a preservative drop.[9] However, there are no randomized controlled trials comparing preservative and preservative free eye drops. Guidelines from the National Institute of Clinical Excellence (NICE) recommend offering a preservative-free preparation to people only if there is evidence that the person is sensitive to the preservative and there is no direct clinical evidence to recommend a PF preparation over a PC preparation.[7] Currently the only other prostaglandin analogue that does not include the commonly used preservative benzalkonium chloride is travoprost, marketed under the brand Travatan Z™. This formulation does contain another preservative, SofZia.

Methods:

A Medline literature search for meta-analyses or randomized active-controlled trials (RCT's) comparing glaucoma agents to each other for the treatment of open angle glaucoma or ocular hypertension from the October 2011 to June 2012 was performed. The Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs (VA), Dynamed and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for relevant systematic reviews. The FDA website was searched for background information from advisory committees, new indications, and safety alerts. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. Randomized controlled trials will be emphasized only if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

ARHQ

A recent comparative effectiveness was performed to summarize the evidence for the safety and effectiveness of medical, laser, and other surgical treatments for OAG in adults.[2] The comparative effectiveness review included studies and systematic reviews through a search up to October 2011. Medical treatments included prostaglandin analogs (excluding tafluprost), beta agonists, carbonic anhydrase inhibitors, alpha 2 agonists, and combination treatments. Drugs that are no longer commonly used were excluded (pilocarpine, apraclonidine, epinephrine, unoprostone, diprivaphrin, ocusert, iopidine, metipranolol).[2]

Twelve systematic reviews of medical interventions were included. The most common comparisons included head-to-head comparisons of prostaglandin analogues, prostaglandin analogues compared to timolol, latanoprost compared to brimonidine, and timolol compared to brimonidine. There were no studies of

medical therapy addressing outcomes relating to reducing visual impairment and the studies addressing change in visual acuity as a secondary outcome were of too short a duration to answer this question. There was also insufficient evidence to determine effectiveness of agents in patient-reported outcomes and quality of life or that treatments influence patient quality of life. [2]

There was low quality of evidence that prostaglandins lower IOP better than dorzolamide (carbonic anhydrase inhibitor, 2.64 mmHg, 3 trials, brimonidine (alpha-adrenergic agonist, 1.64 mmHg, 4 trials), and timolol (beta-adrenergic blocker, 5% greater at 6 months, 4 trials) and that the combination dorzolamide/timolol has similar effect as prostaglandins. [2] The mean reduction in IOP after 3 or more months was 0.81 mmHg lower for participants receiving travoprost than timolol (95% CI, -1.16 to -0.45, four trials). The percent IOP reduction from baseline to 6 month was 5% greater at 6 months with travoprost compared to timolol (95% CI, 2.8 to 7.3, four trials). [2] Evidence from one systematic review reported no difference in the mean reduction in IOP between latanoprost and the combination of dorzolamide/timolol. One study assessed patient satisfaction with either the fixed combination of timolol and dorzolamide or the unfixed combination (separate bottles) and found no statistically significant differences in reported convenience (87% fixed combination vs. 80% unfixed; p=0.056) or reported satisfaction (87% fixed combination vs. 85% unfixed; p=0.643). [2] There was also low quality evidence that prostaglandins are similar in the extent at which they lower IOP; although some studies reported a greater drop with bimatoprost, this has not been a consistent finding. A difference was demonstrated at 3 months (RD 12; 95% CI 4 to 21, two trials) but there was no difference at 1 and 6 months between bimatoprost and latanoprost. Mean IOP reduction was similar when comparing travoprost to latanoprost from two separate systematic reviews.

Harms associated with medical treatments for OAG was also evaluated. The prostaglandins were found to produce more ocular redness than timolol and within the prostaglandin class; latanoprost was less likely to cause redness. [2] Timolol was more likely to result in systemic side effects like shortness of breath or bradycardia, though these are rarely severe, and a systematic review found that subjects on timolol were less likely to drop out of studies due to side effects than those on brimonidine, latanoprost, travoprost, or betaxolol. However, the overall strength of the evidence was graded as insufficient to make conclusions of differential harms for one therapy compared to another. [2]

New Drug Evaluation: Tafluprost

FDA Approved Indications: Tafluprost ophthalmic solution 0.0015% is a prostaglandin analog indicated for reducing intraocular pressure in those with open-angle glaucoma or ocular hypertension.[3]

Efficacy: FDA approval of tafluprost was based on three phase III, randomized, non-inferiority efficacy trials in patients with a baseline IOP of 23-26 mmHg with open-angle glaucoma or ocular hypertension. [10–13] Two were published, including a fair quality 12-week study comparing preservative free (PF) tafluprost with PF timolol and a 24-month fair to poor quality study comparing preservative-containing (PC) tafluprost and PC latanoprost.[10,11] Details of these studies are found in the following evidence table. A third, unpublished trial, compared PC tafluprost to PC timolol over 12 months. Only one of these trials was conducted in sites in the US, the other trials were all conducted in sites outside of the US, mostly in Europe. The primary outcome in the studies was change in baseline IOP and a pre-specified a non-inferiority limit of 1.5 mmHg for the upper limit of the 95% CI was used to establish non-inferiority, as this is the standard acceptance level of non-inferiority in glaucoma studies.[13] The FDA medical reviewer concluded that "a 1.5 mmHg non-inferiority margin for a non-inferiority study using timolol as the active comparator seems reasonable."[12] . Studies using the PC tafluprost also served as support for drug approval as a result of a pharmacodynamic study conducted by Hamacher, et al. designed to demonstrate the equivalence of the two formulations (PC and PF).[14] This 8 week, investigator masked, randomized

trial demonstrated similar IOP-lowering effects at week 1 and 4, meeting the 1.5 mmHg non-inferiority margin.[14] The PC formulation of tafluprost is only available in countries outside the United States.

A study by Chabi et al. was a 12-week trial comparing PF tafluprost and PF timolol.[10] Both products showed IOP lowering effects throughout the 12 weeks, and the effects of tafluprost met the pre-specified non-inferiority margin of 1.5 mmHg compared to PF timolol at all visits and time points. [10] More than half of the patients had ≥25% reduction in diurnal IOP from baseline in both treatment groups (secondary endpoint). A per protocol population was used for analysis of the efficacy end point in which patients who violated pre-specified criteria were excluded. The authors declared that the results were also similar using an analysis based on a full analysis set population (including all randomized patients who received at least 1 dose of study treatment and had at least 1 efficacy measurement available for the analysis endpoint), and the FDA medical reviewer confirmed that using the full analysis set, the confidence interval was within 1.5 mmHg at all time points.[12] It is unclear how many patients were excluded from the full analysis set population. Missing IOP data were imputed by carrying the last observation forward from previous treatment visits. The between group differences in mean IOP change from baseline at each time point at week 12 was generally consistent among the subgroups that were defined by age, race, sex, baseline IOP, and ocular diagnosis. [10]

Another fair quality randomized study by Usitalo et al. was a 24-month multinational trial comparing PC tafluprost with PC latanoprost; both preserved with benzalkonium chloride.[11] Both tafluprost and latanoprost had a substantial IOP-lowering effect throughout the study; on average 6-8 mmHg and 7-9 mmHg, respectively. [11] This result was seen by week 2 and was continued up to the month 24 visit. However, for the primary outcome of reduction in IOP, tafluprost failed to meet the pre-specified non-inferiority margin of 1.5 mmHg (1.20 mmHg with the upper 95% CI limit of 1.52) versus latanoprost.[11] At month 24, the mean decrease in IOP from baseline was -7.1 mmHg (29.1%) and -7.7 mmHg (32.2%) for tafluprost and latanoprost, respectively. There was a statistically significant difference in the lack of efficacy discontinuation rates in favor of latanoprost (13 vs. 3, p=0.01) and this may have been due to more people in the tafluprost group being more treatment resistant and prior to the trial requiring both prostaglandins and β-blockers concurrently, as well as a slightly higher baseline IOP. [11] According to the dossier submission, the proportion of responders at 6 months was somewhat smaller in the tafluprost group compared to the latanoprost group (≥20% decrease: 80.3% vs. 89.9%; ≥25% decrease: 62.8% vs. 79.0%; ≥30% decrease: 46.4% vs. 67.3%).[13]

The third, unpublished trial compared PC tafluprost with PC timolol in 458 patients over 12 months, randomized at a ratio of 3:2 in centers only in the United States.[3,12] Treatments were masked to the subject, investigator, and site staff. There was a total attrition rate of 12% and 17 (6.4%) discontinued the study in the tafluprost group and 23 (12.0%) in the timolol group. In the modified intention to treat (ITT) analysis, the estimated overall treatment difference at 6 months was -0.28 mmHg (upper 95% CI =0.21 mmHg). [3,12] The results of mean IOP's met the pre-defined 1.5 mmHg margin of noninferiority and most 95% CI limits were within a 1 mmHg margin.. The proportion of responders with a ≥25% decrease in mean diurnal IOP were similar between the two groups (43.8% tafluprost vs. 46.2% timolol, p=0.69). This study also demonstrated more ocular adverse events for patients treated with tafluprost (50.9%) compared to timolol (44%).[3, 11]

Lastly, a fair quality study by Egorov et al. evaluated the efficacy and safety of tafluprost as adjunctive therapy to timolol in prostaglandin naïve patients who were only partially controlled with timolol.[15] At the 6-week time point the timolol-tafluprost group showed an IOP reduction of 5.5 to 5.8 mmHg compared to the timolol-vehicle group that showed an IOP reduction of 4.0 to 4.2 mmHg. [15] The effect seen in this study is in line with previous studies that investigate the addition of prostaglandin analogues as adjunctive therapy to patients uncontrolled by timolol monotherapy.[12]

Safety: In general tafluprost was well tolerated and there was no occurrence of any serious adverse events. According to the FDA medical review, most adverse events were of mild severity.[12] The rates of adverse events were not significantly different between tafluprost, timolol, and latanoprost. In the study between PF tafluprost and PF timolol, the tafluprost group had significantly higher rate of conjunctival hyperemia than the timolol group (4.4% vs. 1.2%, p=0.016).[10] The most common adverse events that were reported in the tafluprost group were ocular hyperemia (11%), ocular stinging/irritation (7%), ocular pruritis (5%), dry eye (3%), ocular pain (3%), eyelash darkening (2%), growth of eyelashes (2%), blurred vision (2%), headache (6%), common cold (4%), cough (3%), and urinary tract infection (2%).[12] The most common non ocular event was headache. When investigated, there were no clinically significant differences identified for effects of age, gender, race, prior prostaglandin use, baseline IOP, central corneal thickness, and iris color. [12]

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints

Preservation of visual function
Maintenance of quality of life
Withdrawal due to adverse events

Study Endpoints

Primary: Difference in change in IOP from baseline
Secondary: Proportion of patients with ≥25% reduction in diurnal IOP from baseline

Evidence Table

Ref/Study Design[1]	Drug Regimens[2]	Patient Population	N	Duration	Efficacy Results[3] (CI, p-values)	ARR/ NNT[4]	Safety Results (CI, p-values)	ARI/ NNH[4]	Quality Rating[5]; Comments

1. Chabi A, et. al[8] Phase III, RCT, DB, PG, AC, noninferiority Study 001	PF tafluprost 1 drop QHS + placebo instilled QAM PF timolol (0.5%) 1 drop "study eye" BID x12-week Mean duration 80.6 days for PF tafluprost and 82.1 days for PF timolol	Mean Age: 63.3 yrs Female 58.3% Black 22.7% 60% primary open-angle glaucoma 40% had ocular hypertension Inclusion Criteria: >18 yrs, Mean IOP of ≥23 and ≤36 mmHg Exclusions Criteria: Mean IOP >36, abnormal corneal sensation, significant visual field defect, history of ocular surgeries, ocular medications other than anti-glaucoma medications within 1 week of screening, significant CV disease, asthma or a history of pulmonary disease, allergic conjunctivitis	PF tafluprost: 320 PF timolol: 323	IOP was measured at baseline, 3 times during the day (08:00, 10:00 and 16:00) on weeks 2, 6, and 12 Noninferiority margin of 1.5 mmHg at each of the 9 time points assessed	<u>Difference in change in IOP from baseline (least squares mean) at 0800, 1000, and 1600*</u> *Week 2* -0.4 (-0.8, 0.1)*, -0.7 (-1.1, -0.3)* -0.8 (-1.3, -0.4)* *Week 6* 0.1 (-0.3, 0.6)* -0.4 (-0.9, 0.0)* -0.8 (-1.3, -0.3)* *Week 12* 0.0 (-0.4, 0.5)* -0.4 (-0.9, 0.0)* -0.6 (-1.0, -0.1)* *The criterion for declaring PF tafluprost noninferior to PF timolol was met since all the upper limits of the 95% CIs were less than the prespecified noninferiority margin of 1.5 mm Hg. <u>Proportion of patients with ≥25% reduction in diurnal IOP from baseline to week 12:</u> *Taf:* 178/298 (59.7%) 95% CI (53.9 – 65.3) Tim: 173/312 (55.4%) 95% CI (49.7-61.0) RR 0.93; 95% CI (0.8 to 1.1) P=0.3	NA NS	<u>Discontinuations due to adverse event</u> Taf: 4/320 (1.3%) Tim: 3/323 (0.9%) P=0.695 RR 1.3; 95% CI (0.23 - 7.5) <u>Conjunctival hyperemia</u> Taf: 14 (4.4%) Tim: 4 (1.2%) P=0.016 RR 3.5; 95% CI (1.1 to 12.6)	NS ARI 3.2% NNH 31	**Quality Rating**: Fair; **Internal Validity**: RoB: <u>Selection</u> – Appropriate methods for randomization sequence generation and concealment of allocation. More patients in the tafluprost group had prior prostaglandin use at baseline (59.7% vs. 55.1%), and consistently on almost all ophthalmologic medications. <u>Performance</u> – Patients and investigators masked to treatment allocation/ Identical unit dose containers used. Patients randomized to PF tafluprost received masked PF vehicle in the morning pouches and active PF tafluprost in the evening pouches, and patients randomized to timolol received unit dose pouches marked for morning and evening administration. Good compliance. <u>Detection</u>-Merck monitoring staff and site staff masked to treatment <u>Attrition</u> – Per protocol population used for primary efficacy analysis and 31 patients (4.8%) were excluded (21 in tafluprost group, 10 in timolol group). More patients excluded in tafluprost group due to medical history and receiving incorrect study medication. LOCF used to impute missing data (7.1% data imputed for tafluprost and 3.9% for timolol). **External Validity** <u>Recruitment</u> – not reported <u>Patient Characteristics –</u> Extensive exclusion criteria, a threefold higher prevalence of glaucoma occurs in African Americans and only 22.7% of patients in study <u>Setting</u> – multinational sites <u>Outcomes</u> - Surrogate endpoints utilized. No quality of life or visual acuity outcomes measured. Unclear how to relate LSM outcome to clinical relevance.

2. Uusitalo, et. al[9] Phase III, RCT, DB, PG, AC, noninferiority Study 74458	PC tafluprost (0.0015%) 1 drop QHS PC latanoprost (0.005%) 1 drop QHS X24-months (initially a 12-month study then extended)	Mean Age: 62.5 yrs 99% Caucasians 56% primary open-angle glaucoma 37% had ocular hypertensior Inclusion Criteria: ≥18 yrs w/ diagnosis of primary open-angle glaucoma, capsular glaucoma, pigmentary glaucoma or ocular hypertension, an untreated IOP of 22/34 mmHg (after washout if applicable) in at least one eye and ETDRS visual acuity score of +0.6 logMAR (Snellen equiv 20/80) or better in each eye Exclusion Criteria: Pregnant, any uncontrolled systemic disease, IOP >34mmHg, active ocular disease, advanced visual fiel defect, use of any other antiglaucoma medications, current alcohol or drug abuse.	PC taf: 269 PC lat: 264	Assessed at baseline and at 2 and 6 weeks, and 3 6, 9, 12, 12.5-13, 15, 18 and 24 months Noninferiority margin of 1.5 mmHg	Overall diurnal IOP from baseline at 24 months taf: -7.1 mmHg (29.1%) lat: -7.7 mmHg (32.2%) Mean Difference in IOP *Estimated overall difference(tafluprost – latanoprost; ITT population):* 1.20 mmHg; upper CI of 1.52 (RM-ANCOVA*) 0.95 mmHg; upper CI of 1.38 (RM-ANOVA*) *the noninferiority of tafluprost to latanoprost over all diurnal IOP measurements was shown with ANOVA and almost reached with ANCOVA (upper limits of the 95% confidence intervals 1.38 and 1.52 for the overall period, respectively). The noninferiority limit was 1.5 mmHg. Proportion of patients with ≥25% reduction in diurnal IOP from baseline to 6 months*: Taf: 62.8% Lat: 79.0% *From Merck Dossier (raw data not available)	NA/NS NA/NS NA*	Withdrawals due to adverse events: taf: 6/269 (2.2%) lat: 5/264(1.9%) p=0.8 RR 1.2; 95% CI (0.3-4.4) Overall Attrition: Taf:84/269 (31%) Lat: 47/264 (18%) P<0.001 RR 1.75; 95% CI (1.2-2.5) Conjunctival hyperemia Taf: 11/264 (4.2%) Lat: 4/264 (1.5%) P=0.073 RR 2.7; 95% CI (0.9-10.2) Ocular Adverse Events: taf: 127/264 (48.1%) lat: 117/264 (44.3%) p=0.503 RR 1.1; 95% CI (0.9 to 1.3)	NS N/A NS NS	**Quality Rating**: Fair **Internal Validity**: RoB: Selection – Unclear randomization sequence generation and allocation concealment. Slightly more prior use of anti-glaucoma meds requiring washout in tafluprost group (77% vs. 73%) and a worse mean IOP in tafluprost group, more treatment resistant patients in tafluprost group Performance –low risk; blinding of patients and investigators Detection- unclear blinding of evaluators Attrition – Overall 25% attrition rates in full 13-month period with higher rate in tafluprost: **External Validity** Recruitment – not reported Patient Characteristics – 3 fold highe incidence of glaucoma in African Americans than Caucasians – this study included >99% Caucasian patients Setting – multinational Outcomes – Surrogate endpoint of change in IOP measured -More discontinuations due to lack o efficacy in tafluprost group (13 vs. 3; p=0.01).

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover, DM = double-masked, AC = active-controlled [2]**Drug Regimens:** PF = preservative-free, PC = preservative-containing, IOP = intraocular pressure, PG = prostaglandin, ETDRS = Early Treatment Diabetic Retinopathy Study, Taf = Tafluprost, Lat = Latanoprost, Tim = Timolol [3]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval, ARI = absolute risk increase [4]**NNT/NNH** are reported only for statistically significant results [5]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY

Tafluprost is a prostaglandin analog that is selective for the FP prostanoid receptor agonist. The exact mechanism is unknown but it is thought that it decreases intraocular pressure by increasing uveoscleral outflow.[1]

DRUG SAFETY

Serious (REMS, Black Box Warnings, Contraindications): Currently there are no contraindications listed for tafluprost. This drug should only be used to treat conditions in which there is an increase in intraocular pressure.[1]

Tolerability (Drop-out rates, management strategies): According to the FDA review, a total of 94 (10.4%) in the tafluprost group, 41 (7.6%) in the timolol maleate group, and 25 (8.0%) in the latanoprost group withdrew from the phase III trials mostly due to adverse event, lack of efficacy, and patient request.[12] Of those discontinuations a somewhat higher number of patients discontinued due to lack of efficacy 23 on tafluprost (2.5%), 9 on timolol (1.7%), and 3 (1%) on latanoprost.[12]

Pregnancy/Lactation rating: C. Pregnant women were not included in the studies but studies from rats and rabbits did show tafluprost to be teratogenic when administered intravenously. The manufacturer recommends that tafluprost should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. A study in lactating rats demonstrated that tafluprost and/or its metabolites were excreted in milk but this is not known in humans. Tafluprost should be used in caution in nursing women.[1]

Dose Index (efficacy/toxic): In two phase II trials doses of tafluprost ranged from 0.0003% to 0.005%, 0.0015% was selected because it has similar effects of 0.001% and 0.0025% and slightly better effects than 0.005%.[12] It was reported that no systemic toxicity was observed in several repeat-dose topical ocular studies in monkeys at 100-fold higher than anticipated in man.[12]

Adverse event comparison between tafluprost, timolol, and latanoprost[1, 12]

ADE	Tafluprost n (%)	Timolol n (%)	Latanoprost n (%)
	N=905	N=543	N=311
OCULAR			
Conjunctival hyperemia	97 (10.7)	23 (4.2)	22 (7.1)
Ocular stinging/irritation	65 (7.2)	38 (7.0)	22 (7.1)
Ocular pruritus	44 (4.9)	11 (2.0)	5 (1.6)
Ocular pain	31 (3.4)	15 (2.8)	6 (1.9)
Dry eye	27 (3.0)	11 (2.0)	9 (2.9)
Growth of eyelashes	21 (2.3)	0 (0.0)	11 (3.5)
Blurred vision	19 (2.1)	15 (2.8)	2 (0.6)
Eyelash darkening	15 (1.7)	0 (0.0)	9 (2.9)
NONOCULAR			
Headache	51 (5.6)	15 (2.8)	15 (4.8)
Common cold	36 (4.0)	13 (2.4)	8 (2.6)
Cough	27 (3.0)	9 (1.7)	7 (2.3)
UTI	18 (2.0)	6 (1.1)	2 (0.6)

DOSE & AVAILABILITY[1]:

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
0.0015%	Solution	Ophthalmic	1 drop once daily in the evening	No adjustment	No adjustment	Not recommended due to safety concerns related to increased pigmentation following long-term chronic use	No differences in safety or effectiveness	If other medications are to be used in the eye waiting at least 5 minutes between Store unopened foil pouches in refrigerator

PHARMACOKINETICS[1]

Parameter	Result
Onset of action	2-4 hrs
Absorption	Through the cornea
Peak effect	~12 hrs
Cmax	26pg/mL
Half-Life	30 minutes
Metabolism	Ester prodrug hydrolyzed to active acid metabolite in the eye, further metabolized via fatty acid β-oxidation and phase II conjugation

ALLERGIES/INTERACTIONS

Drug-Drug: Tafluprost does not have any specific drug-drug interactions listed. However if other medications need to be instilled in the eye, then the patient should wait five minutes between the instillations.[1]

Food-Drug: Tafluprost is not affected by food.[1]

Abbreviated Review:
Vascular endothelial growth factor (VEGF) inhibitors

Month/Year of Review: August 2012 **End of Literature Search:** June 2012
Drugs Included: aflibercept, bevacizumab, pegaptanib, ranibuizumab

Research Questions:

- What is the evidence for effectiveness and safety for VEGF inhibitors to treat of diabetic macular edema?
- Is there evidence to determine if one anti-VEGF is more effective or safer than another agent for age-related macular degeneration (AMD), diabetic macular edema (DME), or retinal vein occlusion (RVO)?

Conclusions:

- There is moderate to high quality evidence that VEGF inhibitors improve visual acuity in patients with neovascular AMD and are recommended as first line treatment.
- There is low quality evidence that bevacizumab is equivalent to ranibizumab in improving visual outcomes over two years in neovascular AMD (difference in mean improvement with bevacizumab compared to ranibizumab was -1.4 letters; 95% CI -3.7 to 0.8) and that bevacizumab is associated with a higher rate of serious, nonspecific systemic adverse events over 2 years (31.7% vs. 39.9%; p=0.004, RR 1.30).
- There is insufficient evidence to make comparative conclusions for the use of pegaptanib in AMD.
- There is low quality evidence that aflibercept is equivalent to ranibizumab in maintaining vision at 1 year in the treatment of AMD.
- There is moderate to high quality evidence that anti-VEGF therapy improves visual acuity in patients with DME relative to laser treatment and sham injection, with similar improvements across agents.
- There is insufficient evidence to determine whether there are clinically meaningful differences in health outcomes between the available agents for the treatment of DME.
- There is insufficient direct comparative evidence (no RCTs and indirect observational data) comparing intravitreal bevacizumab with ranibizumab in patients with DME.
- There is insufficient evidence to support the use of pegaptanib in the use of DME.

- There is moderate quality evidence that anti-VEGF therapy improves visual acuity compared to sham injections in central RVO related macular edema with no direct comparative evidence of any agents.

Recommendations:

- Due to a lack of clinical benefit in both AMD and DME over other anti-VEGF agents, make pegaptanib non-preferred.
- There is not strong evidence of superiority of one anti-VEGF agent over another for the treatment of AMD or DME and low quality evidence demonstrating equivalence of bevacizumab to ranibizumab and aflibercept to ranibizumab in AMD. Compare costs of bevacizumab, ranibizumab, and aflibercept.

Reason for Review: There are currently no anti-VEGF agents approved in the US for treatment of DME. However, on July 26, 2012, the Food and Drug Administration (FDA) advisory committee recommended the approval of ranibizumab for treatment of DME and the FDA is expected to make a decision in August, 2012.[1] Currently bevacizumab is reportedly used off-label in clinical practice and to improve visual acuity in patients with diabetic macular edema refractory to laser therapy and for age-related macular degeneration (AMD). Aflibercept was recently FDA approved for the treatment of AMD in November 2011 and ranibizumab is the only agent approved for the indication of RVO by the FDA. This review will evaluate the available evidence to compare efficacy and safety of the VEGF-inhibitors in the treatment or DME, AMD, and RVO.

Background: DME is a frequent result of diabetic retinopathy and is the foremost cause of central vision loss and a leading cause of blindness in the diabetic population.[2,3] DME is the swelling of the retina due to leakage of fluid from blood vessels within the macula. Vision impairment is very much related to how well the diabetes is controlled and intensive metabolic control remains a highly effective means of controlling retinopathy. The goal of treatment is to preserve current visual acuity and reduce the progression to visual loss. Previous treatment approaches include laser photocoagulation, intravitreal steroid injections, and vitrectomy. Laser photocoagulation has become the gold standard but has not been successful in improving vision, only preserving it, reducing the risk of visual loss by 50% of patients with focal DME.[4,5] Intravitreal steroids may improve visual outcomes associated with DME based on moderate evidence from a Cochrane review of 7 trials (two with low risk of bias, 1 with medium risk of bias, 2 with high risk of bias, and 2 unable to assess).[5] Evidence suggests that intravitreal triamcinolone results in improved visual acuity compared with no treatment, and it can offer short-term improvements in acuity in eyes refractory to laser treatment.[3] However, the risk of elevated intraocular pressure (IOP) and cataracts are increased with steroid use, and are no longer used in favor.[6]

Change in visual acuity is one of the important outcomes evaluated in trials of patients with vascular eye diseases. It is commonly measured as the best-corrected visual acuity (BCVA). The Eye Disease Prevalence Research Group (EDPRS) developed a series of

charts to standardize visual acuity evaluation which are commonly used a standard outcome measure in RCTs.[6] Serious adverse events of interest include endophthalmitis, glaucoma, stroke, myocardial infarction, other cardiovascular events, and death.

There are currently four anti-VEGF agents available, although only ranibizumab is under review for approval for treatment of DME and only three are approved for one or more ophthalmologic indications. On July 26, 2012 the FDA Drug Advisory Committee voted to recommend approval of ranibizumab for treatment of DME based on a review of data from two phase III trials, RIDE and RISE, comparing sham injections to ranibizumab 0.3mg and 0.5mg over 24 months. These studies demonstrated a statistically significant difference between treatment and sham groups in the proportion of subjects who gained 15 letters or more in BCVA from baseline to month 24.[7] Bevacizumab was originally approved for the treatment of colorectal cancer, but has been used off-label for many vascular diseases of the eye, including AMD and DME.[2] Ranibizumab comes from the same parent molecule as bevacizumab but is a humanized monoclonal antibody fragment that binds active forms of VEGF-A, whereas bevacizumab is a full-length antibody and binds to all types of VEGF. In final guidance from NICE in November 2011, ranibizumab was not recommended for use in patients with DME, although the evidence was found to be acceptable supporting its efficacy in sustained gains in BCVA over 2 years, whereas improvement with laser photocoagulation alone is significantly less marked, and it does not provide distinctive innovation above other treatments.[8]

Current guidelines from the American Diabetes Association (ADA) give a recommendation based on level A evidence for laser photocoagulation to reduce the risk of vision loss in patients with high-risk proliferative diabetic retinopathy (PDR), clinically significant macular edema, and in cases of severe nonproliferative diabetic retinopathy (NPDR).[9] These guidelines state that emerging therapy with anti-VEGF seems to halt progression of DME and may in fact improve vision in some patients but do not give specific recommendations regarding therapy. The American Academy of Ophthalmology (AAO) 2008 guidelines also recommend laser photocoagulations as the standard of care, as well as virectomy for advanced proliferative diabetic retinopathy (PDR) which has been shown to increase vision-related quality of life.[10] These guidelines refer that adjunctive treatments such as intravitreal corticosteroids or anti-VEGF may be considered with laser treatment only when in the presence of clinically significant macular edema (CSME). Guidelines from the American Optometric Association (AOA) on care of patient of diabetes mellitus again recognizes the potential impact of anti-VEGF treatment in clinically significant macular edema but has yet to develop recommendations with any specifics regarding treatment with these agents.[11]

A randomized clinical trial by the Diabetic Retinopathy Clinical Research Network found that ranibizumab therapy with either prompt or deferred focal/grid laser treatment provided better visual acuity outcomes compared with prompt laser alone through two years in patients with DME.[12–14] In addition, the RESTORE study was a 12-month, double blind, randomized trial comparing

ranibizumab 0.5mg monotherapy or combined with laser to laser treatment alone and found that ranibizumab alone and in combination with laser were superior to laser monotherapy in improving BCVA at 12 months ($p<0.0001$).[15] Another prospective RCT confirmed that bevacizumab through two years also improved BCVA compared to laser therapy alone.[16,17] At 12 months, there was a significant difference between the mean ETDRS BCVA in the bevacizumab group (61.3±10.4; range 34–79) and laser arm (50.0±16.6; range 8–76) ($P = 0.0006$).[16] This was maintained at 24 months (64.4±13.3; range 34-88 vs. 54.8±12.6; range 33-75 for bevacizumab and laser groups, respectively, $p=0.005$). [16]

AMD is a progressive chronic disease of the central retina and leading cause of vision loss worldwide.[18] Patients are typically over 50 years of age and the goal of treatment is to minimize or reverse loss of vision and to maximize the vision-related quality of life related to AMD. Treatment options for AMD include observation, antioxidant vitamin and mineral supplements, photodynamic therapy (PDT) with verteporfin, intravitreal injection of VEGF inhibitors, and laser photocoagulation surgery.[19] VEGF inhibitors have become the standard of care for neovascular AMD and are recommended first line. They have demonstrated improved visual outcomes compared with other therapies. 2008 guidelines from The American Academy of Ophthalmology (AAO) recommend VEGF inhibitors as first line treatment for AMD with no specific distinctions between ranibizumab, bevacizumab, or pegaptanib. These guidelines were developed before the approval of aflibercept. Two controversies in the treatment of AMD with VEGF inhibitors include the preferred dosing regimen and systemic safety. Trials have evaluated a stricter monthly dosing regimen versus a less frequent, as needed protocol based on clinical and imaging features. Safety is a concern as the drugs enter the systemic circulation after ocular injection and there exists a theoretical higher risk of systemic vascular events. Clinical data on the systemic safety is sparse and available studies are not large enough to address safety concerns.

The National Institute for Health and Clinical Excellence (NICE) recommends ranibizumab as an option for wet AMD if the best-corrected visual acuity is between 6/12 and 6/96, there is no permanent structural damage, the lesion size is less than or equal to 12 disc areas, and there is evidence of recent presumed disease progression.[20] It is also recommended that it only be continued in people who maintain adequate response to therapy. NICE guidance states that pegaptanib is not recommended for the treatment of AMD. Based on four randomized controlled trials (RCTs) of ranibizumab and two of pegaptanib, the committee concluded that ranibizumab is more clinically effective than pegaptanib in improving visual acuity, although both are clinically effective in the treatment of wet AMD. [20]

RVO is the second most common retinal vascular disease after diabetic retinopathy with main risk factors being age over 50 and hypertension and branch retinal vein occlusion (BRVO) occurring 2-3 times more often than central retinal vein occlusion (CRVO).[21,22]

Ophthalmological treatments focus on the prevention and management of the main sight threatening complications – ocular neovascularization and macular edema. [21] In the absence of either of these complications, there is no evidence that treatment improves outcomes, and treatment is associated with some adverse effects. Macular edema is the most common cause of visual loss in patients with RVO. Laser photocoagulation, steroids, and intravitreal injections of anti-VEGF have been evaluated as treatments. Currently only ranibizumab is approved for the indication of RVO.

Methods:

A Medline literature search ending June 2012 for new systematic reviews and randomized controlled trials (RCT's) comparing VEGF inhibitors in patients with DME, AMD, and RVO was conducted. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Institute for Clinical and Economic Review (ICER), Dynamed, 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 review. Randomized controlled trials (RCTs) will be emphasized only if evidence is lacking or insufficient from those preferred sources. The literature search for RCT's was done from the date of search in high quality systematic reviews to current.

Drugs included in review

Anti-VEGF	FDA approved Indications	Mechanism of Action	Dosing
Pegaptanib (Macugen®)	Age-related macular degeneration	Targets only the VEGF 165 isoform	Intravitreous injection every 6 weeks
Bevacizumab (Avastin®)	Tumor therapy	Binds to all types of VEGF	Intravitreous injection every 4 weeks
Aflibercept (Eylea®)	Neovascular (wet) Age-related macular degeneration	Binds VEGF-A and placental growth factor, another angiogenic factor	Intravitreous injection every 4 weeks x 3 months, then every 8 weeks
Ranibizumab* (Lucentis®)	Neovascular (Wet) Age-related macular degeneration and macular edema following retinal vein occlusion	Binds all active forms of VEGF-A	Intravitreous injection every 4 weeks. Although less effective, treatment may be reduced to one injection every three months after the first four injections if monthly injections are not feasible for AMD only.

*Approved in Europe, Canada, and Australia for DME, and under review in the United States for the treatment of DME.

Systematic Reviews: Diabetic Macular Edema

CADTH

In May 2012, CADTH performed a rapid response report including a systematic review of intravitreal bevacizumab for the treatment of DME to evaluate if bevacizumab provides a therapeutic advantage on visual acuity, morbidity, and/or mortality, in comparison with other standard therapy, including ranibizumab.[3] A literature search up to May 2012 was conducted and ten publications were included in the review; one RCT comparing bevacizumab versus placebo, five with laser photocoagulation, and four with triamcinolone therapy. No trials compared bevacizumab with ranibizumab in patients with DME. Mortality and serious adverse events did not differ versus any comparator, and no trials reported on activities of daily living or quality of life.
Bevacizumab was found to improve vision compared to laser therapy. Three trials with a low risk of bias measured effect on BCVA and showed that more subjects demonstrated improvement in 3 lines or greater in the bevacizumab group compared to those in the laser groups at 6 weeks (15% vs. 5% at 6 weeks, risk ratio (RR) 3.33, 95% CI 0.56 to 19.74, p=0.009), 12-16 weeks (21% vs. 7%, RR 3.73 95% CI 1.51 to 9.25, p=0.005; NNT 6), and at 36-52 weeks (23% vs. 9%, RR 2.57 95% CI 1.21 to 5.44, p=0.01; NNT 8). [3]

There was insufficient evidence comparing bevacizumab to triamcinolone (4 trials). None of the trials reported all-cause mortality, mean visual acuity change, activities of daily living, quality of life, or withdrawals due to adverse events. All of the trials had both inadequate masking and allocation concealment. [3]

There was a consistent lack of evidence for the long term safety profile and sparse reporting of adverse events in the reviewed trials. Therefore, in addition to the reviewed literature, an additional non-systematic safety analysis was performed to include systematic reviews in other ocular conditions, a trial comparing bevacizumab and ranibizumab in age-related macular edema, cohort analyses, and a multicentre case series. [3] These results showed no conclusive evidence of serious safety signals with bevacizumab or important differences with other agents, such as ranibizumab, due to the generally lower quality of harms data for bevacizumab. The single head-to-head randomized trial between bevacizumab and ranibizumab for the treatment of AMD suggested an increased risk of non-specific serious systemic adverse events for bevacizumab-treated patients over two years, however the importance of the difference remains unclear.[3]

Institute for Clinical and Economic Review (ICER)

A technology assessment report was prepared by ICER and systematically included 15 RCTs and 8 observational studies of VEGF-inhibitors for DME.[6] Since there are no head-to-head trials comparing VEGF-inhibitors for DME, the authors conducted a series of pairwise indirect meta-analyses to find the mean difference in BCVA change, and the rate ratio of the likelihood of gaining 10 or more letters of vision, including only fair or good quality trials of 6-24 months duration. For the outcome of mean difference in

BCVA, these results found no statistically significant differences between ranibizumab and bevacizumab (MD -4.32; 95% CI -9.13 to 0.49), ranibizumab and aflibercept (MD 0.34; 95% CI -2.81 to 3.49), or bevacizumab and aflibercept (MD 4.66; 95% CI -0.05 to 9.37). Data for pegaptanib were unable to be used for the analysis in change in BCVA. Indirect analyses also demonstrated no significant difference in the likelihood of gain of >10 letters between any anti-VEGF therapies (ranibizumab vs. bevacizumab RR 0.71; 95% CI 0.34 to 1.46). Conclusions from these indirect comparisons need to be drawn with caution. Relatively few trials have been conducted in DME and there was between-agent trial heterogeneity in patient populations, duration of follow-up, and treatment regimens.

Zechmeister, et al.

A recent systematic review evaluated whether anti-VEGF leads to better clinical outcomes than current treatments in patients with DME including laser photocoagulation, intravitreal application of glucocorticoids, and vitrectomy.[4] Eleven RCTs were included in the review; 6 of bevacizumab, 3 evaluated ranibizumab, and 1 on pegaptanib. The principles of GRADE were used to assess the quality of evidence and the overall quality of the evidence of anti-VEGF therapy is moderate. There were no head-to-head comparative trials between the three products. This review did not find the evidence to strongly support the superiority of one anti-VEGF agent over another, although overall the quality of evidence was higher for ranibizumab efficacy than for bevacizumab. Quality of evidence for safety of any of the anti-VEGF products is very low and ocular events were the most frequently reported. There was insufficient evidence to support the use of pegaptanib in DME. One study was found comparing pegaptanib with sham injections, and the differences in visual acuity were either not clinically relevant or of unknown significance.

Based on one study comparing bevacizumab with sham injections, low quality evidence demonstrated a significant and clinically relevant improvement in mean visual acuity (effect size -0.21 better). Two studies comparing bevacizumab with laser photocoagulation showed greater and clinically relevant gains in mean visual acuity (high quality evidence). One small study did not demonstrate a difference in visual acuity between bevacizumab and intravitreal steroids.

There was moderate quality evidence, based on one single high quality study that compared with sham injections, ranibizumab significantly improved mean visual acuity and the percentage of patients who gained at least 15 letters was significantly higher. There was also moderate quality evidence that ranibizumab significantly improved visual acuity and vision-related quality of life compared to laser photocoagulation, although the difference was not clinically relevant. No evidence was available comparing ranibizumab to intravitreal steroids.

Goyal, et al.:

A meta-analysis and systematic review was performed to evaluate the effect of bevacizumab in diabetic macular edema (DME).[2] This review was evaluated by the Centre for Reviews and Dissemination (CRD) and met the criteria for inclusion in the Database of Abstracts of Reviews and Effects (DARE). Four randomized controlled trials were included in the review and were assessed for quality using criteria from the Delphi List including randomization, allocation concealment, baseline group similarity, specified eligibility criteria, blinding, and intention to treat analysis. All four trials were rated as moderate to good quality. Trials included comparisons of bevacizumab with bevacizumab plus intravitreal triamcinolone, with macular laser photocoagulation, or with sham control groups.

At 6 weeks, there was a significant reduction in center subfield macular thickness (WMD -48.2µm, 95% CI -86.2 to -10.2; I^2=71.4%; three RCCTs), but no significant differences at 12 or 24 weeks between bevacizumab and photocoagulation. No significant between group differences were found for intravitreal bevacizumab versus intravitreal bevacizumab plus intravitreal triamcinolone acetonide at any time point. At 6 weeks, there was also a significant improvement in best-corrected visual acuity (BCVA) with bevacizumab compared to control (WMD -0.13 log MAR, 95% CI -0.23 to -0.02; I^2=85.1%; three RCCTs) and at 24 weeks (only 2 trials), but no significant difference was seen at 12 weeks. There was no significant gain in outcomes with the combination of bevacizumab and intravitreal steroids compared to bevacizumab alone. This review demonstrated the short-term beneficial effects of bevacizumab compared to standard laser therapy and that there is no significant benefit of adding steroids to bevacizumab, with an added risk of cumulative side effects. There was insufficient evidence to make conclusions regarding its long term efficacy either used alone or in combination with other treatments for DME. This meta-analysis was limited due to the small number of trials eligible for analysis and most of them were conducted in Iran. CRD concluded that the conclusions should be interpreted with caution due to this main limitation.

Systematic Reviews: Age-related Macular Degeneration

CADTH

A systematic drug class review and economic evaluation for the management of neovascular AMD was conducted by CADTH in 2008 and concluded that uncertainty still exists with no direct evidence demonstrating the effect of timing or retreatment on health and that evidence for bevacizumab's effectiveness was less compelling than other anti-VEGF agents. Pegatanib or ranibizumab were recommended as optimal treatment strategies.[23]

Cochrane Collaboration:

A 2008 Cochrane systematic review was conducted to investigate the effects of, and quality of life associated with, anti-VEGF therapies for the treatment of neovascular AMD.[24] The primary outcome was BCVA after at least one year of follow up, as

demonstrated by loss of 15 or more letters. The literature search was through February 2008 and resulted in five trials in ten reports for the analysis. All five trials were of good methodological quality and there were no direct head to head trials comparing ranibizumab to pegaptanib. At the time of this review, all trials evaluating bevacizumab were still ongoing or were uncontrolled and did not meet the criteria for inclusion. [24]

Compared to sham injections, pegaptanib demonstrated fewer patients losing 15 letters or more (RR 0.70; 95% CI 0.6 to 0.84) based on two trials. The calculated number needed to treat (NNT) was 6.67 for 0.3mg, 6.25 for 1 mg, and 14.28 for 3 mg pegaptanib. [24] The final mean visual acuity was also greater in all three dosages compared to sham, with the weighted mean difference (WMD) ranging from 3.64 to 7.2 letters. [24]

The overall RR for ranibizumab versus sham for loss of 15 or more letters of visual acuity was 0.14 (95% CI 0.10 to 0.22). The calculated NNT was 3.13 for 0.3mg ranibizumab and 3.13 for 0.5 mg (3 trials). [24] Patients treated with ranibizumab had greater mean visual acuity at one year compared with those treated with sham. The WMD for the mean change was 16.9 for 0.3 mg and 17.6 for 0.5mg. [24]

The authors concluded that based on trials of good methodological quality, ranibizumab and pegaptanib demonstrate efficacy in terms of proportion with loss of 15 letters of more and ranibizumab resulted in a greater proportion with loss of 15 letters or more than pegaptanib.[24]

Mitchell, et al:

A literature search up to June 2010 was used to review ocular and systemic events in AMD with the treatment of ranibizumab and bevacizumab. Nine prospective, randomized, controlled trials considered Level I evidence (8 for ranibizumab and 1 for bevacizumab) and 11 studies considered to be Level II evidence (five ranibizumab and 6 bevacizumab) were included. Level I evidence was defined as strong evidence and level II indicates substantial evidence that lacks some qualities or study flaws. One comparative study of the two agents was included.[25]

Seven large trials of level I evidence including 1301 demonstrated significant improvements in visual acuity in patients with AMD with the use of ranibizumab versus sham, in combination with PDT versus PDT, and in combination with PDT versus sham-PDT. The range of mean visual acuity change in letters from the studies was -1.6 to +11.3 and comparators from -16.3 to -7.8. Four additional open-label studies with 4484 patients also demonstrated significant improvements versus usual care following, although these studies compared different dosing and treatment schedules of ranibizumab. [25]

Six studies (5 being of level II evidence) of bevacizumab included 424 patients and demonstrated significant improvements in visual acuity, as assessed by mean gain of letters. The one trial of Level I evidence compared bevacizumab 1.25mg to PDT/pegaptanib/sham in 131 patients. There was a significant improvement in mean gain of letters (+7 for bevacizumab versus -9.4, $p<0.001$). There were low rates of serious ocular adverse events and two myocardial infarctions (3.1%).[25]

One small (n=20) study compared the efficacy of ranibizumab and bevacizumab over 6 months and resulted in bevacizumab with a tendency to be associated with a greater gain of letters from baseline, and ranibizumab with a greater reduction in central macular thickness. Differences between the groups were not statistically significant. One year data demonstrated similar results (+6.3 letters for ranibizumab vs. _12.1 for bevacizumab). [25]

Limited safety results could be concluded from the bevacizumab trials, as only three of the studies reported details of adverse ocular or systemic events. Results of this study demonstrated that Level I and Level II evidence supports the efficacy and safety of ranibizumab in wet AMD and that data suggests bevacizumab may also provide efficacy, with insufficient evidence to determine the safety profile of bevacizumab. [25]

Systematic Reviews: Retinal Vein Occlusion

Cochrane Collaboration

A 2010 Cochrane systematic review was performed to investigate the effectiveness and safety of anti-VEGF therapies for the treatment of macular edema secondary to central retinal vein occlusion (CRVO).[26] A literature search through August 10, 2010 found only two RCTs comparing an anti-VEGF agent to sham injection that met the inclusion criteria; both considered to have a low risk of bias although both with relatively small sample sizes and short follow-up periods (six months and 30 weeks). The primary outcome was defined as the proportion of patients with an improvement from baseline in BCVA of greater than or equal to 15 letters or 3 lines on the ETDRS Chart, which has been the standard primary outcome measure for evaluating the efficacy of treatments for retinal diseases. [26]

One of the included trials (Wroblewski) compared pegaptanib (n=33) with sham injection (n=32) for 30 weeks in patients with CRVO-macular edema. The other study (CRUISE) was a sham-controlled trial of ranibizumab comparing 0.3 mg (n=132) or 0.5 mg (n=130) ranibizumab to sham injection (n=130) for six months. The two trials included patients with similar baseline characteristics and mean age. [26]

In the Wroblewski study, there was no significant difference demonstrated between the groups in the primary endpoint. In the sham group, 28% of patients gained 15 or more letters compared to 36% in the 0.3 pegaptanib group (p=0.48) and 39% in the 1.0 mg group (p=0.35). [26] There was a significant difference in average visual acuity gain at week 30 in the 1.0 mg group compared to sham (+9.9 letters vs. +3.2 letters, p=0.02; 95% CI 1.5 to 24.6 letters). The difference was not statistically significant between 0.3 mg pegaptanib and sham (+7.1 letters vs. +3.2, p=0.09, 95% CI -1.3 to 21.8 letters). [26] No quality of life or visual functioning data were included.

In CRUISE, there was a significant difference in mean change BCVA at 6 months between both ranibizumab 0.3 mg and 0.5 mg compared to sham (+12.7 letters 0.3 mg vs. +14.9 letters 0.5 mg vs. +0.8 letters sham, p<0.00001). At six months, the percentage of patients gaining 15 letters or more from baseline was also significantly higher in both treatment groups compared to sham (P<0.0001). For the 0.3 mg group the RR was 2.73 (95% CI 1.79 to 4.17) and was 2.82 (95% CI 1.85 to 4.29) for the 0.5 mg ranibizumab group compared to sham. [26] There were few serious adverse ocular events at six months and some systemic serious adverse events occurred in all groups (one non-fatal myocardial infarct in each group). [26] There was also an improvement in quality of life as measured by the National Eye Institute Visual Functioning Questionnaire 25 item instrument (NEI VFQ-25) in the treatment groups compared to sham.

The authors of this review concluded that the available RCT data presents relatively good evidence that repeated treatment of non-ischemic CRVO related macular edema with the anti-VEGF agents' ranibizumab or pegaptanib may improve numerous outcomes at six months. However, the applicability of the evidence to clinical practice is relatively limited, and there were no data on bevacizumab or other agents. [26]

The Royal College of Ophthalmologists

Guidance for the management of RVO was updated in 2010 due to developments in treatment options.[27] This was based on a literature search through February 2010 for selected RCT's, systematic reviews, and observational studies. Relevant literature was identified and the level of evidence was graded. Guidelines are separated into recommendations for BRVO and CRVO. For macular edema associated with CRVO, the guidelines give grade A strength of evidence for the use of ranibizumab in macular edema based on results of the CRUISE trial and grade D for the strength of the evidence supporting the use of bevacizumab due to an unknown dosing schedule and unclear long-term outcomes. [27]

In macular edema associated with BRVO, guidance also demonstrated grade A strength of evidence for ranibizumab based on results from the BRAVO study which compared it to sham over six months. [27] The BRAVO study was a 12-month, randomized trial that

included a 6-month, injection-controlled treatment period followed by a 6-month observation period In this study, sixty-one percent of subjects in the ranibizumab 0.5mg group achieved a 15 letter gain vs. 29% in the sham treated group and the mean improvement in BCVA at month 12 in the sham group than that of the 0.3 mg and 0.5 mg treatment groups ($p<0.01$). Bevacizumab was given grade B strength of evidence based on increasing short-term data supporting that multiple injections may reduce macular edema associated with BRVO. [27]

Ranibizumab vs. Bevacizumab (details in evidence table in Appendix 1):

Subramanian et al.

The first head to head trial of bevacizumab and ranibizumab in AMD was a small (n=22), 1-year, prospective, single-center, randomized, double-blind study comparing bevacizumab and ranibizumab for the treatment of neovascular AMD. Patients were randomized 2:1 to bevacizumab or ranibizumab. Patient's received monthly treatment for 3 months followed by an as needed dosing schedule. Twenty-two (78.6%) patients completed the year of follow-up, 15 in the bevacizumab and 7 in the ranibizumab groups. There were no significant differences in mean change in visual acuity (+6.3 letters for ranibizumab and +7.6 etters for bevacizumab, p=0.74) or central macular thickness at one year. The quality of this trial is fair due to the small sample size and inadequate power to detect a real difference. The applicability to the real world population is also limited; as the study population was an almost entirely male, Caucasian patient population in a VA setting.[28]

CATT

Ranibizumab and bevacizumab have been compared in the treatment of age-related macular degeneration (AMD) in the Comparison of AMD Treatment Trials (CATT), a randomized, single-blind, noninferiority trial.[29,30] Patients were randomly assigned and treated with one of four regimens. They received ranibizumab monthly or as needed, or bevacizumab monthly or as needed. The primary outcome was the mean change in visual acuity at 1 year, with a noninferiority limit of 5 letters on the eye chart. One year results demonstrated that bevacizumab and ranibizumab had nearly identical effects on visual acuity (99.2% confidence interval for the difference in the mean change in visual-acuity score within -5 to +5 letters) both when drugs were given monthly and when given as needed. Ranibizumab given as needed was also equivalent to ranibizumab given monthly. The comparison between bevacizumab as needed and bevacizumab monthly and ranibizumab monthly was inconclusive. At 1 year, 24 of the 1185 patients had died and the proportions of patients with arteriothrombotic events were similar among the groups, at 2 to 3% (p=0.97). One or more serious systemic adverse events occurred in 255 patients (21.5%) with no statistically significant differences between the four

groups (p=0.11), but when dosing regimens groups were combined there were 24.1% for bevacizumab and 19% for ranibizumab (p=0.04; RR 1.29 95% CI 1.01 to 1.66), driven primarily by hospitalizations. The rates of death, myocardial infarction, and stroke were numerically higher in the bevacizumab-treated groups, but the differences were not statistically significant when compared to ranibizumab (p>0.2). One major limitation of the fair-poor quality CATT trial is the incomplete blinding to the assigned study groups. If receiving ranibizumab, this was displayed in patients' billing documents which unblinded drug assignments, although the assessors remained blinded. The study size was also not sufficient to evaluate drug safety.

After year 1 of the CATT study, patients initially assigned to monthly treatment were reassigned randomly to either continue receiving monthly treatments or switch to as-needed treatments and year two was conducted to describe longer-term effects and the impact of switching from monthly to as-needed treatment.[30] Patients assigned to as-needed treatment initially had no change in assignment. Most of the change in mean visual acuity occurred during year 1, with relatively little change during year 2. There was no significant difference in visual acuity score between the drugs or between the different regimens. The difference in mean improvement with bevacizumab compared to ranibizumab was -1.4 letters (95% CI -3.7 to 0.8) and the difference between those treated by an as-needed regimen compared to those treated monthly was -2.4 letters (95% CI -4.8 to -0.1). [30] There was no significant difference in the proportion of patients without a decrease in vision of 15 letters or more between the groups (88.4% for bevacizumab vs. 93.3% for ranibizumab, p=0.24). Small differences in mean gain in visual acuity emerged between dosing regimens.[30]

Two year data demonstrated no significant difference in the number of patients who died (5.3% vs. 6.1%; p=0.62), proportion of patients with arteriothrombotic events (4.7% vs. 5.0%; p=0.89), or venous thrombotic events (0.5% vs. 1.7%; p=0.054) between patients assigned to ranibizumab and bevacizumab, respectively. [30] The higher rate of serious adverse events observed in patients in the bevacizumab group persisted during year 2 (31.7% vs. 39.9%; p=0.004, RR 1.30). Patients treated as-needed had higher rates of serious adverse events than patients treated monthly (RR 1.20; 95% CI 0.98-1.47; p=0.08).

<u>IVAN</u>

A UK equivalent of the CATT study (IVAN trial) was conducted to compare the efficacy and safety of ranibizumab and bevacizumab in AMD in a noninferiority trial. Although still ongoing, interim results from a pre-specified 1 year analysis have been published. A total of 610 patients were randomized to 4 groups: ranibizumab or bevacizumab, given either every month or as-needed.[31] Both groups received 3 months of treatment and then were allocated to continuous or as needed treatment. Patients and clinicians were blinded to drug allocation but not to treatment regimen allocation. The primary outcome was best-corrected distance visual acuity measured as ETDRS letters, with a noninferiority limit of 3.5 letters. The difference between drugs (bevacizumab minus

ranibizumab) was -1.99 letters (95% CI -4.04 to 0.06) and between treatment regimens was -0.35 letters (95% CI -2.40 to 1.70), favoring continuous therapy. [31] Overall, the comparison between study drugs was inconclusive using the 3.5 letter limit and as-needed treatment was shown to be equivalent to monthly treatment. There were no significant differences between drugs or regimens for quality of life. There were no differences at year 1 between drugs or treatment regimens in mortality, the odds of a serious adverse event, and arteriothrombotic events occurred infrequently, but more often with ranibizumab than bevacizumab. [31]

Authors of the IVAN study also combined results from the CATT study and by Subramanian to develop a weighted mean difference in visual acuity of 1.06 letters in favor of ranibizumab (95% CI -0.29 to 2.41 letters), meeting the noninferiority margin to establish equivalence of the two drugs. The pooled analysis also showed no difference between the drugs in mortality or arteriothrombotic events (p=0.34 and p=0.55, respectively). [31]

There are no head-to-head trials comparing bevacizumab to ranibizumab in patients with DME. There has been one retrospective study with many limitations, including its design, small population studied (n=29), short duration of only 1 injection, and potential unblinding of the patients. This low quality study demonstrated no significant difference in median change in BCVA between bevacizumab and ranibizumab (4.5 letters vs. 6 letters, p=0.58).[32]

<u>New Drug: Aflibercept (Eylea)</u>

Aflibercept was FDA approved for the treatment of AMD in November 2011.[33] Approval was based on two randomized, double blinded, unpublished, non-inferiority Phase III trials (VIEW 1 and VIEW 2) in 2,412 patients, comparing it to ranibizumab on efficacy in visual acuity after one year of treatment in patients with neovascular AMD. [33] Doses of 2mg every 4 weeks, 0.5mg every 4 weeks, and 2mg every 8 weeks were compared to ranibizumab. Patients were at least 50 years of age with active primary subfoveal choroidal neovascularization lesions secondary to AMD. Treatment failure was defined as a decrease from baseline in the BCVA by 15 or more letters at two consecutive assessments that were 4 weeks apart. In both studies, all three doses of aflibercept were non-inferior to ranibizumab in regards to the primary endpoint; the proportion of patients who maintained vision at week 52 with a noninferiority margin of 10% and none of the doses were found to be superior [33] During year 2, all patients received the same dose on an as needed basis and the proportion of patients maintain vision and/or gaining vision remained similar between ranibizumab 0.5 mg and aflibercept 2 mg. Overall, 26.5% of ranibizumab patients received six or greater injections during year 2 compared to 15.9% of those in the aflibercept 2 mg every 8 weeks group. The 2mg every 8 week dosing was approved based on the theoretical benefit of less injection related risks.

In addition, all treatment groups experienced improvements in the ETDRS letter scores versus baseline with the most rapid improvement during the first three months of treatment.[33] The mean change in the BCVA was 8.4 for aflibercept 2mg every 8 weeks, 9.3 for aflibercept 2mg every 4 weeks, and 8.7 for ranibizumab. The proportion of patients who gained more than 15 letters was 31% for aflibercept 2mg every 8 weeks, 33.4% for aflibercept 2mg every 4 weeks and 32.4% for ranibizumab. The most common side effects include conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters and increased intraocular pressure.[33] These studies have not been published yet and cannot adequately be assessed for quality and risk of bias.

Aflibercept has also been evaluated in the treatment of DME in one fair quality phase II RCT (DA VINCI) comparing four different doses to macular laser photocoagulation in 221 patients for 6 months.[34] This was a double-blind, sham-controlled study. At 6 months, mean BCVA improved by 8.5-11.4 letters in each group vs. 2.5 letters in the laser group ($p<0.009$ for all comparisons). Greater numbers of patients in each aflibercept group gained greater than 10 and greater than 15 letters compared to laser but the differences were not statistically tested. [34] There was an overall attrition rate of close to 20% and the treatment group had a higher prevalence of proliferative diabetic retinopathy and history of cardiac disease. Statistically significant differences in improvements in BCVA continued to be seen up to week 52 with all treatment groups compared to laser ($p<0.001$) and no significant differences were seen between the treatment groups. The proportion of eyes that gained 15 letters or more was also statistically greater than in the laser treatment group in all groups except the group dosed every 8 weeks.[34]

The Phase III COPERNICUS study was a randomized, double-blind study assessing the efficacy and safety of aflibercept in patients with macular edema associated with CRVO randomized 3:2 to receive aflibercept 2 mg or sham injection monthly for 6 months.[35] This is currently an ongoing, 2 year study with six month data reported and published. A total of 189 subjects were evaluated and the primary efficacy end point was the proportion of eyes with a gain of 15 ETDRS letters or more in BCVA from baseline to week 24. In the efficacy analysis, 56.1% of eyes treated with aflibercept gained 15 letters or more from baseline, compared with 12.3% of sham-treated eyes, with a difference of 43.8% (95% CI 33.0%-56.6%; $p<0.0001$). There were similar occurrences of ocular adverse events in each group (68.4% aflibercept vs. 68.9% sham). Five patients in the sham group compared to one patient receiving treatment discontinued study drug because of ocular adverse events. [35]

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Appendix 1: Evidence Table

Ref/ Study Design[1]	Drug Regimens[2]	Patient Population	N	Duration	Efficacy Results[3] (CI, p-values)	ARR/ NNT[4]	Safety Results (CI, p-values)	ARI/ NNH[4]	Quality Rating[5]; Comments
Subramanian et al.[28] DB, RCT	Ranibizumab (RZ) Bevacizumab (BZ) Both given every month for the first 3 months. Following the third injection, decision to administer further treatment was guided primarily by optical coherence tomography changes	All Caucasian descent, all but one subject were male, mean age for patients in the BZ and RZ group was 78 and 80 respectively Inclusion criteria: age greate than 50, symptomatic CNV, cooperative patient, baseline visulal acuities equal to or better than 20/400 Exclusion criteria: previous treatment for AMD within past year, advanced glaucoma, coexisting macular disease, history of malignant or uncontrolled hypertension, history of thromboembolic phenomena.	RZ = 7 BZ = 15	One year	Visual Acuity: Mean change (letters): RZ: +6.3 BZ: +7.6 Difference between the two groups: + 1.3 ±14.9 (95% CI 0.64-15.5) P=0.74 Mean Number of injections: RZ:4 BZ: 8 P=0.001	N/A N/A	Details of events not provided but stated that no major ocular adverse effects reported and no systemic adverse events were found in those who completed 1-year follow-up.		**Quality Rating**: Fair **Internal Validity**: Selection –2:1 randomization with the research pharmacist responsible for randomization Performance – Patients and physicians blinded Detection- All other investigators and office personnel masked to treatment assignments, too small of a sample size to detect a real, moderate effect size difference Attrition – 78.6% of randomized patients completed one year of follow-up **External Validity** Recruitment –Subjects volunteered from clinic; costs of medications were covered by VA. Patient Characteristics – limited applicability due to entire VA population, Caucasian males. Setting – outpatient VA clinic Outcomes – Visual Acuity is a valid outcome, limited safety data available.

CATT[29] SB, NI, MC, RCT	Ranibizumab monthly (RZ1) Bevacizumab (BZ1) monthly Ranibizumab as needed (RZ2) BZ as needed (BZ2)	Mean age : RZ1: 79.2 BZ1: 80.1 RZ2: 78.4 Bz2: 79.3 Inclusion criteria: age ≥50, visual acuity between 20/25 and 20/320, active disease Exclusion criteria: Previous treatment with AMD therapy, Previous treatment with intravenous bevacizumab, history of surgical intervention for AMD, concurrent use of systemic anti-VEGF agents, Evidence of significant uncontrolled concomitant diseases such as cardiovascular disease, nervous system, pulmonary, renal, hepatic, endocrine, or gastrointestinal disorders	RZ1=301 BZ1=286 RZ2=298 BZ2=300	One year	<u>Mean change in visual acuity (VA) at 1 year (no. of letters; non-inferiority limit of 5 letters):</u> RZ1: +8.5±0.8 BZ1: +8.0±1.0 RZ2: +6.8±0.9 BZ2: +5.9±1.0 P=0.16 <u>Proportion of patients who did not have a decrease in visual acuity of 15 letters or more from baseline:</u> RZ1: 94.4% BZ1: 94% RZ2: 95.4% BZ2: 91.5% P=0.29	 NA NS	<u>Serious Systemic Events</u> RZ1: 53 (17.6%) BZ1: 64 (22.4%) RZ2: 61 (20.5%) BZ2: 77 (25.7%) P=0.11 BZ (1+2): 24.1% RZ (1+2):19.0% RR 1.29; 95% CI (1.01 to 1.66). P=0.04 <u>Arteriothrombotic event</u>: RZ1: 7 (2.3%) BZ1: 6 (2.1%) RZ2: 6 (2.0%) BZ2: 8 (2.7%) P=0.97	 NS ARI 5.1% NNH 20 NS	**Quality Rating**: Fair-poor **Internal Validity**: <u>Selection</u> –adequate randomization, Computerized treatment allocation with eligibility review preceding enrollment; significant differences in baseline medical history for CHF (7.6% vs. 4.2% vs. 4%, 8.7%), higher mean age in bevacizumab group (80.1 years vs. 79.2 for ranibizumab) <u>Performance</u> – Ophthalmologist blinded to drug but not dosing schedule (identify known in 0.2%); Patients were initially masked to the study drug but may find out the identity of the drug from billing documents. <u>Detection</u>- VA examiner blinded; image graders masked to drug and schedule; <u>Attrition</u> – Low overall attrition; ITT analysis which can bias towards equivalence. **External Validity** <u>Recruitment</u> –Most patients were identified from the clinical practices at the participating centers and from referring ophthalmologists in the community. <u>Patient Characteristics –</u> <u>Setting</u> –in US, where many ophthalmologists already choosing bevacizumab <u>Outcomes</u> – no significant concerns

CATT two year results[30] SB, NI, MC, RCT	RZ monthly (RZm): RZ switched (RZs): BZ monthly (BZm): BZ switched (BZs): RZ PRN (RZp): BZ PRN (BZp): RZ monthly = RZ1 BZ monthly = BZ1 RZ PRN = RZ2 BZ PRN = BZ2	Inclusion criteria: age ≥50, visual acuity between 20/25 and 20/320, active disease Exclusion criteria: Previous treatment with AMD therapy, Previous treatment with intravenous bevacizumab, history of surgical intervention for AMD, concurrent use of systemic anti-VEGF agents, Evidence of significant uncontrolled concomitant diseases such as cardiovascular disease, nervous system, pulmonary, renal, hepatic, endocrine, or gastrointestinal disorders	RZm=146 RZs=138 BZm=135 BZs=131 RZp=287 BZp=270	2 years	<u>Patients with same dosing regimen</u> <u>Mean change in visual acuity (VA) at year 2 (no. of letters; non-inferiority limit of 5 letters):</u> RZ1: +8.8 BZ1: +7.8 RZ2: +6.7 BZ2: +5.0 P=0.21; between drug P=0.046; between regimen <u>Proportion of patients who did not have a decrease in visual acuity of 15 letters or more from baseline:</u> RZ1: 93.3% BZ1: 92.2% RZ2: 92.8% BZ2: 88.4% P=0.24 Patients with dosing regimen reassigned <u>Mean change in visual acuity (VA) at year 2</u> RZ: -1.8 BZ-3.6 P=0.03; regimen		<u>Deaths:</u> RZ: 32 (5.3%) BZ: 36 (6.1%) P=0.62 RR1.15, 95% CI (0.7-1.9) <u>Serious Systemic Events:</u> RZ: 190 (31.7%) BZ: 234 (39.9%) P=0.004 RR 1.3; 95% CI (1.07-1.57)	NS ARI 8.2% NNH 12	**Quality Rating**: Fair-poor **Internal Validity**: <u>Selection</u> –adequate randomization, Computerized treatment allocation with eligibility review preceding enrollment; <u>Performance</u> – Ophthalmologist blinded to drug assignment; patients were not informed of drug assignment but insurance and billing documents specified ranibizumab but not bevacizumab. In exit interview 48% assigned to RZ and 24.8% assigned to BZ responded they knew which drug they were on. <u>Detection</u>- VA examiner blinded; image graders masked to drug and schedule; <u>Attrition</u> – Low overall attrition (7%); ITT analysis **External Validity** <u>Recruitment</u> –Most patients were identified from the clinical practices at the participating centers and from referring ophthalmologists in the community. <u>Patient Characteristics –</u> <u>Setting</u> – in US, where many ophthalmologists already choosing bevacizumab <u>Outcomes</u> - no significant concerns

IVAN[31] MC, NI, RCT, DB	Ranibizumab monthly (RZ1) Bevacizumab (BZ1) monthly Ranibizumab as needed (RZ2) BZ as needed (BZ2) RZ = total RZ patients (RZ1 + RZ2) BZ = total BZ patients (BZ1 + BZ2)	Mean age 77.7 ±7.4 40% male Inclusions Criteria: patients aged 50+ years, newly referred for the treatment o nAMD in the first or second eye, with BCVA ≥25 letters read on a standard ETDRS chart. Exclusion criteria: long standing CNV (fibrosis >50% of the total lesion), a greatest linear diameter >6000µm, thick blood involving the centre of the fovea, 8 or more dioptres of myopia or other active ocular disease causing concurrent vision loss. Previous treatment	RZ1=157 BZ1=149 RZ2=155 BZ2=145	Two years; Interim one year results here	<u>Best corrected visual acuity, letters</u> RZ (total): 69 BZ (total): 66.1 Difference of -1.99 95% CI(-4.04 to 0.06)* Monthly (BZ+RZ): 66.8 PRN (BZ + RZ) : 68.4 Difference of -0.35 95% CI (-2.4 to 1.7)* * bevacizumab and discontinuous treatment inferior to continuous treatment if the lower limit of the 95% confidence interva is >-3.5 <u>Proportion of patients who did not have a decrease in visual acuity of 15 letters or more from baseline:</u> RZ1: 93.3% BZ1: 92.2% RZ2: 92.8% BZ2: 88.4% P=0.24	N/A NS NS	<u>Deaths:</u> RZ (total): 6 (1.9%) BZ (total): 5 (1.7%) P=0.81; drug Monthly (BZ+RZ): 1.6% PRN (BZ + RZ) : 2% P=0.74; regimen <u>Serious Systemic Events</u> RZ (total): 30 (9.6%) BZ (total): 37 (12.5%) P=0.25 RR 1.3; 95% CI (1.07-1.57) <u>Arteriothrombotic events</u>: BZ (total): 1(0.7%) RZ (total): 6(2.9%) OR 0.23; 95% CI (0.05 to 1.07); p=0.03 P=0.34; between regimens	NS NS NS ARI 2.2% NNH 45 NS	**Quality Rating**: Fair **Internal Validity**: <u>Selection</u> – Block randomization, allocations generated by computer and concealed using an internet based system; patients similar at baseline <u>Performance</u> – Participants and clinicians blinded, except ophthalmologists who injected the drug were unblinded and had no other role in trial. Nobody was blinded to whether patients were allocated to continue or stop treatment at 3 months. Adherence of 98.2% <u>Detection</u>- Trial personnel blinded <u>Attrition</u> – overall attrition of 11%; ITT analysis performed **External Validity** <u>Recruitment</u> – recruited from 23 teaching and general hospitals. <u>Patient Characteristics –</u> mean age slightly younger than other trials <u>Setting</u> – United Kingdom <u>Outcomes</u> – Small difference between drugs in BCVA from a clinical perspective

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, NI = noninferiority, MC = multicentre, SB = single blinded [2]**Drug Regimens:** RZ = ranibizumab, BZ = bevacizumab, PRN = as needed [3]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval, ARI = absolute risk increase [4]**NNT/NNH** are reported only for statistically significant results [5]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)