

Class Update: Calcium Channel Blockers (dihydropyridine and non-dihydropyridine) and Fixed-dose Combinations

Month/Year of Review: July 2015

Date of Last Review: January 2014

Current Status of PDL Class:

See **Appendix 1**.

Research Questions:

- Is there new comparative evidence between dihydropyridine or non-dihydropyridine calcium channel blockers (CCBs) in the treatment of hypertension, morbidity outcomes, or mortality?
- Is there any new evidence of comparative safety between dihydropyridine or non-dihydropyridine CCBs?
- Are there any specific populations identified (e.g., based on age, race, co-morbid conditions, etc.) in which one dihydropyridine CCB or non-dihydropyridine CCB may be more effective or associated with more harms than another CCB?
- Is there evidence that fixed-dose combination products containing a CCB are associated with improved clinical outcomes relative to the respective drugs taken concomitantly as separate formulations for the treatment of hypertension?
- Is there comparative evidence for other fixed-dose antihypertensive combination products that have not been previously reviewed by the Oregon Pharmacy and Therapeutics committee?

Purpose for Class Update:

The Pharmacy and Therapeutics (P&T) Committee has not previously reviewed the evidence of fixed-dose combination products containing a CCB. In addition, fixed-dose combination products containing a beta-blocker have not been previously reviewed. This class update will evaluate new comparative evidence of CCBs since the class was reviewed in January 2014 and will also evaluate comparative evidence of fixed-dose drug combination products containing a CCB or a beta-blocker. Direct comparative evidence between fixed-dose combination products, or between a fixed-dose combination product and its respective drugs taken concomitantly as separate formulations, will be considered for Preferred Drug List (PDL) placement.

Conclusions:

- There is moderate to high quality of evidence CCBs, particularly amlodipine, have some benefits at reducing stroke when compared to angiotensin-2 blockers (ARB).¹ The CCB, when compared to ARB, was associated with a slightly lower reduction in stroke incidence (3.2% CCB vs 3.7% ARB; relative risk [RR] 0.87; 95% CI, 0.75-0.99; p=0.04; numbers needed to treat (NNT) = 200).¹ There is low to moderate quality evidence whether CCBs are associated with greater reduction in incidence of MI relative to ARBs.¹ A fixed-effect model showed statistically significant reduction in MI with CCBs compared to ARBs (3.3% CCB vs. 3.8% ARB; RR 0.86; 95% CI, 0.76-0.98; p=0.02, NNT = 200).¹ However, the random-effects model did not demonstrate a statistical significance between the two arms. There were no significant differences in all-cause death, heart failure (HF), and blood pressure (BP) between CCBs and ARBs.¹

- There is insufficient evidence comparing relative efficacy and safety of CCBs with each other. Current guidelines continue to recommend CCBs as a first-line treatment option for hypertension.²⁻⁴
- There is insufficient evidence comparing a fixed-dose combination product containing a CCB with the respective drugs taken concomitantly as separate formulations for the treatment of hypertension.
- There is insufficient evidence comparing a fixed-dose combination product containing a beta-blocker with the respective drugs taken concomitantly as separate formulations for the treatment of hypertension. There is low quality evidence that fixed-dose combination products containing a beta-blocker with a diuretic may be inferior at lowering blood pressure than fixed-dose combination products containing a CCB with a diuretic.

Recommendations:

- Maintain at least 2 preferred dihydropyridine CCBs, including amlodipine, in the CCB PDL class.
- Maintain at least 1 preferred extended-acting and immediate-release formulation of diltiazem and verapamil in the CCB PDL class.
- Incorporate fixed-dose antihypertensive combination agents reviewed here into the “ACEI-HCTZ, ARB-HCTZ, & DRI-HCTZ” PDL class and rename the class “Combination Antihypertensives”.
- Fixed-dose combination products that contain an antihypertensive drug with a non-antihypertensive drug will be incorporated into the “Combination Antihypertensive” PDL class to simplify management of these drugs.
- Make the following fixed-dose combinations preferred: amlodipine/olmesartan; enalapril/HCTZ; lisinoprol/HCTZ; losartan/HCTZ; metoprolol succinate/HCTZ; olmesartan/amlodipine/HCTZ; olmesartan/HCTZ; and propranolol/HCTZ. Make all other non-preferred fixed-dose combination antihypertensive agents non-preferred.
- No other PMPDP changes recommended.

Previous Conclusions and Recommendations:

There is no new significant comparative evidence for the efficacy or safety of CCBs; no further review or research needed.

Background:

Hypertension is one of the most common and preventable conditions that contributes to stroke, myocardial infarction, chronic kidney disease, and premature death if left untreated.² In the United States, approximately 70 million adults are diagnosed with hypertension, but only 52% of patients have controlled hypertension.⁵ The onset of hypertension occurs at age 20 to 50 years, usually with a higher prevalence with increasing age.⁶ A normal blood pressure is defined as less than 120/80 mm Hg. Pre-hypertension is defined as a systolic blood pressure of 120 to 139 mm Hg or a diastolic blood pressure of 80 to 89 mm Hg. Diagnosis of hypertension requires two separate sphygmomanometer measurements by a health care professional of equal or greater than 140/90 mm Hg.⁶

The CCBs are one of the first-line antihypertensive agents for the management of non-complicated hypertension.² Additionally, CCBs are FDA approved for coronary artery disease (CAD) and certain arrhythmias.⁶ There are two types of CCB based on their predominant physiologic effects, dihydropyridine CCBs (nifedipine, felodipine, isradipine, nicardipine, and amlodipine) and non-dihydropyridine CCBs (verapamil and diltiazem). Dihydropyridine CCBs are potent arterial vasodilators by acting on vascular smooth muscle causing reduction in peripheral vascular resistance and lowering blood pressure. Non-dihydropyridine CCBs are depressors of cardiac contractility through inhibition of calcium ion influx across membranes of myocardial cells, but have minor effects of vasodilation.⁶

The recommended target blood pressure is less than 140/90 mm Hg in most patients. In elder patients, greater than 60 years (JNC 8) or greater than 80 years (ESH/ESC, CHEP, NICE) depending on guideline, have a recommended systolic BP of less than 150 mm Hg. For diabetes and chronic kidney disease population, current guidelines recommend less than 140/90 (JNC 8, ADA) mm Hg, however, other guidelines suggest less than 130/80 mm Hg (CHEP, KDIGO).⁶

Blood pressure management often requires additional antihypertensive therapy to achieve hypertensive goals. Current guidelines recommend adding additional drugs from other classes recommended for first-line therapy (CCBs, angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker, thiazide-type diuretic). Fixed-dose combination antihypertensive agents were developed to reduce pill burden for patients. The first fixed-dose calcium channel blocker (FD CCB) combination, Lotrel (amlodipine and benazepril), was approved by the FDA in March 1995.⁷ There are 11 FDA approved fixed-dose CCB combinations, dual and triple therapy, in the market.⁷

Methods:

A Medline literature search from October 2013 to present for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes between dihydropyridine CCBs, non-dihydropyridine CCBs, and fixed-dose combination products containing CCBs was conducted. A separate Medline literature search was conducted for fixed-dose antihypertensive combination products not previously reviewed by the Oregon P&T committee, which is limited to combinations containing a beta-blocker. The Medline search strategies used for this review are available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drugs, indications, and safety alerts. Finally, 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. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. Randomized controlled trials of fixed-dose combination products will only be included if the fixed-dose drug product is compared to both its individual components or another fixed-dose combination product.

Systematic Reviews:

Calcium channel blocker compared with angiotensin receptor blocker for patients with hypertension: a meta-analysis of randomized controlled trials¹

A meta-analysis of RCTs comparing initial antihypertensive treatment of CCBs to angiotensin receptor blockers (ARBs) on major clinical outcomes was evaluated. Eight head-to-head RCTs were identified, which assessed all-cause mortality, stroke, myocardial infarction (MI), and heart failure (HF). All but one trial studied amlodipine as the CCB treatment arm. No statistically significant difference in mortality was observed in the two arms (8.5% CCB vs. 8.6% ARB; RR 0.99; 95% CI, 0.91-1.07; p=0.72). The CCBs were more effective at reducing incidence of stroke when compared with ARBs (3.2% CCB vs. 3.7% ARB; RR 0.87; 95% CI, 0.76-0.99; p=0.04). A fixed-effect model demonstrated CCBs were superior at reducing incidence of MI compared to ARBs (3.3% CCB vs. 3.8% ARB; RR 0.86; 95% CI, 0.76-0.98; p=0.02). However, no MI reduction was observed using a random-effects model (RR 0.87; 95% CI, 0.69-1.09; p=0.22). The conflict between the two models was potentially derived by the MOSES trial; when removed, it resulted in no statistical heterogeneity (RR 0.83; 95% CI, 0.72 – 0.95; $I^2 = 0\%$). Lastly, the MOSES trial was a PROBE study which has higher risk of investigator and patient bias compared to the other double-blinded studies. There was no statistically significant differences in incidence of HF between the CCBs and ARBs (5% CCB vs. 3.9% ARB; RR 1.4; 95% CI, 0.99-1.98; p=0.06).

New Guidelines:**2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)**²

The Joint National Committee updated their 2003 JNC 7 guideline recommendations in 2014. The JNC 8 emphasizes evidence-based recommendations and targeted blood pressure control based on specific patient populations. The recommended target blood pressure in adult patients less than 60 years of age is less than 140/90 mm Hg. In patients 60 years of age or older, the recommended target blood pressure is less than 150/90 mm Hg, although there are limited data to support this recommendation. The JNC 8 based their targeted blood pressure goals in diabetes patients from evidence in the ACCORD-BP trial which showed no difference in clinical outcomes between a goal SBP <140 mm Hg compared to SBP <120 mm Hg. However, data are limited to be able to identify the optimum blood pressure goal for various populations. Additionally, patients under the age of 60 years of age with chronic kidney disease, with or without diabetes, have a targeted blood pressure goal of less than 140/90 mm Hg. First-line treatment options for non-complicated hypertension include CCBs, Angiotensin-Converting Enzyme Inhibitors (ACE-Is), ARBs, or thiazide diuretics.³

The 2015 Canadian Hypertension Education Program (CHEP)³

The Hypertension Canada organization updated their 2014 CHEP guideline in 2015. The CHEP 2015 hypertension guideline utilizes an algorithm that requires out-of-office measurements along with clinic visits for diagnosis of hypertension. The recommended blood pressure target in diabetes patients is less than 130/80 mm Hg. In patients less than 80 years old, including CKD patients, the recommended target blood pressure is less than 140/90 mm Hg. Elderly patients older than 80 years of age have a target systolic blood pressure goal of less than 150 mm Hg. CCBs, specifically long-acting DHP-CCBs, are a recommended first-line treatment option for hypertension as both a monotherapy and dual therapy.

Clinical Practice Guidelines for the Management of Hypertension in the Community: A Statement by the American Society of Hypertension and the International Society of Hypertension⁴

The American Society of Hypertension and International Society of Hypertension updated their 2013 guideline recommendations in 2014. Recommendations were based on evidence and expert opinion. Stage 1 hypertension is defined as SBP of 140 to 159 mm Hg and DBP of 90 to 99 mm Hg. The CCBs are the recommended first-line treatment option in African Americans, regardless of hypertension stage, and non-black patients over the age of 60 years with stage 1 hypertension. Stage 2 hypertension is defined as blood pressure greater than or equal to 160/100 mm Hg. The CCBs are recommended as a first-line therapy option in combination with either an ACE-I or ARB for patients with stage 2 hypertension.

New Safety Alerts:

None identified.

New Formulations or Indications:

None Identified.

Randomized Controlled Trials:

No clinical trials of a fixed-dose combination product containing a CCB compared to its respective drugs taken concomitantly as separate formulations were identified. Three potentially relevant clinical trials evaluating a CCB and assessing a clinically relevant outcome were evaluated from the literature search. After

further review, two trials were excluded. The remaining trial is briefly described in the table 1 below. The abstract is included in **Appendix 2**. In addition, abstracts of trials comparing a fixed-dose combination that included a beta-blocker are listed in **Appendix 2**.

Table 1: Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Outcome	Results	Quality*
Reisin, et al. ⁸	Chlorthalidone (C) vs. Amlodipine (A) vs. Lisinopril (L) Dosing: Titrate dose of blinded study drug and adding open-label step two (atenolol, clonidine, or reserpine) or step three (hydralazine) agents as necessary to obtain a BP goal of <140/90 mm Hg.	Age ≥55 yo, HTN men & women, Risk factor for CHD >1	Primary: Composite of fatal CHD or nonfatal MI Secondary: All-cause mortality, fatal and nonfatal stroke, combined CHD, and combined CVD	<p>Primary: (A vs C) Fatal CHD or nonfatal MI</p> <ul style="list-style-type: none"> - BMI <25: HR 1.04, 0.86 – 1.26 (p=0.669) - BMI 25-29: HR 1.04, 0.91 – 1.19 (p=0.568) - BMI ≥30: HR 0.91, 0.79 – 1.05 (p=0.192) <p>Secondary: (A vs C) All-cause mortality</p> <ul style="list-style-type: none"> - BMI <25: HR 1.00, 0.88 – 1.14 - BMI 25-29: HR 0.98, 0.87 – 1.09 - BMI ≥30: HR 0.90, 0.81 – 1.01 <p>*Combined CHD</p> <ul style="list-style-type: none"> - BMI <25: HR 1.02, 0.87 – 1.18 (p=0.840) - BMI 25-29: HR 1.04, 0.94 – 1.15 (p=0.430) - BMI ≥30: HR 0.96, 0.87 – 1.06 (p=0.96) <p>**Combined CVD</p> <ul style="list-style-type: none"> - BMI <25: HR 1.07, 0.95 – 1.19 (p=0.264) - BMI 25-29: HR 1.02, 0.94 – 1.11 (p=0.606) - BMI ≥30: HR 1.03, 0.96 – 1.12 (p=0.417) <p>Stroke</p> <ul style="list-style-type: none"> - BMI <25: HR 0.97, 0.74 – 1.25 (p=0.792) - BMI 25-29: HR 0.89, 0.72 – 1.09 (p=0.256) - BMI ≥30: HR 0.95, 0.78 – 1.16 (p=0.95) <p>Heart failure exacerbation</p> <ul style="list-style-type: none"> - BMI <25: HR 1.34, 1.07 – 1.68 (p=0.012) - BMI 25-29: HR 1.23, 1.03 – 1.46 (p=0.019) - BMI ≥30: HR 1.48, 1.28 – 1.71 (p <0.001) 	Poor

Abbreviations: BMI = body mass index; CHD = coronary heart disease; CVD = cardiovascular disease; HR = hazard ratio; HTN = hypertension; MI = myocardial infarction; p = p-value

*Combined CHD is defined as the primary outcome, coronary revascularization, or hospitalized angina.

**Combined CVD is defined as combined CHD, stroke, treated angina, heart failure (fatal, hospitalized, or not hospitalized), or peripheral artery disease.

***Quality of each study is ranked as “Good”, “Fair” or “Poor” based on DURM Standard Methods for Quality Assessment and Grading the Evidence.

References:

1. Wu L, Deng SB, She Q. Calcium channel blocker compared with angiotensin receptor blocker for patients with hypertension: a meta-analysis of randomized controlled trials. *J Clin Hypertens (Greenwich)*. 2014;16(11):838-45.
2. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311(5):507-20.
3. Daskalopoulou SS, Rabi DM, Zarnke KB, et al. The 2015 Canadian hypertension education program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. *Can J Cardiol*. 2015;31(5):549-68.
4. Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community a statement by the American Society of Hypertension and the International Society of Hypertension. *J Hypertension*. 2014;32(1):3-15.
5. High blood pressure facts. CDC. 2015. Available at: <http://www.cdc.gov/bloodpressure/facts.htm>. Accessed April 14, 2015.
6. Hypertension. Dynamed, 2015. Available at: <http://web.b.ebscohost.com/dynamed/detail?vid=3&sid=f0818303-8861-46f0-8d7a-af69a2bcefe3%40sessionmgr113&hid=128&bdata=JnNpdGU9ZHluYW1lZC1saXZlJnNjb3BIPXNpdGU%3d#db=dme&AN=115345&anchor=Treatment>. Accessed June 2, 2015.
7. FDA Approved Drug Products. FDA. 2015. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo. Accessed June 2, 2015.
8. Reisin E, Graves JW, Yamal JM, et al. Blood pressure control and cardiovascular outcomes in normal-weight, overweight, and obese hypertensive patients treated with three different antihypertensives in ALLHAT. *J Hypertension*. 2014;32(7):1503-13.

Appendix 1: Current Preferred Drug List

Calcium Channel Blockers, Dihydropyridine

Formulation	Brand	Generic	PDL
TABLET	AMLODIPINE BESYLATE	AMLODIPINE BESYLATE	Y
TABLET	NORVASC	AMLODIPINE BESYLATE	Y
CAPSULE	NICARDIPINE HCL	NICARDIPINE HCL	Y
TABLET ER	ADALAT CC	NIFEDIPINE	Y
TABLET ER	AFEDITAB CR	NIFEDIPINE	Y
TABLET ER	NIFEDIPINE	NIFEDIPINE	Y
TABLET ER	NIFEDIPINE ER	NIFEDIPINE	Y
TABLET ER	ADALAT CC	NIFEDIPINE	Y
TABLET ER	AFEDITAB CR	NIFEDIPINE	Y
TAB ER 24	NIFEDICAL XL	NIFEDIPINE	Y
TAB ER 24	NIFEDIPINE ER	NIFEDIPINE	Y
TAB ER 24	NIFEDIPINE XL	NIFEDIPINE	Y
TAB ER 24	PROCARDIA XL	NIFEDIPINE	Y
TAB ER 24H	FELODIPINE ER	FELODIPINE	N
CAPSULE	DYNACIRC	ISRADIPINE	N
CAPSULE	ISRADIPINE	ISRADIPINE	N
CAPSULE ER	CARDENE SR	NICARDIPINE HCL	N
CAPSULE	NIFEDIPINE	NIFEDIPINE	N
CAPSULE	PROCARDIA	NIFEDIPINE	N
TAB ER 24H	NISOLDIPINE	NISOLDIPINE	N
TAB ER 24H	SULAR	NISOLDIPINE	N

Calcium Channel Blockers, non-Dihydropyridine

Formulation	Brand	Generic	PDL
TABLET	CALAN	VERAPAMIL HCL	Y
TABLET	VERAPAMIL HCL	VERAPAMIL HCL	Y
TABLET ER	CALAN SR	VERAPAMIL HCL	Y
TABLET ER	VERAPAMIL ER	VERAPAMIL HCL	Y
TABLET ER	ISOPTIN S.R.	VERAPAMIL HCL	Y
CAP24H PEL	VERAPAMIL ER	VERAPAMIL HCL	Y
CAP24H PEL	VERAPAMIL SR	VERAPAMIL HCL	Y
CAP24H PEL	VERELAN	VERAPAMIL HCL	Y
TABLET ER	CALAN SR	VERAPAMIL HCL	Y
TABLET ER	ISOPTIN S.R.	VERAPAMIL HCL	Y
TABLET ER	VERAPAMIL ER	VERAPAMIL HCL	Y
CAP24H PEL	VERAPAMIL HCL	VERAPAMIL HCL	Y
CAP ER 12H	CARDIZEM SR	DILTIAZEM HCL	Y
CAP ER 12H	DILTIAZEM 12HR ER	DILTIAZEM HCL	Y
CAP ER 12H	DILTIAZEM HCL	DILTIAZEM HCL	Y
TABLET	CARDIZEM	DILTIAZEM HCL	Y
TABLET	DILTIAZEM HCL	DILTIAZEM HCL	Y
CAP ER 24H	CARDIZEM CD	DILTIAZEM HCL	Y
CAP ER 24H	CARTIA XT	DILTIAZEM HCL	Y
CAP ER 24H	DILTIAZEM 24HR CD	DILTIAZEM HCL	Y
CAP ER 24H	DILTIAZEM 24HR ER	DILTIAZEM HCL	Y
CAP ER 24H	DILTIAZEM HCL	DILTIAZEM HCL	Y
CAP ER DEG	DILTIAZEM ER	DILTIAZEM HCL	Y
CAP ER DEG	DILT-XR	DILTIAZEM HCL	Y
CAP ER DEG	DILACOR XR	DILTIAZEM HCL	Y

CAPSULE ER	DILTIAZEM ER	DILTIAZEM HCL	Y
CAPSULE ER	TAZTIA XT	DILTIAZEM HCL	Y
CAPSULE ER	TIAZAC	DILTIAZEM HCL	Y
CAPSULE ER	TAZTIA XT	DILTIAZEM HCL	Y
CAP24H PCT	VERAPAMIL ER PM	VERAPAMIL HCL	N
CAP24H PCT	VERELAN PM	VERAPAMIL HCL	N
TAB ER 24H	CARDIZEM LA	DILTIAZEM HCL	N
TAB ER 24H	DILTIAZEM ER	DILTIAZEM HCL	N
TAB ER 24H	MATZIM LA	DILTIAZEM HCL	N

Calcium Channel Blocker Fixed-dose Combination Products
Amlodipine/aliskiren (TEKAMLO)
Amlodipine/atorvastatin (CADUET)
Amlodipine/benazepril (LOTREL, generic)
Amlodipine/olmesartan (AZOR)
Amlodipine/perindopril (PRESTALIA)
Amlodipine/telmisartan (TWYNSTA)
Amlodipine/valsartan (EXFORGE, generic)
Amlodipine/aliskiren/hydrochlorothiazide (AMTURNIDE)
Amlodipine/olmesartan/hydrochlorothiazide (TRIBENZOR)
Amlodipine/valsartan/hydrochlorothiazide (EXFORGE HCT)
Verapamil/trandolapril (TARKA)

Appendix 2: Abstracts of Clinical Trials

Reisin E, Graves JW, Yamal JM, et al. Blood pressure control and cardiovascular outcomes in normal-weight, overweight, and obese hypertensive patients treated with three different antihypertensives in ALLHAT. *J Hypertens.* 2014;32(7):1503-13.

Objective: Epidemiologically, there is a strong relationship between BMI and blood pressure (BP) levels. We prospectively examined randomization to first-step chlorthalidone, a thiazide-type diuretic; amlodipine, a calcium-channel blocker; and lisinopril, an angiotensin-converting enzyme inhibitor, on BP control and cardiovascular outcomes in a hypertensive cohort stratified by baseline BMI (kg/m²) [normal weight (BMI <25), overweight (BMI = 25-29.9), and obese (BMI >30)]. Methods: In a randomized, double-blind, practice-based Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, 33,357 hypertensive participants, aged at least 55 years, were followed for an average of 4.9 years, for a primary outcome of fatal coronary heart disease or nonfatal myocardial infarction, and secondary outcomes of stroke, heart failure, combined cardiovascular disease, mortality, and renal failure. Results: Of participants, 37.9% were overweight and 42.1% were obese at randomization. For each medication, BP control (<140/90 mmHg) was equivalent in each BMI stratum. At the fifth year, 66.1, 66.5, and 65.1% of normal-weight, overweight, and obese participants, respectively, were controlled. Those randomized to chlorthalidone had highest BP control (67.2, 68.3, and 68.4%, respectively) and to lisinopril the lowest (60.4, 63.2, and 59.6%, respectively) in each BMI stratum. A significant interaction (P = 0.004) suggests a lower coronary heart disease risk in the obese for lisinopril versus chlorthalidone (hazard ratio 0.85, 95% confidence interval 0.74-0.98) and a significant interaction (P = 0.011) suggests a higher risk of end-stage renal disease for amlodipine versus chlorthalidone in obese participants (hazard ratio 1.49, 95% confidence interval 1.06-2.08). However, these results were not consistent among other outcomes. Conclusion: BMI status does not modify the effects of antihypertensive medications on BP control or cardiovascular disease outcomes.

Beta-blocker Combinations

Radchenko GD, Sirenko YM, Kushnir SM, et al. Comparative effectiveness of a fixed-dose combination of losartan+HCTZ versus bisoprolol+HCTZ in patients with moderate-to-severe hypertension: results of the 6-month ELIZA trial. *Vascular Health and Risk Management*. 2013;9:535–549.

Background: The aim of this study was to compare the antihypertensive efficacy of losartan 100 mg + hydrochlorothiazide (HCTZ) 25 mg versus bisoprolol 10 mg + HCTZ 25 mg and their influence on arterial stiffness and central blood pressure (BP). Methods: Of 60 patients with a mean BP of $173.3 \pm 1.7/98.4 \pm 1.2$ mmHg, 59 were randomized to losartan + HCTZ (n = 32) or bisoprolol + HCTZ (n = 27). Amlodipine was added if target BP was not achieved at 1 month, and doxazosin was added if target BP was not achieved after 3 months. Body mass index, office and 24-hour ambulatory BP, pulse wave velocity (carotid-femoral [PWVE] and radial [PWVM]), noninvasive central systolic BP, augmentation index (Aix), laboratory investigations, and electrocardiography were done at baseline and after 6 months of treatment. Results: Losartan + HCTZ was as effective as bisoprolol + HCTZ, with target office BP achieved in 96.9% and 92.6% of patients and target 24-hour BP in 75% and 66.7% of patients, respectively, after 6 months. Effective treatment of BP led to significant lowering of central systolic BP, but this was decreased to a significantly ($p < 0.05$) greater extent by losartan + HCTZ (-23.0 ± 2.3 mmHg) than by bisoprolol + HCTZ (-15.4 ± 2.9 mmHg) despite equal lowering of brachial BP. Factors correlated with central systolic BP and its lowering differed between the treatment groups. Losartan + HCTZ did not alter arterial stiffness patterns significantly, but bisoprolol + HCTZ significantly increased Aix. We noted differences in Δ PWVE, Δ PWVM, and Δ Aix between the groups in favor of losartan + HCTZ. Decreased heart rate was associated with higher central systolic BP and Aix in the bisoprolol + HCTZ group, but was not associated with increased Aix in the losartan + HCTZ group. Conclusion: Although both treatments decreased both office and 24-hour BP, losartan + HCTZ significantly decreased central systolic BP and had a more positive influence on pulse wave velocity, with a less negative effect of decreased heart rate on Aix and central systolic BP.

Scholze J, Grimm E, Herrmann D, et al. Optimal treatment of obesity-related hypertension: the Hypertension-Obesity-Sibutramine (HOS) Study. *Circulation*. 2007;115:1991-98.

Background: Current guidelines for the treatment of hypertension do not provide specific recommendations for obese hypertensive patients. To identify an optimal treatment regimen for obese hypertensive patients, we studied the interactions between a drug-based weight loss approach by sibutramine and different antihypertensive drug regimens. Methods and Results: This was a prospective, 16-week double-blind placebo-controlled randomized multicenter study in 171 obese hypertensive patients. After a 2-week run-in period, patients receiving 1 of the 3 antihypertensive combination therapies (felodipine 5 mg/ramipril 5 mg [n=57], verapamil 180 mg/trandolapril 2 mg [n=55], or metoprolol succinate 95 mg/hydrochlorothiazide 12.5 mg [metoprolol/hydrochlorothiazide; n=59]) were assigned randomly to sibutramine (15 mg) or placebo. Sibutramine treatment resulted in a significantly greater decrease in body weight, body mass index, and waist circumference and a significant increase in diastolic blood pressure during 24-hour blood pressure monitoring compared with placebo treatment. Sibutramine-induced weight loss and reduction of visceral obesity were markedly attenuated in the metoprolol/hydrochlorothiazide group compared with the other groups. Consistently, improvement in glucose tolerance and hypertriglyceridemia by sibutramine was abrogated in the cohort treated with metoprolol/hydrochlorothiazide compared with the other groups. Conclusions: The present study demonstrates for the first time that an antihypertensive combination therapy regimen with angiotensin-converting enzyme inhibitors and calcium channel blockers is more advantageous than a beta-blocker/diuretic-based regimen in supporting the weight-reducing actions and concomitant metabolic changes induced by sibutramine in obese hypertensive patients. These data may help to develop future comprehensive treatment strategies and guidelines for this high-risk patient population.

Breithaupt-Grogler K, Gerhardt G, Lehmann G, et al. Blood pressure and aortic elastic properties--verapamil SR/trandolapril compared to a metoprolol/hydrochlorothiazide combination therapy. *International Journal of Clinical Pharmacology & Therapeutics*. 1998;36(8):425-31.

The effects of 2 fixed antihypertensive combination drugs on blood pressure and aortic elastic properties were compared in 2 parallel groups. Twenty-six patients for 6 months received a calcium antagonist plus ACE inhibitor (verapamil SR 180 mg/trandolapril 1 mg (Vera/Tran)) and 25 patients a beta-adrenoceptor antagonist plus diuretic (metoprolol 100 mg/hydrochlorothiazide 12.5 mg (Meto/HCTZ)). In addition to blood pressure (SBP, DBP), carotidofemoral pulse wave velocity (PWV) was assessed non-invasively. Total peripheral resistance (TPR) was determined from cardiac output derived by electrical impedance cardiography. Sitting DBP decreased for -14.4 mmHg following Vera/Tran compared with -9.2 mmHg following Meto/HCTZ ($p = 0.02$ for difference between treatments). Blood pressure was normalized (i.e. DBP < 90 mmHg) in 69% of patients with Vera/Tran and in 52% with Meto/HCTZ. PWV was lowered with Vera/Tran to a higher extent than with Meto/HCTZ (differences between group means -0.46 to -0.98 m/sec, statistically not significant). Vera/Tran induced a decrease in TPR of about 15% of baseline values, whereas Meto/HCTZ showed no influence. Treatment-related adverse events following Meto/HCTZ were bradycardia and associated symptoms; following Vera/Tran these were cough and edema in 1 case each. In the Meto/HCTZ group, there were more withdrawals/drop-outs (9/25) than in the Vera/Tran group (2/26). The somewhat more intense reduction in PWV with Vera/Tran is indicative of an increase in aortic elastic properties associated with the more potent decrease in BP. In the present study, the combination of calcium antagonist plus ACE inhibitor was found to be an effective and well tolerated antihypertensive regimen and in these respects appears to have some advantages compared with a combination of beta-blocker plus diuretic.

Stimpel M, Koch B. Antihypertensive treatment with moexipril plus HCTZ vs metoprolol plus HCTZ in patients with mild-to-moderate hypertension. *Journal of Human Hypertension*. 1997;11(2):133-7.

Combination therapy with the new ACE inhibitor moexipril plus hydrochlorothiazide (HCTZ) results in significant blood pressure (BP) reductions. This study compares the efficacy and safety of moexipril plus HCTZ to that of a standard combination treatment in patients with mild-to-moderate hypertension. After a 1 month placebo run-in period, 140 hypertensive patients whose sitting diastolic BP (DBP) averaged 95-114 mm Hg were randomized to receive either once daily moexipril 7.5 mg/HCTZ 12.5 mg or metoprolol 100 mg/HCTZ 12.5 mg for the following 12-week double-blind treatment period. At biweekly visits BP was controlled sphygmomanometrically and the occurrence of adverse events (AE) was documented. At study endpoint adjusted mean reductions in sitting systolic/diastolic BP seen with both combinations were -17.6 mm Hg/-12.8 mm Hg and -17.2 mm Hg/-13.9 mm Hg in the moexipril/HCTZ and metoprolol/HCTZ groups, respectively. The response rate to both kinds of combinations were very similar, 69% and 74% in the moexipril/HCTZ and metoprolol/HCTZ groups, respectively. The percentage of patients which experienced one or more AEs were 46% in the moexipril/HCTZ and 61% in the metoprolol/HCTZ group. Headache and cough which are the most frequently reported AEs after treatment with ACE inhibitors were seen in 9% and 10% of the patients in the moexipril/HCTZ group compared to 10% and 4% in the metoprolol/HCTZ group. The study indicates that the combination of moexipril 7.5 mg plus HCTZ 12.5 mg is as efficacious and safe as metoprolol 100 mg plus HCTZ 12.5 mg in the treatment of mild-to-moderate hypertension.

de Leeuw PW, Notter T, Zilles P. Comparison of different fixed antihypertensive combination drugs: a double-blind, placebo-controlled parallel group study. *Journal of Hypertension*. 1997;15(1):87-91.

To compare the effects of fixed-dose preparations containing 180 mg sustained-release verapamil and 2 mg trandolapril, 100/25 mg atenolol/chlorthalidone, 20/12.5 mg lisinopril/hydrochlorothiazide and placebo in patients with essential hypertension. DESIGN: A 4-week placebo run-in period followed by a double-blind, placebo-controlled parallel group study lasting 8 weeks. SETTING: Office practices (21 centres). PATIENTS: Patients with essential hypertension (World Health Organization grades I or II); supine diastolic blood pressure 101-114 mmHg in week 4 of the run-in period; 215 patients were enrolled, of whom 205 were assigned randomly to double-blind therapy. MAIN OUTCOME MEASURES: Reduction in supine and standing blood pressures. RESULTS: All three active treatments with a single daily dose were significantly more effective than was placebo in reducing the blood pressure of seated subjects ($P=0.0001$). The reductions in sitting diastolic blood pressure (DBP) from baseline to the last visit with each active treatment were

comparable: 13 mmHg [95% confidence interval (CI) 16-9] with sustained-release verapamil/trandolapril, 13 mmHg (16-9) with atenolol/chlorthalidone and 12 mmHg (15-8) with lisinopril/hydrochlorothiazide. Normalization of blood pressure (DBP < 90 mmHg) was observed in 48% of patients with sustained-release verapamil/trandolapril, in 46% with atenolol/chlorthalidone and in 40% with lisinopril/hydrochlorothiazide. Response rates (normalization of DBP or a reduction in DBP by > 10 mmHg) with each active treatment were 72% for sustained-release verapamil/trandolapril, 76% for atenolol/chlorthalidone and 69% for lisinopril/hydrochlorothiazide. All three active treatments were tolerated well. CONCLUSION: This study demonstrates that the low-dose combination sustained-release verapamil/trandolapril may be a suitable alternative for combinations containing a thiazide diuretic or a beta-blocker for longer term management of hypertensive patients for whom combination therapy is indicated.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to May Week 3 2015, [Database Field Guide] Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations May 22, 2015

- 1 exp Calcium Channel Blockers/ 33458
- 2 exp Amlodipine/ 2657
- 3 exp Nifedipine/ 5173
- 4 exp Nicardipine/ 922
- 5 exp Isradipine/ 401
- 6 exp Felodipine/ 494
- 7 exp Nisoldipine/ 217
- 8 exp Diltiazem/ 2147
- 9 exp Verapamil/ 5395
- 10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 33458
- 11 limit 10 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or pragmatic clinical trial or randomized controlled trial) 7832
- 12 limit 11 to (english language and yr="2013 -Current") 431

11

Ovid MEDLINE(R) without Revisions 1996 to January Week 3 2015, [Database Field Guide] Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 22, 2015

- 1 exp Calcium Channel Blockers/ 33132
- 2 exp Amlodipine/ 2609
- 3 exp Nifedipine/ 5149
- 4 exp Nicardipine/ 912
- 5 exp Isradipine/ 399
- 6 exp Felodipine/ 488
- 7 exp Nisoldipine/ 216
- 8 exp Diltiazem/ 2132
- 9 exp Verapamil/ 5352
- 10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 33132
- 11 limit 10 to (meta analysis or systematic reviews) 633
- 12 limit 11 to (english language and yr="2013 -Current") 73

Ovid MEDLINE(R) without Revisions 1996 to May Week 3 2015, [Database Field Guide] Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations May 22, 2015

- 1 exp Verapamil/ 5395
- 2 trandolapril.mp./ 561
- 3 combination.mp./ 508676
- 4 1 and 2 and 3/ 110
- 5 exp Amlodipine/ 2657

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- 6 atrovastatin.mp./ 6780
 - 7 3 and 5 and 6/ 94
 - 8 olmesartan.mp./ 1181
 - 9 3 and 5 and 8/ 111
 - 10 aliskiren.mp./ 960
 11. 3 and 5 and 10/ 42
 - 12 benazepril/ 550
 - 13 3 and 5 and 12/ 83
 - 14 exp perindopril/ 1150
 - 15 3 and 5 and 14/ 54
 - 16 telmisartan.mp./ 1765
 - 17 3 and 5 and 16/ 60
 - 18 valsartan.mp./ 2518
 - 19 3 and 5 and 18/ 149
 - 20 exp felodipine/ 494
 - 21 exp enalapril/ 3117
 - 22 3 and 20 and 21/ 11
 - 23 4 or 7 or 9 or 11 or 13 or 15 or 17 or 19 or 22/ 669
 - 24 limit 23 to (English language and (clinical trial, phase III or clinical trial, phase IV or comparative study or controlled clinical trial or pragmatic clinical trial or randomized controlled trial))/ 383

- 1 exp Atenolol/ 4890
- 2 exp Bisoprolol/ 863
- 3 exp Metoprolol/ 4902
- 4 exp Propranolol/ 31093
- 5 exp Chlorthalidone/ 1365
- 6 exp Hydrochlorothiazide/ 6060
- 7 1 and 5 138
- 8 2 and 6 47
- 9 3 and 6 101
- 10 4 and 6 235
- 11 7 or 8 or 9 or 10 508
- 12 combination.mp. or exp Drug Therapy, Combination/ 729776
- 13 11 and 12 273
- 14 limit 13 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or pragmatic clinical trial or randomized controlled trial) 192

Evidence for nadolol/bendroflumethiazide was also manually searched and considered.