

Drug Class Review on Calcium Channel Blockers



Update #3: Preliminary Scan Report 3

April 2009

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

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OBJECTIVE:

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

Date of Last Update:

Original Final Report March 2005 (searches through February 2004)

Date of Last Update Scans:

Preliminary Update Scan #2: December 2007

Preliminary Update Scan #1: December 2006

SCOPE AND KEY QUESTIONS:

The purpose of this review is to compare the benefits and harms of calcium channel blockers when used to treat hypertension, supraventricular arrhythmias, angina or left ventricular dysfunction. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. Do CCBs differ in effectiveness in the treatment of adult patients with essential hypertension (blood pressure \geq 140/90 mm Hg), angina, supraventricular arrhythmias, or systolic dysfunction (left ventricular ejection fraction [LVEF] <45%)?
2. Do CCBs differ in their safety or adverse effects in the treatment of adult patients with essential hypertension (blood pressure \geq 140/90 mm Hg), angina, supraventricular arrhythmias, or systolic dysfunction (LVEF<45%)?
3. Based on demographics (age, racial groups, gender), other medications, or comorbidities, are there subgroups of patients for which one CCB is more effective or is associated with fewer adverse effects?

Inclusion Criteria

Population

Adults with hypertension (blood pressure \geq 140/90 mm Hg), angina, supraventricular arrhythmia or supraventricular tachycardia (SVT), and systolic dysfunction (LVEF <45%).

Interventions

Amlodipine
Bepridil
Diltiazem
Felodipine
Isradipine
Nicardipine
Nifedipine
Nisoldipine
Verapamil

Outcomes

Hypertension

All cause mortality
Cardiovascular (CV) disease mortality
CV events (stroke, MI, development of CHF)
Development of renal failure (end stage renal disease/dialysis/transplant/ clinically significant, permanent increase in serum creatinine or decrease in creatinine clearance)
Quality of Life

Angina

All cause mortality
Cardiovascular (CV) disease mortality
CV events (stroke, MI, development of CHF)
Symptoms
Quality of Life

Supraventricular Arrhythmias

All cause mortality
Cardiovascular (CV) disease mortality
Stroke
Symptoms (rate or rhythm control)
Quality of Life

Left-ventricular Dysfunction

All cause mortality
Cardiovascular (CV) disease mortality
CV events (stroke, MI, development of CHF)
Symptoms
Quality of Life

METHODS

Literature Search

To identify new potentially relevant citations, we searched MEDLINE (December 2007 to April 2009). We used terms for included drugs and limits for humans, English and controlled clinical trials. We searched FDA and Health Canada websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote 9.0).

Study Selection

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

RESULTS

Overview

We identified 139 citations. Of those, there are 4 new potentially relevant trials, 3 publications that provide outcomes from trials that had still been in progress at the time of our last update (CASE-J, ASCOT), and 6 publications of subgroup analyses from previously included trials (ALLHAT, VALUE, JMIC-B). Taken together with the 27 publications identified in the previous preliminary update scans, now there are a total of 40.

New Drugs

In January 2008, FDA approved a change in the formulation of extended-release nisoldipine to lower the strengths and replace all current tablets (i.e., 10 mg, 20 mg, 30 mg and 40 mg) with new lower, bioequivalent strengths (i.e., 8.5 mg, 17 mg, 25.5 mg and 34 mg)

New Indications

None

New Safety Alerts

None

APPENDIX A

New trials

Jamerson, K., M. A. Weber, et al. (2008). "Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients.[see comment]." New England Journal of Medicine **359**(23): 2417-28.

BACKGROUND: The optimal combination drug therapy for hypertension is not established, although current U.S. guidelines recommend inclusion of a diuretic. We hypothesized that treatment with the combination of an angiotensin-converting-enzyme (ACE) inhibitor and a dihydropyridine calcium-channel blocker would be more effective in reducing the rate of cardiovascular events than treatment with an ACE inhibitor plus a thiazide diuretic. **METHODS:** In a randomized, double-blind trial, we assigned 11,506 patients with hypertension who were at high risk for cardiovascular events to receive treatment with either benazepril plus amlodipine or benazepril plus hydrochlorothiazide. The primary end point was the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization. **RESULTS:** The baseline characteristics of the two groups were similar. The trial was terminated early after a mean follow-up of 36 months, when the boundary of the prespecified stopping rule was exceeded. Mean blood pressures after dose adjustment were 131.6/73.3 mm Hg in the benazepril-amlodipine group and 132.5/74.4 mm Hg in the benazepril-hydrochlorothiazide group. There were 552 primary-outcome events in the benazepril-amlodipine group (9.6%) and 679 in the benazepril-hydrochlorothiazide group (11.8%), representing an absolute risk reduction with benazepril-amlodipine therapy of 2.2% and a relative risk reduction of 19.6% (hazard ratio, 0.80, 95% confidence interval [CI], 0.72 to 0.90; $P < 0.001$). For the secondary end point of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke, the hazard ratio was 0.79 (95% CI, 0.67 to 0.92; $P = 0.002$). Rates of adverse events were consistent with those observed from clinical experience with the study drugs. **CONCLUSIONS:** The benazepril-amlodipine combination was superior to the benazepril-hydrochlorothiazide combination in reducing cardiovascular events in patients with hypertension who were at high risk for such events. (ClinicalTrials.gov number, NCT00170950.) 2008 Massachusetts Medical Society

Nakamura, T., T. Inoue, et al. (2008). "Comparison of renal and vascular protective effects between telmisartan and amlodipine in hypertensive patients with chronic kidney disease with mild renal insufficiency." Hypertension Research - Clinical & Experimental **31**(5): 841-50.

The present study was conducted to compare the renal and vascular protective effects of telmisartan and amlodipine in untreated hypertensive chronic kidney disease (CKD) patients with moderate renal insufficiency. Thirty hypertensive CKD patients were randomly assigned to receive telmisartan 40 mg ($n = 15$) or amlodipine 5 mg ($n = 15$) once daily for 12 months. Changes in blood pressure, serum creatinine, 24-h creatinine clearance (Ccr), proteinuria, brachial-ankle pulse wave velocity (baPWV), intima-media

thickness (IMT), plasma interleukin-6 (IL-6), plasma matrix metalloproteinase (MMP)-9 and lipid profiles were monitored in all patients. Before treatment, there were no significant differences in these parameters between the telmisartan and amlodipine groups. Over the 12 month observation period, blood pressure decreased equally in both groups. However, serum creatinine, proteinuria, baPWV, IMT, plasma levels of IL-6 and MMP-9 and total cholesterol decreased and 24-h Ccr increased more strikingly in the telmisartan group than the amlodipine group. These data suggest that telmisartan is more effective than amlodipine for protecting renovascular functions, and potentially for ameliorating atherosclerosis, in hypertensive CKD patients with moderate renal insufficiency.

Nakayama, K., Y. Kuwabara, et al. (2008). "Valsartan Amlodipine Randomized Trial (VART): design, methods, and preliminary results." Hypertension Research - Clinical & Experimental **31**(1): 21-8.

Antihypertensive therapy has been well established to reduce hypertension related morbidity and mortality, but the optimal therapy for Japanese patients remains unknown. The Valsartan Amlodipine Randomized Trial (VART), a prospective randomized open-label trial, was designed to determine whether treatment with an angiotensin II type 1 receptor blocker (valsartan) or a calcium channel blocker (amlodipine) lowers cardiovascular disease events in essential hypertensives in Japan. Registration, randomization and data entry were performed over the Internet. The minimization method (to control for age, gender, blood pressure level and history) was used at random assignment to ensure that the background factors were equivalent between the groups at baseline. After the registration, patients were followed-up for cardiovascular events (primary endpoints), echocardiography, (123)I-metaiodobenzylguanidine (MIBG) imaging, laboratory tests and blood pressure for 3 years. Currently, 797 patients have been enrolled and assigned to two groups: a valsartan (n=399) and an amlodipine (n=398) group. At baseline, controlled factors (age, gender, blood pressure level, and left ventricular hypertrophy) and the proportions of patients with diabetes and hyperlipidemia were equally allocated. At 12 months, both drugs evenly and significantly lowered blood pressure to the target level (valsartan: 133/79 mmHg; amlodipine: 132/79 mmHg). In conclusion, by combining the data on cardiovascular events with the results of echocardiographic, radionuclide imaging, and blood/urine studies, the VART study will provide mechanistic insights into the clinical outcomes and treatment effects of the trial.

Tepel, M., W. Hopfenmueller, et al. (2008). "Effect of amlodipine on cardiovascular events in hypertensive haemodialysis patients." Nephrology Dialysis Transplantation **23**(11): 3605-12.

BACKGROUND: Hypertensive haemodialysis patients may be at a high risk for cardiovascular events. This study was undertaken to ascertain whether the calcium channel blocker amlodipine reduces mortality and cardiovascular events in these high-risk patients. METHODS: We evaluated the effects of amlodipine on cardiovascular events in 251 hypertensive haemodialysis patients in an investigator-designed, prospective, randomized, double-blind, placebo-controlled, multicenter trial. One

hundred and twenty-three patients were randomly assigned to amlodipine (10 mg once daily) and 128 to placebo. The primary endpoint was mortality from any cause. The secondary endpoint was a composite variable consisting of mortality from any cause or cardiovascular event. Analysis was by intention-to-treat. The trial was registered with ClinicalTrials.gov (number NCT00124969). RESULTS: The median age of patients was 61 years (25% percentile - 75% percentile, 47-69), and the median follow-up was 19 months (8-30). Fifteen (12%) of the 123 patients assigned to amlodipine and 22 (17%) of the 128 patients assigned to placebo had a primary endpoint [hazard ratio 0.65 (95% CI 0.34-1.23); P = 0.19]. Nineteen (15%) of the 123 haemodialysis patients assigned to amlodipine and 32 (25%) of the 128 haemodialysis patients assigned to placebo reached the secondary composite endpoint [hazard ratio 0.53 (95% CI 0.31-0.93); P = 0.03]. CONCLUSION: Amlodipine safely reduces systolic blood pressure and it may have a beneficial effect on cardiovascular outcomes in hypertensive haemodialysis patients.

Publications of final outcomes from previous ongoing trials

Ogihara, T., A. Fujimoto, et al. (2008). "ARB candesartan and CCB amlodipine in hypertensive patients: the CASE-J trial." Expert Review of Cardiovascular Therapy 6(9): 1195-201.

The Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial was a comparative study of the angiotensin II receptor blocker (ARB), candesartan, and a calcium channel blocker (CCB), amlodipine, regarding the incidence of cardiovascular events in high-risk Japanese hypertensive patients. The study design was a prospective, multicenter, randomized, open-label, active-controlled, two-arm, parallel-group comparison study with a response-dependent dose titration and blinded assessment of the end point. The CASE-J trial enrolled 4728 patients, with a mean age of 63.8 years and a mean BMI of 24.6 kg/m², who were randomly assigned to either candesartan- or amlodipine-based treatment regimens. Blood pressure was well controlled to the level of less than 140/80 mmHg in both of the treatment regimens. During 3.2 years of follow-up, primary cardiovascular events occurred in 134 patients in each of the two treatment-based regimens, resulting in no significant difference in the incidence of cardiovascular events between them (hazard ratio: 1.01; 95% confidence interval: 0.79-1.28; p = 0.969). In 404 patients with left ventricular hypertrophy, a significantly larger decrease in left ventricular mass index 3 years after enrollment was observed in candesartan-based (n = 205) than amlodipine-based (n = 199) regimens (-22.9 vs -13.4 g/m², respectively; p = 0.023). Furthermore, new-onset diabetes occurred in fewer patients taking candesartan than in those taking amlodipine, resulting in a 36% relative risk reduction (p = 0.030). The CASE-J trial demonstrated that both an ARB, candesartan, and a CCB, amlodipine, equally suppressed the incidence of cardiovascular events. The ARB may confer more beneficial effects to hypertensive patients with left ventricular hypertrophy or for those at-risk of diabetes than CCB.

Ogihara, T., K. Nakao, et al. (2008). "Effects of candesartan compared with amlodipine in hypertensive patients with high cardiovascular risks: candesartan antihypertensive survival evaluation in Japan trial." Hypertension 51(2): 393-8.

The Candesartan Antihypertensive Survival Evaluation in Japan Trial was designed to compare the long-term effects of the angiotensin II receptor blocker candesartan and the calcium channel blocker amlodipine on the incidence of cardiovascular events, represented as a composite of sudden death and cerebrovascular, cardiac, renal, and vascular events in high-risk Japanese hypertensive patients. We conducted a prospective, randomized, open-label study with blinded assessment of the end point in 4728 Japanese hypertensive patients (mean age: 63.8 years; mean body mass index: 24.6 kg/m²). Patients were followed for an average of 3.2 years. Blood pressure was well controlled with both treatment-based regimens (systolic blood pressure/diastolic blood pressure: 136.1/77.3 mm Hg for candesartan-based regimens and 134.4/76.7 mm Hg for amlodipine-based regimens after 3 years). Primary cardiovascular events occurred in 134 patients with both the candesartan- and amlodipine-based regimens. The 2 treatment-based regimens produced no significant differences in cardiovascular morbidity or mortality in the high-risk Japanese hypertensive patients (hazard ratio:

1.01; 95% CI: 0.79 to 1.28; P=0.969). In each primary end point category, there was no significant difference between the 2 treatment-based regimens. New-onset diabetes occurred in fewer patients taking candesartan (8.7/1000 person-years) than in those taking amlodipine (13.6/1000 person-years), which resulted in a 36% relative risk reduction (hazard ratio: 0.64; 95% CI: 0.43 to 0.97; P=0.033). We disclosed that candesartan-based and amlodipine-based regimens produced no statistical differences in terms of the primary cardiovascular end point, whereas candesartan prevented new-onset diabetes more effectively than amlodipine.

Ostergren, J., N. R. Poulter, et al. (2008). "The Anglo-Scandinavian Cardiac Outcomes Trial: blood pressure-lowering limb: effects in patients with type II diabetes." Journal of Hypertension **26**(11): 2103-11.

OBJECTIVE: To compare the effects of two antihypertensive treatment strategies for the prevention of coronary heart disease and other cardiovascular events in the large subpopulation (n=5137) with diabetes mellitus in the blood pressure-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial. **METHODS:** Patients had either untreated hypertension or treated hypertension. For those with type II diabetes mellitus, inclusion criteria required at least two additional risk factors. Patients were randomized to amlodipine with addition of perindopril as required (amlodipine-based) or atenolol with addition of thiazide as required (atenolol-based). Therapy was titrated to achieve a target blood pressure of less than 130/80 mmHg. **RESULTS:** The trial was terminated early due to significant benefits on mortality and stroke associated with the amlodipine-based regimen. In patients with diabetes mellitus, the amlodipine-based treatment reduced the incidence of the composite endpoint--total cardiovascular events and procedures--compared with the atenolol-based regimen (hazard ratio 0.86, confidence interval 0.76-0.98, P=0.026). Fatal and nonfatal strokes were reduced by 25% (P=0.017), peripheral arterial disease by 48% (P=0.004) and noncoronary revascularization procedures by 57% (P<0.001). For the other endpoints included in the composite, the endpoint differences were less clear including coronary heart disease deaths and nonfatal myocardial infarctions (the primary endpoint), which were reduced nonsignificantly by 8% (hazard ratio 0.92, confidence interval 0.74-1.15). **CONCLUSION:** In the large diabetic subgroup in the blood pressure-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial, the benefits of amlodipine-based treatment, compared with atenolol-based treatment, on the incidence of total cardiovascular events and procedures was significant (14% reduction) and similar to that observed in the total trial population (16% reduction).

New subgroup analyses from previously included trials

Bangalore, S., F. H. Messerli, et al. (2008). "Verapamil-sustained release-based treatment strategy is equivalent to atenolol-based treatment strategy at reducing cardiovascular events in patients with prior myocardial infarction: an INternational VERapamil SR-Trandolapril (INVEST) substudy." *American Heart Journal* **156**(2): 241-7.

BACKGROUND: In patients with prior myocardial infarction (MI), beta-blockers reduce mortality by 23% to 40%. However, despite this favorable effect, adverse effects limit compliance to this medication. The purpose of the study was to compare a beta-blocker-based strategy with a heart rate-lowering calcium antagonists-based strategy in patients with prior MI. **METHODS:** We evaluated 7,218 patients with prior MI enrolled in the INternational VERapamil SR-Trandolapril (INVEST) substudy randomized to verapamil-sustained release (SR)- or atenolol-based strategies. Primary outcome was time to first occurrence of death (all-cause), nonfatal MI, or nonfatal stroke. Secondary outcomes included death, total MI (fatal and nonfatal), and total stroke (fatal and nonfatal) considered separately. **RESULTS:** During the 2.8 +/- 1.0 years of follow-up, patients assigned to the verapamil-SR-based and atenolol-based strategies had comparable blood pressure control, and the incidence of the primary outcome was equivalent. There was no difference between the 2 strategies for the outcomes of either death or total MI. However, more patients reported excellent/good well-being (82.3% vs 78.0%, $P = .02$) at 24 months with a trend toward less incidence of angina pectoris (12.0% vs 14.3%, adjusted $P = .07$), nonfatal stroke (1.4% vs 2.0%; $P = .06$), and total stroke (2.0% vs 2.5%, $P = .18$) in the verapamil-SR-based strategy group. **CONCLUSIONS:** In hypertensive patients with prior MI, a verapamil-SR-based strategy was equivalent to a beta-blocker-based strategy for blood pressure control and prevention of cardiovascular events, with greater subjective feeling of well-being and a trend toward lower incidence of angina pectoris and stroke in the verapamil-SR-based group.

Black, H. R., B. Davis, et al. (2008). "Metabolic and clinical outcomes in nondiabetic individuals with the metabolic syndrome assigned to chlorthalidone, amlodipine, or lisinopril as initial treatment for hypertension: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)." *Diabetes Care* **31**(2): 353-60.

OBJECTIVE: Optimal initial antihypertensive drug therapy in people with the metabolic syndrome is unknown. **RESEARCH DESIGN AND METHODS:** We conducted a subgroup analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) to compare metabolic, cardiovascular, and renal outcomes in individuals assigned to initial hypertension treatment with a thiazide-like diuretic (chlorthalidone), a calcium channel blocker (CCB; amlodipine), or an ACE inhibitor (lisinopril) in nondiabetic individuals with or without metabolic syndrome. **RESULTS:** In participants with metabolic syndrome, at 4 years of follow-up, the incidence of newly diagnosed diabetes (fasting glucose ≥ 126 mg/dl) was 17.1% for chlorthalidone, 16.0% for amlodipine ($P = 0.49$, chlorthalidone vs. amlodipine) and 12.6% for lisinopril ($P < 0.05$, lisinopril vs. chlorthalidone). For those without metabolic syndrome, the rate of newly diagnosed diabetes was 7.7% for chlorthalidone, 4.2% for amlodipine, and 4.7% for

lisinopril ($P < 0.05$ for both comparisons). There were no differences in relative risks (RRs) for outcomes with amlodipine compared with chlorthalidone in those with metabolic syndrome; in those without metabolic syndrome, there was a higher risk for heart failure (RR 1.55 [95% CI 1.25-1.35]). In comparison with lisinopril, chlorthalidone was superior in those with metabolic syndrome with respect to heart failure (1.31 [1.04-1.64]) and combined cardiovascular disease (CVD) (1.19 [1.07-1.32]). No significant treatment group-metabolic syndrome interaction was noted. CONCLUSIONS: Despite a less favorable metabolic profile, thiazide-like diuretic initial therapy for hypertension offers similar, and in some instances possibly superior, CVD outcomes in older hypertensive adults with metabolic syndrome, as compared with treatment with CCBs and ACE inhibitors.

Davis, B. R., J. B. Kostis, et al. (2008). "Heart failure with preserved and reduced left ventricular ejection fraction in the antihypertensive and lipid-lowering treatment to prevent heart attack trial.[see comment]." *Circulation* **118**(22): 2259-67.

BACKGROUND: Heart failure (HF) developing in hypertensive patients may occur with preserved or reduced left ventricular ejection fraction (PEF [$\geq 50\%$] or REF [$< 50\%$]). In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), 42 418 high-risk hypertensive patients were randomized to chlorthalidone, amlodipine, lisinopril, or doxazosin, providing an opportunity to compare these treatments with regard to occurrence of hospitalized HFPEF or HFREF. METHODS AND RESULTS: HF diagnostic criteria were prespecified in the ALLHAT protocol. EF estimated by contrast ventriculography, echocardiography, or radionuclide study was available in 910 of 1367 patients (66.6%) with hospitalized events meeting ALLHAT criteria. Cox regression models adjusted for baseline characteristics were used to examine treatment differences for HF (overall and by PEF and REF). HF case fatality rates were examined. Of those with EF data, 44.4% had HFPEF and 55.6% had HFREF. Chlorthalidone reduced the risk of HFPEF compared with amlodipine, lisinopril, or doxazosin; the hazard ratios were 0.69 (95% confidence interval [CI], 0.53 to 0.91; $P=0.009$), 0.74 (95% CI, 0.56 to 0.97; $P=0.032$), and 0.53 (95% CI, 0.38 to 0.73; $P<0.001$), respectively. Chlorthalidone reduced the risk of HFREF compared with amlodipine or doxazosin; the hazard ratios were 0.74 (95% CI, 0.59 to 0.94; $P=0.013$) and 0.61 (95% CI, 0.47 to 0.79; $P<0.001$), respectively. Chlorthalidone was similar to lisinopril with regard to incidence of HFREF (hazard ratio, 1.07; 95% CI, 0.82 to 1.40; $P=0.596$). After HF onset, death occurred in 29.2% of participants (chlorthalidone/amlodipine/lisinopril) with new-onset HFPEF versus 41.9% in those with HFREF ($P<0.001$; median follow-up, 1.74 years); and in the chlorthalidone/doxazosin comparison that was terminated early, 20.0% of HFPEF and 26.0% of HFREF patients died ($P=0.185$; median follow-up, 1.55 years). CONCLUSIONS: In ALLHAT, with adjudicated outcomes, chlorthalidone significantly reduced the occurrence of new-onset hospitalized HFPEF and HFREF compared with amlodipine and doxazosin. Chlorthalidone also reduced the incidence of new-onset HFPEF compared with lisinopril. Among high-risk hypertensive men and women, HFPEF has a better prognosis than HFREF.

Schmieder, R. E., S. E. Kjeldsen, et al. (2008). "Reduced incidence of new-onset atrial fibrillation with angiotensin II receptor blockade: the VALUE trial." Journal of Hypertension **26**(3): 403-11.

BACKGROUND: Atrial fibrillation (AF) is the most common arrhythmia and increases cardiovascular risk in hypertensive patients. Therefore, in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) a prespecified objective was to compare the effects of valsartan and amlodipine on new-onset AF. **METHODS:** A total of 15 245 hypertensive patients at high cardiovascular risk received valsartan 80-160 mg/day or amlodipine 5-10 mg/day combined with additional antihypertensive agents. Electrocardiograms were obtained every year and analyzed centrally for evidence of left ventricular hypertrophy and new-onset AF. **RESULTS:** At baseline, AF was diagnosed in 2.6% of 7649 valsartan recipients and 2.6% of 7596 amlodipine recipients. During antihypertensive treatment the incidence of at least one documented occurrence of new-onset AF was 3.67% with valsartan and 4.34% with amlodipine [unadjusted hazard ratio 0.843, [95% confidence interval (CI): 0.713, 0.997], P = 0.0455]. The incidence of persistent AF was 1.35% with valsartan and 1.97% with amlodipine [unadjusted hazard ratio 0.683 (95% CI: 0.525, 0.889), P = 0.0046]. **CONCLUSIONS:** Valsartan-based treatment reduced the development of new-onset AF, particularly sustained AF in hypertensive patients, compared with amlodipine-based therapy. These findings suggest that angiotensin II receptor blockers may result in greater benefits than calcium antagonists in hypertensive patients at risk of new-onset AF.

Wright, J. T., Jr., S. Harris-Haywood, et al. (2008). "Clinical outcomes by race in hypertensive patients with and without the metabolic syndrome: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[see comment]." Archives of Internal Medicine **168**(2): 207-17.

BACKGROUND: Antihypertensive drugs with favorable metabolic effects are advocated for first-line therapy in hypertensive patients with metabolic/cardiometabolic syndrome (MetS). We compared outcomes by race in hypertensive individuals with and without MetS treated with a thiazide-type diuretic (chlorthalidone), a calcium channel blocker (amlodipine besylate), an alpha-blocker (doxazosin mesylate), or an angiotensin-converting enzyme inhibitor (lisinopril). **METHODS:** A subgroup analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a randomized, double-blind hypertension treatment trial of 42 418 participants. We defined MetS as hypertension plus at least 2 of the following: fasting serum glucose level of at least 100 mg/dL, body mass index (calculated as weight in kilograms divided by height in meters squared) of at least 30, fasting triglyceride levels of at least 150 mg/dL, and high-density lipoprotein cholesterol levels of less than 40 mg/dL in men or less than 50 mg/dL in women. **RESULTS:** Significantly higher rates of heart failure were consistent across all treatment comparisons in those with MetS. Relative risks (RRs) were 1.50 (95% confidence interval, 1.18-1.90), 1.49 (1.17-1.90), and 1.88 (1.42-2.47) in black participants and 1.25 (1.06-1.47), 1.20 (1.01-1.41), and 1.82 (1.51-2.19) in nonblack participants for amlodipine, lisinopril, and doxazosin comparisons with

chlorthalidone, respectively. Higher rates for combined cardiovascular disease were observed with lisinopril-chlorthalidone (RRs, 1.24 [1.09-1.40] and 1.10 [1.02-1.19], respectively) and doxazosin-chlorthalidone comparisons (RRs, 1.37 [1.19-1.58] and 1.18 [1.08-1.30], respectively) in black and nonblack participants with MetS. Higher rates of stroke were seen in black participants only (RR, 1.37 [1.07-1.76] for the lisinopril-chlorthalidone comparison, and RR, 1.49 [1.09-2.03] for the doxazosin-chlorthalidone comparison). Black patients with MetS also had higher rates of end-stage renal disease (RR, 1.70 [1.13-2.55]) with lisinopril compared with chlorthalidone. CONCLUSIONS: The ALLHAT findings fail to support the preference for calcium channel blockers, alpha-blockers, or angiotensin-converting enzyme inhibitors compared with thiazide-type diuretics in patients with the MetS, despite their more favorable metabolic profiles. This was particularly true for black participants.

Yui, Y., E. Shinoda, et al. (2007). "Nifedipine retard prevents hospitalization for angina pectoris better than angiotensin-converting enzyme inhibitors in hypertensive Japanese patients with previous myocardial infarction (JMIC-B substudy)." Journal of Hypertension **25**(10): 2019-26.

OBJECTIVES AND BACKGROUND: We previously reported that nifedipine retard showed comparable efficacy to angiotensin-converting enzyme (ACE) inhibitors for the prevention of cardiac events in hypertensive patients with coronary artery disease during the Japan Multicenter Investigation for Cardiovascular Diseases B study. In the nifedipine group, patients with a history of myocardial infarction (MI) showed a significant reduction in hospitalization for angina pectoris compared with the ACE inhibitor group. We investigated whether this difference was related to the progression of coronary arteriosclerosis. METHODS: To evaluate coronary arteriosclerosis, we performed coronary angiography (CAG) and a quantitative analysis of coronary angiograms. RESULTS: The cumulative incidence of hospitalization for angina was significantly lower in the nifedipine group (log-rank test $P = 0.013$). The etiology of angina requiring hospitalization was determined on the basis of CAG findings. Its incidence secondary to the development of new lesions or the progression of existing lesions was significantly lower in the nifedipine group than in the ACE inhibitor group (log-rank test $P = 0.042$ and $P = 0.028$, respectively). Using quantitative coronary analysis, changes in the coronary artery luminal diameter were compared between the nifedipine and ACE inhibitor groups. The minimum coronary lumen diameter did not show a significant change in the nifedipine group, whereas it decreased significantly in the ACE inhibitor group (paired t-test $P = 0.002$), and there was a significant difference between the two groups by analysis of covariance ($P = 0.047$). CONCLUSION: These results indicate that nifedipine more effectively prevented admission for angina pectoris by inhibiting the progression of coronary artery disease in patients with a history of MI.