Drug Class Review

Calcium Channel Blockers

Preliminary Scan Report #5

October 2013

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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 to assist with Participating Organizations' consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Date of Last Update Report

Update #2, March 2005 (searches through February 2004)

Date of Last Preliminary Update Scan Report

April 2009

Scope and Key Questions

Key Questions

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

Inclusion Criteria

POPULATION

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

Interventions

Amlodipine
Bepridil
Diltiazem
Felodipine

Isradipine
Nicardipine
Nifedipine
Nisoldipine
Verapamil

OUTCOMES

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

Angina (Follow-up duration ≥ 2 months)
All cause mortality
Cardiovascular (CV) disease mortality
CV events (stroke, MI, development of CHF)
Symptoms
Quality of Life

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

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

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from January 2009 through October 2013 using terms for included drugs. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, indications, and safety alerts. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) and the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/). All citations were imported into an electronic database (EndNote X3) and duplicate citations were removed.

Study Selection

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

RESULTS

New Drugs

New drugs identified in current Preliminary Update Scan

The current scan did not identify any new drugs.

New drugs identified in previous Preliminary Update Scan

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

New Indications

New indications identified in current Preliminary Update Scan

The current scan did not identify any new indications.

New indications identified in previous Preliminary Update Scan

Amlodipine indicated for use in patients with angiographically documented coronary artery disease– expanded population (9/05).

New Black Box Warnings

We did not identify any new black box warnings in this or the previous scan.

Comparative Effectiveness Reviews

We did not identify any new potentially relevant comparative effectiveness reviews in this or the previous scan.

Randomized Controlled Trials

Trials identified since the most recent Full Report

Medline searches from this scan resulted in 341 citations. Of those, there were 20 potentially relevant new trials (see Appendix A for abstracts). Together with the 37 potentially relevant trials identified in the last scan (Appendix B), now there are a total of 57. Characteristics of these trials are shown in Table(s) 2-4, below. The majority are subanalyses from previously included or identified trials (Table 4). Shading indicates publications that are new in this scan.

Table 1. New head-to-head trials

Author Year	Trial Name	Interventions	Population
Melcher 1998	N/A	Nisoldipine Coat-Core vs Diltiazem Retard in Combination with a Beta-Blocker	Angina

Table 2. New active-control trials

Author Year	Trial Name	Interventions	Population
Yamashita 2011	J-RHYTHM II (Japanese Rhythm Management Trial II for Atrial Fibrillation)	Amlodipine vs candesartan	Paroxysmal atrial fibrillation
Ogihara 2008	CASE-J (Candesartan Antihypertensive Survival Evaluation in Japan)	Amlodipine vs candesartan	High-risk Japanese hypertensive patients
Investigators 2006	J-ELAN (The Effect of Losartan and Amlodipine on Left Ventricular Diastolic Function in Patients with Mild-to-Moderate Hypertension)	Amlodipine vs losartan	Hypertension
Nakamura 2008	N/A	Amlodipine vs telmisartan	Hypertension with chronic kidney disease
Fogari 2012	N/A	Amlodipine vs telmisartan	Hypertensive patients with paroxysmal AF and normal or increased left atrial dimension (LAD)
Fogari 2012	N/A	Amlodipine vs telmisartan vs ramipril	Hypertensive patients with metabolic syndrome and recurrent symptomatic

			paroxysmal and persistent atrial fibrillation
Muramatsu 2012	NAGOYA HEART Study	Amlodipine vs valsartan	Hypertensive patients with glucose intolerance
Nakamaya 2008	VART (Valsartan Amlodipine Randomized Trial)	Amlodipine vs valsartan	Hypertensive patients in Japan
Schmieder 2008	VALUE (Valsartan Antihypertensive Long-term Use Evaluation)	Amlodipine vs valsartan	High-risk hypertensive patients
Nissen 2004	CAMELOT (Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis)	Amlodipine vs enalapril vs placebo	Coronary disease and normal blood pressure
Jamerson 2008	ACCOMPLISH (Avoiding Cardiovascular events through COMbination therapy in Patients LIving with Systolic Hypertension)	Amlodipine vs HCTZ added to benazepril	Hypertension
Ruzyllo 2007	N/A	Amlodipine vs ivabradine	Angina
Kojima 2004	N/A	Amlodipine vs cilnidipine	Hypertension with renal disease
Koylan 2004	TTS (Turkish Trimetazidine Study)	Diltiazem vs trimetazidine	Angina
Vora 2004	N/A	Diltiazem vs amiodarone	Rheumatic atrial fibrillation
Frishman 2006	M-FACT (Metoprolol Succinate-Felodipine Antihypertension Combination Trial)	Metoprolol ER, felodipine ER, or their combination	Hypertension
Derosa 2004	N/A	Nifedipine GITS vs telmisartan	Hypertension and type 2 diabetes
Inoue 2004	N/A	Nifedipine vs benidipine	Hypertensive patients with renal dysfunction
Ruggenenti 2004	BENEDICT (Bergamo Nephrologic Diabetes Complications Trial)	Verapamil vs trandolapril vs their combination vs placebo	Hypertension, type 2 diabetes mellitus, and normal urinary albumin excretion
Hemels 2006	VERDICT (Verapamil Versus Digoxin and Acute Versus Routine Serial Cardioversion Trial)	Verapamil vs digoxin	Persistent atrial fibrillation
Vranic 2006	N/A	Verapamil vs adenosine	Paroxysmal supraventricular

	tachycardia

Table 3. New placebo-controlled trials

Author Year	Trial Name	CCB	Population
Tepel 2008	N/A	Amlodipine	Hypertensive hemodialysis patients
Liu 2005	FEVER (Felodipine Event Reduction)	Felodipine	Chinese hypertensive patients

Table 4. Subanalyses from previously included/identified trials

Author Year	Trial Name	CCB	Population	Focus
Bakris 2013	ACCOMPLISH	Amlodipine	Hypertension	High-risk subgroup with known coronary artery disease
Weber 2013	ACCOMPLISH	Amlodipine	Hypertension	Effects of body size
Weir 2012	ACCOMPLISH	Amlodipine	Hypertension	Renal outcomes in Black patients
Bakris 2010	ACCOMPLISH	Amlodipine	Hypertension	Renal outcomes in high-risk subgroup with known coronary artery disease
Weber 2010	ACCOMPLISH	Amlodipine	Hypertension	Subgroup with diabetes
Oparil 2013	ALLHAT	Amlodipine	Hypertension	Results by sex
Rahman 2012	ALLHAT	Amlodipine	Hypertension	Results by baseline estimated GFR
Cushman 2012	ALLHAT	Amlodipine	Hypertension	Persistence of mortality and morbidity differences during extended follow-up
Black 2008	ALLHAT	Amlodipine	Hypertension	Metabolic syndrome subgroup
Davis 2008	ALLHAT	Amlodipine	Hypertension	HF events
Wright 2008	ALLHAT	Amlodipine	Hypertension	Influence of race
Leenen 2006	ALLHAT	Amlodipine	Hypertension	Demographic subgroups
Whelton 2005	ALLHAT	Amlodipine	Hypertension	Influence of type 2 diabetes mellitus or impaired fasting glucose levels
Ostergren 2008	ASCOT	Amlodipine	Hypertension	Type II diabetes subgroup

Collier 2011	ASCOT-BPLA	Amlodipine	Hypertension	Influence of age
Ogihara 2011	CASE-J	Amlodipine	Hypertension	Long-term outcomes
Saruta 2009	CASE-J	Amlodipine	Hypertension	Chronic Kidney Disease subgroup
Ogihara 2008	CASE-J	Amlodipine	Hypertension	Survival evaluation
Takano 2012	VART	Amlodipine	Hypertension	Relationship between home blood pressure (HBP) levels and cardiovascular events
Narumi 2011	VART	Amlodipine	Hypertension	Additional cardiorenal outcomes
Yui 2007	JMIC-B	Nifedipine	Hypertensive Japanese patients with previous myocardial infarction	Role of coronary arteriosclerosis progression
Elliot 2011	ACTION	Long-acting nifedipine GITS	Angina	Diabetes mellitus subgroup
Elliot 2011	ACTION	Long-acting nifedipine GITS	Angina	Angina subgroup
Ruilope 2007	ACTION	Long-acting nifedipine GITS	Angina	Role of renal function
Lubsen 2005	ACTION	Long-acting nifedipine GITS	Angina	Stratified by baseline hypertension
de Leeuw 2004	INSIGHT	Long-acting nifedipine GITS	High-risk hypertension	Role of renal function
Mancia 2004	INSIGHT	Long-acting nifedipine GITS	High-risk hypertension	Isolated systolic hypertension subgroup
Bangalore 2008	INVEST	Verapamil sustained release	Hypertension	Prior myocardial infarction subgroup
Cooper-DeHoff 2007	INVEST	Verapamil sustained release	Hypertension	Influence of Hispanic ethnicity
Cooper-DeHoff 2006	INVEST	Verapamil sustained release	Hypertension	Predictors of diabetes mellitus development
Messerli 2006	INVEST	Verapamil sustained release	Hypertension	Influence of aggressive blood pressure lowering

Ruggenenti 2011	BENEDICT-B	Verapamil	Hypertension	Subgroup with type 2 diabetes and microalbuminuria
Black 2005	CONVINCE	COER verapamil	Hypertension	Influence of geographical region

Appendix A. Abstracts of potentially relevant new trials of Calcium Channel Blockers from current scan

New Head-to-Head Trials

Melcher, A., J. Abelin, et al. (1998). "Efficacy and Tolerability of Nisoldipine Coat-Core vs Diltiazem Retard in Combination with a Beta-Blocker in Patients with Stable Exertional Angina Pectoris." Clinical Drug Investigation **15**(5): 389-396.

A randomised, double-blind, placebo-controlled, parallel-group trial with forced titration study to investigate possible equivalence of efficacy and tolerability between nisoldipine coat-core (CC) 40mg once daily, and diltiazem retard 120mg twice daily, was carried out in 176 patients with stable angina pectoris who were already receiving beta-blocker therapy. A total of 164 patients were included in the tolerability analysis and 135 patients were evaluable for efficacy (nisoldipine CC, n = 69; diltiazem retard, n = 66). During bicycle exercise tolerance tests, time to 1mm ST-segment depression, total exercise time, and time to angina were assessed at baseline and at the end of the treatment period. The number of angina attacks and of consumed nitroglycerin tablets were recorded in weekly diaries. Time to onset of 1mm ST-segment depression increased by 69.4 +/- 100.0 seconds with nisoldipine CC and by 65.9 +/- 87.6 seconds with diltiazem retard. The two treatment regimens were equally effective in time to onset of 1mm ST-segment depression, time to angina pectoris, and in exercise duration. A beneficial effect on angina attacks and nitroglycerin consumption was achieved with both treatments. Patient compliance, as assessed by the number of returned tablets, was high, at over 80%. Six patients withdrew from the treatment because of adverse events. Mild and transient adverse events were reported by 24 patients during treatment. One patient experienced a severe circulatory shock on the combination of diltiazem retard and atenolol. Peripheral oedema and headache were more common on nisoldipine CC. We concluded that the two treatments were equally efficacious and tolerated in patients with stable angina pectoris.

New Active-Control Trials

Fogari, R., A. Mugellini, et al. (2012). "Effect of telmisartan and ramipril on atrial fibrillation recurrence and severity in hypertensive patients with metabolic syndrome and recurrent symptomatic paroxysmal and persistent atrial fibrillation." Journal of Cardiovascular Pharmacology & Therapeutics **17**(1): 34-43.

This study evaluated the effect of telmisartan, ramipril, and amlodipine on atrial fibrillation (AF) recurrence and severity in hypertensive patients with metabolic syndrome. A total of 391 hypertensive outpatients with metabolic syndrome, in sinus rhythm but with at least 2 episodes of AF in the previous 6 months were randomized to telmisartan, ramipril, or amlodipine for 1 year. At the first AF, ventricular rate (VR) and plasma cardiac troponin I (TnI) were evaluated. P-wave dispersion (PWD) and procollagen type I carboxy-terminal peptide (PIP) were evaluated before and after 12 months of treatment. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were similarly and significantly reduced by all treatments ($P < .001$). In all, 49% of patients treated with amlodipine had a recurrence of AF as did 25.5% of patients with ramipril and 12.9% of patients with telmisartan ($P < .01$ vs amlodipine and $P < .05$ vs ramipril). Ventricular rate and TnI at the first AF recurrence were significantly lower with telmisartan and ramipril than with amlodipine. P-wave dispersion was reduced by ramipril (-5.1 ms, $P < .05$) and even more by telmisartan (-11 ms, $P < .01$). Telmisartan and ramipril induced a similar PIP reduction (-52.8 and -49.8 g/L, respectively, $P < .01$). These findings suggested that in these patients telmisartan was more effective than ramipril in reducing AF recurrence and severity as well as in improving PWD, despite a similar BP reduction and a similar improvement in cardiac fibrosis. This could be related to a specific effect of telmisartan on atrial electric remodeling.

Fogari, R., A. Zoppi, et al. (2012). "Effect of telmisartan on paroxysmal atrial fibrillation recurrence in hypertensive patients with normal or increased left atrial size." Clinical Cardiology **35**(6): 359-364.

BACKGROUND: Hypertension is the most prevalent and potentially modifiable risk factor for atrial fibrillation (AF). In a previous secondary prevention study, the authors observed that the angiotensin II receptor blocker telmisartan was more effective than the calcium channel blocker amlodipine in preventing AF relapse in hypertensive patients with normal atrial size.

HYPOTHESIS: Telmisartan may be more effective than amlodipine in preventing AF recurrence in hypertensive patients with paroxysmal AF and normal or increased left atrial dimension (LAD).

METHODS: The authors assigned 378 mild hypertensive outpatients in sinus rhythm, but with >=2 episodes of AF in the previous 6 months, to 1 of 2 groups. Group 1 comprised patients with LAD <40 mm in females and <45 mm in males. Group 2 comprised patients with LAD >40 mm and <45 mm in females and >45 mm and <50 mm in males. In both groups, patients were randomly treated with telmisartan or amlodipine for 1 year.

RESULTS: Systolic and diastolic blood pressure were similarly reduced by telmisartan and amlodipine in both groups. The AF recurrence rate was significantly lower in the telmisartan-treated patients than in the amlodipine-treated patients in both group 1 (12 vs 39, $P < 0.01$) and group 2 (40 vs 59, $P < 0.05$). Under telmisartan, the AF recurrence rate was significantly lower in group 1 than in group 2 (12.9% vs 42.1%, $P < 0.05$). Time to a

first AF relapse was significantly longer with telmisartan than with amlodipine in both group 1 (176 +/- 94 days vs 74 +/- 61 days, P < 0.05) and group 2 (119 +/- 65 days vs 38 +/- 35 days, P < 0.05).

CONCLUSIONS: Telmisartan was more effective than amlodipine in preventing AF recurrences in hypertensive patients with paroxysmal AF. 2012 Wiley Periodicals, Inc.

Muramatsu, T., K. Matsushita, et al. (2012). "Comparison between valsartan and amlodipine regarding cardiovascular morbidity and mortality in hypertensive patients with glucose intolerance: NAGOYA HEART Study." Hypertension **59**(3): 580-586.

It has not been fully examined whether angiotensin II receptor blocker is superior to calcium channel blocker to reduce cardiovascular events in hypertensive patients with glucose intolerance. A prospective, open-labeled, randomized, controlled trial was conducted for Japanese hypertensive patients with type 2 diabetes mellitus or impaired glucose tolerance. A total of 1150 patients (women: 34%; mean age: 63 years; diabetes mellitus: 82%) were randomly assigned to receive either valsartan- or amlodipine-based antihypertensive treatment. Primary outcome was a composite of acute myocardial infarction, stroke, coronary revascularization, admission attributed to heart failure, or sudden cardiac death. Blood pressure was 145/82 and 144/81 mm Hg, and glycosylated hemoglobin was 7.0% and 6.9% at baseline in the valsartan group and the amlodipine group, respectively. Both of them were equally controlled between the 2 groups during the study. The median follow-up period was 3.2 years, and primary outcome had occurred in 54 patients in the valsartan group and 56 in the amlodipine group (hazard ratio: 0.97 [95% CI: 0.66-1.40]; P=0.85). Patients in the valsartan group had a significantly lower incidence of heart failure than in the amlodipine group (hazard ratio: 0.20 [95% CI: 0.06-0.69]; P=0.01). Other components and all-cause mortality were not significantly different between the 2 groups. Composite cardiovascular outcomes were comparable between the valsartan- and amlodipine-based treatments in Japanese hypertensive patients with glucose intolerance. Admission because of heart failure was significantly less in the valsartan group.

Yamashita, T., H. Inoue, et al. (2011). "Randomized trial of angiotensin II-receptor blocker vs. dihydropiridine calcium channel blocker in the treatment of paroxysmal atrial fibrillation with hypertension (J-RHYTHM II study)." Europace **13**(4): 473-479.

AIMS: Atrial fibrillation (AF) is a common arrhythmia frequently associated with hypertension. This study was designed to test the hypothesis that lowering blood pressure by angiotensin II-receptor blockers (ARB) has more beneficial effects than by conventional calcium channel blockers (CCB) on the frequency of paroxysmal AF with hypertension.

METHODS AND RESULTS: The Japanese Rhythm Management Trial II for Atrial Fibrillation (J-RHYTHM II study) is an open-label randomized comparison between an ARB (candesartan) and a CCB (amlodipine) in the treatment of paroxysmal AF associated with hypertension. Using daily transtelephonic monitoring, we examined asymptomatic and symptomatic paroxysmal AF episodes during a maximum 1 year treatment. The primary endpoint was the difference in AF frequency between the pre-treatment period and the final month of the follow-up. The secondary endpoints included cardiovascular events, development of persistent AF, left atrial dimension, and quality-of-life (QOL). The study enrolled 318 patients (66 years, male/female 219/99, 158 in the ARB group and 160 in the CCB group) treated at 48 sites throughout Japan. At baseline, the frequency of AF episodes (days/month) was 3.8 +/- 5.0 in the ARB group vs. 4.8 +/- 6.3 in the CCB group

(not significant). During the follow-up, blood pressure was significantly lower in the CCB group than in the ARB group ($P < 0.001$). The AF frequency decreased similarly in both groups, and there was no significant difference in the primary endpoint between the two groups. There were no significant differences between the two groups in the development of persistent AF, changes in left atrial dimension, occurrence of cardiovascular events, or changes in QOL.

CONCLUSIONS: In patients with paroxysmal AF and hypertension, treatment of hypertension by candesartan did not have an advantage over amlodipine in the reduction in the frequency of paroxysmal AF (umin CTR C000000427).

Subanalyses from previously included/identified trials

Bakris, G., A. Briasoulis, et al. (2013). "Comparison of benazepril plus amlodipine or hydrochlorothiazide in high-risk patients with hypertension and coronary artery disease." American Journal of Cardiology **112**(2): 255-259.

Combination therapy with benazepril 40 mg and amlodipine 10 mg (B+A) has been shown to be more effective than benazepril 40 mg and hydrochlorothiazide (HCTZ) 25 mg (B+H) in reducing cardiovascular (CV) events in high-risk patients with stage 2 hypertension with similar blood pressure reductions. In the present post hoc analysis, we evaluated whether B+A is more effective than B+H for reducing CV events in patients with known coronary artery disease (CAD) at baseline in a subgroup analysis of the Avoiding Cardiovascular events through COMbination therapy in Patients LIving with Systolic Hypertension (ACCOMPLISH) study. The main trial randomized 11,506 patients. Of those, 5,744 received B+A and 5,762 received B+H. Of the 11,506 patients, 5,314 (46%) were classified as having CAD at baseline. The mean patient follow-up period was 35.7 months for the B+A group and 35.6 months for the B+H group. The primary end point was the interval to the first event of composite CV morbidity and mortality. At baseline, significant differences were present between the 5,314 with CAD and the 6,192 without CAD. The patients with CAD had a lower systolic blood pressure and heart rate, a lower incidence of diabetes, and greater incidence of dyslipidemia. However, no baseline differences were found between the randomized B+A and B+H groups. In the patients with CAD, an 18% reduction occurred in the hazard ratio for CV events (primary end point) with B+A versus B+H (p= 0.0016). In a prespecified secondary analysis of the composite end point, including only CV death, myocardial infarction, and stroke, the hazard ratio in the patients with CAD was reduced by 25% (p= 0.0033) in the B+A group compared with the B+H group. B+A was more effective than B+H at comparable blood pressure reductions for reducing CV events in patients, regardless of the presence of CAD. In conclusion, our findings suggest that the combination of B+A should be preferentially used for older patients with high-risk, stage 2 hypertension. Copyright 2013 Elsevier Inc. All rights reserved.

Bakris, G. L., P. A. Sarafidis, et al. (2010). "Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomised controlled trial." Lancet **375**(9721): 1173-1181.

BACKGROUND: The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial showed that initial antihypertensive therapy with benazepril plus amlodipine was superior to benazepril plus hydrochlorothiazide in reducing cardiovascular morbidity and mortality. We assessed the effects of these drug combinations on progression of chronic kidney disease.

METHODS: ACCOMPLISH was a double-blind, randomised trial undertaken in five countries (USA, Sweden, Norway, Denmark, and Finland). 11 506 patients with hypertension who were at high risk for cardiovascular events were randomly assigned via a central, telephone-based interactive voice response system in a 1:1 ratio to receive benazepril (20 mg) plus amlodipine (5 mg; n=5744) or benazepril (20 mg) plus hydrochlorothiazide (12.5 mg; n=5762), orally once daily. Drug doses were force-titrated for patients to attain recommended blood pressure goals. Progression of chronic kidney disease, a prespecified

endpoint, was defined as doubling of serum creatinine concentration or end-stage renal disease (estimated glomerular filtration rate <15 mL/min/1.73 m(2) or need for dialysis). Analysis was by intention to treat (ITT). This trial is registered with ClinicalTrials.gov, number NCT00170950.

FINDINGS: The trial was terminated early (mean follow-up 2.9 years [SD 0.4]) because of superior efficacy of benazepril plus amlodipine compared with benazepril plus hydrochlorothiazide. At trial completion, vital status was not known for 143 (1%) patients who were lost to follow-up (benazepril plus amlodipine, n=70; benazepril plus hydrochlorothiazide, n=73). All randomised patients were included in the ITT analysis. There were 113 (2.0%) events of chronic kidney disease progression in the benazepril plus amlodipine group compared with 215 (3.7%) in the benazepril plus hydrochlorothiazide group (HR 0.52, 0.41-0.65, p<0.0001). The most frequent adverse event in patients with chronic kidney disease was peripheral oedema (benazepril plus amlodipine, 189 of 561, 33.7%; benazepril plus hydrochlorothiazide, 85 of 532, 16.0%). In patients with chronic kidney disease, angio-oedema was more frequent in the benazepril plus amlodipine group than in the benazepril plus hydrochlorothiazide group. In patients without chronic kidney disease, dizziness, hypokalaemia, and hypotension were more frequent in the benazepril plus hydrochlorothiazide group than in the benazepril plus amlodipine group.

INTERPRETATION: Initial antihypertensive treatment with benazepril plus amlodipine should be considered in preference to benazepril plus hydrochlorothiazide since it slows progression of nephropathy to a greater extent.

FUNDING: Novartis.

Collier, D. J., N. R. Poulter, et al. (2011). "Impact of amlodipine-based therapy among older and younger patients in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA)." Journal of Hypertension **29**(3): 583-591.

OBJECTIVES: Older patients experience higher rates of cardiovascular disease than younger patients, but studies have suggested that relative risk reductions due to antihypertensive therapy are lower in older than younger patients. The Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) allowed an evaluation of the efficacy and safety of an amlodipine versus an atenolol-based antihypertensive regimen among older (>= 65 years) and younger (<65 years) patients.

METHODS: In ASCOT-BPLA 19 257 patients (8137 aged >= 65 years and 11 020 <65 years) were randomly assigned to receive amlodipine or atenolol-based antihypertensive therapy. The primary endpoint (nonfatal myocardial infarction and fatal coronary heart disease) and seven secondary endpoints were consistent with the original trial design.

RESULTS: All cardiovascular endpoints evaluated favoured the amlodipine-based regimen, significantly so in seven of the 16 age-stratified endpoints. Compared with the atenolol-based regimen, the amlodipine-based regimen reduced the relative risk of cardiovascular events by 17% in older and 15% in younger patients (P < 0.01). Overall, older patients experienced more cardiovascular events [n = 1625 (20%)] than younger patients [n = 1339 (12%)]. Discontinuations due to serious adverse events were low in both age groups and less frequent in the amlodipine-based versus atenolol-based regimen: 0.6 versus 1.1% among older patients and 0.4 versus 0.8% among younger patients.

CONCLUSIONS: The amlodipine-based regimen reduced the relative risk of cardiovascular events more effectively than the atenolol-based regimen in both older and younger patients. However, because event rates were higher among older patients, the absolute benefits were greater for older compared with younger patients.

Cushman, W. C., B. R. Davis, et al. (2012). "Mortality and morbidity during and after the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial." Journal of Clinical Hypertension **14**(1): 20-31.

A randomized, double-blind, active-controlled, multicenter trial assigned 32,804 participants aged 55 years and older with hypertension and >= 1 other coronary heart disease risk factors to receive chlorthalidone (n=15,002), amlodipine (n=8898), or lisinopril (n=8904) for 4 to 8 years, when double-blinded therapy was discontinued. Passive surveillance continued for a total follow-up of 8 to 13 years using national administrative databases to ascertain deaths and hospitalizations. During the post-trial period, fatal outcomes and nonfatal outcomes were available for 98% and 65% of participants, respectively, due to lack of access to administrative databases for the remainder. This paper assesses whether mortality and morbidity differences persisted or new differences developed during the extended follow-up. Primary outcome was cardiovascular mortality and secondary outcomes were mortality, stroke, coronary heart disease, heart failure, cardiovascular disease, and end-stage renal disease. For the post-trial period, data are not available on medications or blood pressure levels. No significant differences (P<.05) appeared in cardiovascular mortality for amlodipine (hazard ratio [HR], 1.00; 95% confidence interval [CI], 0.93-1.06) or lisinopril (HR, 0.97; CI, 0.90-1.03), each compared with chlorthalidone. The only significant differences in secondary outcomes were for heart failure, which was higher with amlodipine (HR, 1.12; CI, 1.02-1.22), and stroke mortality, which was higher with lisinopril (HR, 1.20; CI, 1.01-1.41), each compared with chlorthalidone. Similar to the previously reported in-trial result, there was a significant treatment-by-race interaction for cardiovascular disease for lisinopril vs chlorthalidone. Black participants had higher risk than non-black participants taking lisinopril compared with chlorthalidone. After accounting for multiple comparisons, none of these results were significant. These findings suggest that neither calcium channel blockers nor angiotensin-converting enzyme inhibitors are superior to diuretics for the long-term prevention of major cardiovascular complications of hypertension. 2011 Wiley Periodicals, Inc.

Elliott, H. L., S. M. Lloyd, et al. (2011). "Improving blood pressure control in patients with diabetes mellitus and high cardiovascular risk." International Journal Of Hypertension **2010**: 490769.

Patients with diabetes mellitus and symptomatic coronary artery disease are also likely to be hypertensive and, overall, are at very high cardiovascular (CV) risk. This paper reports the findings of a posthoc analysis of the 1113 patients with diabetes mellitus in the ACTION trial: ACTION itself showed that outcomes in patients with stable angina and hypertension were significantly improved when a long-acting calcium channel blocking drug (nifedipine GITS) was added to their treatment regimens. This further analysis of the ACTION database in those patients with diabetes has identified a number of practical therapeutic issues which are still relevant because of potential outcome benefits, particularly in relation to BP control. For example, despite background CV treatment and, specifically, despite the widespread use of ACE Inhibitor drugs, the addition of nifedipine

GITS was associated with significant benefits: improvement in BP control by an average of 6/3mmHg and significant improvements in outcome. In summary, this retrospective analysis has identified that the addition of nifedipine GITS resulted in improved BP control and significant outcome benefits in patients with diabetes who were at high CV risk. There is evidence to suggest that these findings are of direct relevance to current therapeutic practice.

Elliott, H. L. and P. A. Meredith (2011). "Preferential benefits of nifedipine GITS in systolic hypertension and in combination with RAS blockade: further analysis of the 'ACTION' database in patients with angina." Journal of Human Hypertension **25**(1): 63-70.

A retrospective analysis of the database from A Coronary Disease Trial Investigating Outcome with Nifedipine (ACTION) evaluated the effectiveness of nifedipine gastrointestinal therapeutic system (GITS) (i) in combination with renin angiotensin system (RAS) blockers and (ii) in patients with isolated systolic hypertension (ISH). Analysed on an intention-to-treat basis, treatment groups were compared by the log-rank test without adjustment for covariates and hazard ratios with 95% CIs were obtained using Cox proportional hazards models. Of 7665 randomized patients, 1732 patients were receiving RAS blockade at baseline, the addition of nifedipine GITS significantly reduced any cardiovascular (CV) event (-20%; P<0.05), the composite of death, any CV event and revascularization (-16%; P<0.05) and coronary angiography (-22%; P<0.01). These benefits were achieved with relatively small differences in systolic (3.2mmHg) and diastolic blood pressure (BP) (2.3mmHg). In 2303 patients (30.0%) who had ISH at baseline (1145 nifedipine GITS and 1158 placebo), nifedipine significantly reduced the primary efficacy end point (-18%; P<0.03), any CV event (-22%; P<0.01) and new heart failure (-40%; P<0.01). The benefits were associated with between-group differences in achieved BP of 4.7 and 3.3mmHg for systolic and diastolic BP, respectively. In summary, the lowest CV event rates were seen in those receiving (i) the combination of RAS blockade and nifedipine GITS and (ii) in those specifically treated for ISH.

Narumi, H., H. Takano, et al. (2011). "Effects of valsartan and amlodipine on cardiorenal protection in Japanese hypertensive patients: the Valsartan Amlodipine Randomized Trial.[Erratum appears in Hypertens Res. 2011 Jan;34(1):152]." Hypertension Research - Clinical & Experimental **34**(1): 62-69.

The Valsartan Amlodipine Randomized Trial, a multicenter, prospective, randomized, open-labeled, blinded-end point trial, was designed to compare the beneficial effects of the angiotensin II receptor blocker valsartan and the calcium channel blocker amlodipine on cardiovascular events in Japanese essential hypertensive patients. The primary end point was a composite of all-cause death, sudden death, cerebrovascular death, cardiac events, vascular events and renal events. The secondary endpoints were effects on left ventricular hypertrophy, cardiac sympathetic nerve activity and renal function. A total of 1021 patients were enrolled in the present trial. The mean follow-up period was 3.4 years. There were no significant differences in blood pressure (BP) levels between the valsartan group and the amlodipine group throughout the trial. There was no significant difference in the primary endpoint between the two groups (hazard ratio: 1.0, P = 0.843). No difference in any event category of the primary endpoint was noted for either group. However, we observed a significant reduction of left ventricular mass index, as determined by echocardiography, in the valsartan group compared with the amlodipine

group. We also observed a significant decrease in cardiac sympathetic nerve activity in the valsartan group but not in the amlodipine group. Moreover, there was a significant reduction in the urinary albumin to creatinine ratio in the valsartan group but not in the amlodipine group. Therefore, although BP levels were well controlled and remained equal in the two groups, valsartan had more protective effects on the heart and kidney than amlodipine in Japanese hypertensive patients.

Ogihara, T., K. Ueshima, et al. (2011). "Long-term effects of candesartan and amlodipine on cardiovascular morbidity and mortality in Japanese high-risk hypertensive patients: the Candesartan Antihypertensive Survival Evaluation in Japan Extension Study (CASE-J Ex)." Hypertension Research - Clinical & Experimental **34**(12): 1295-1301.

In the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial, comparable efficacy was noted between candesartan and amlodipine in the incidence of cardiovascular (CV) morbidity and mortality during 3.2 years of follow up. Candesartan suppressed new-onset diabetes more effectively than amlodipine. In this observational study, we investigated whether or not the efficacy of the two drugs is sustainable for another 3 years beyond the experimental period of the CASE-J trial. Of the 4728 high-risk hypertensive patients initially enrolled in the CASE-J trial, 2232 agreed to further follow up. The primary endpoint was a composite of CV morbidity and mortality. The distribution of demographic characteristics for the 2232 patients in the CASE-J extension was similar to that in the initial 4703 patients in the CASE-J trial. Both drugs controlled blood pressure well over the relatively long period of time. The incidence of CV events was 15.5/1000 patient years in the candesartan group and 16.3/1000 patient years in the amlodipine group (Hazard ratio (HR)=0.95, 95% confidence interval (CI)=0.77-1.18; P=0.650). The incidence of new-onset diabetes was significantly lower in the candesartan group (9.5/1000 patient years) than in the amlodipine group (13.3/1000 patient years), representing a 29% risk reduction for new-onset diabetes (HR=0.71, 95% CI=0.51-1.00, P=0.0495). In conclusion, candesartan and amlodipine showed comparable efficacy against CV events beyond the experimental period of the CASE-J trial in high-risk hypertensive patients. In addition, the effects of candesartan on new-onset diabetes observed during the CASE-J trial were sustained in the CASE-J extension. The CASE-J extension, which covered a 3-year extension of follow-up from the original trial, corroborated the results of the CASE-J trial.

Oparil, S., B. R. Davis, et al. (2013). "Mortality and morbidity during and after Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial: results by sex." Hypertension **61**(5): 977-986.

To determine whether an angiotensin-converting enzyme inhibitor (lisinopril) or calcium channel blocker (amlodipine) is superior to a diuretic (chlorthalidone) in reducing cardiovascular disease incidence in sex subgroups, we carried out a prespecified subgroup analysis of 15 638 women and 17 719 men in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Total follow-up (active treatment + passive surveillance using national administrative databases to ascertain deaths and hospitalizations) was 8 to 13 years. The primary outcome was fatal coronary heart disease or nonfatal myocardial infarction. Secondary outcomes included all-cause mortality, stroke, combined cardiovascular disease (coronary heart disease death, nonfatal myocardial infarction, stroke, angina, coronary revascularization, heart failure [HF], or peripheral vascular disease), and end-stage renal disease. In-trial rates of HF, stroke, and combined cardiovascular disease were significantly higher for lisinopril compared with

chlorthalidone, and rates of HF were significantly higher for amlodipine compared with chlorthalidone in both men and women. There were no significant treatment sex interactions. These findings did not persist through the extension period with the exception of the HF result for amlodipine versus chlorthalidone, which did not differ significantly by sex. For both women and men, rates were not lower in the amlodipine or lisinopril groups than in the chlorthalidone group for either the primary coronary heart disease outcome or any other cardiovascular disease outcome, and chlorthalidone-based treatment resulted in the lowest risk of HF. Neither lisinopril nor amlodipine is superior to chlorthalidone for initial treatment of hypertension in either women or men. Clinical Trial Registration- clinicaltrials.gov; Identifier: NCT00000542.

Rahman, M., C. E. Ford, et al. (2012). "Long-term renal and cardiovascular outcomes in Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) participants by baseline estimated GFR." Clinical Journal of The American Society of Nephrology: CJASN **7**(6): 989-1002.

BACKGROUND AND OBJECTIVES: CKD is common among older patients. This article assesses long-term renal and cardiovascular outcomes in older high-risk hypertensive patients, stratified by baseline estimated GFR (eGFR), and long-term outcome efficacy of 5-year first-step treatment with amlodipine or lisinopril, each compared with chlorthalidone.

DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS: This was a long-term post-trial follow-up of hypertensive participants (n=31,350), aged >=55 years, randomized to receive chlorthalidone, amlodipine, or lisinopril for 4-8 years at 593 centers. Participants were stratified by baseline eGFR (ml/min per 1.73 m(2)) as follows: normal/increased (>=90; n=8027), mild reduction (60-89; n=17,778), and moderate/severe reduction (<60; n=5545). Outcomes were cardiovascular mortality (primary outcome), total mortality, coronary heart disease, cardiovascular disease, stroke, heart failure, and ESRD.

RESULTS: After an average 8.8-year follow-up, total mortality was significantly higher in participants with moderate/severe eGFR reduction compared with those with normal and mildly reduced eGFR (P<0.001). In participants with an eGFR <60, there was no significant difference in cardiovascular mortality between chlorthalidone and amlodipine (P=0.64), or chlorthalidone and lisinopril (P=0.56). Likewise, no significant differences were observed for total mortality, coronary heart disease, cardiovascular disease, stroke, or ESRD.

CONCLUSIONS: CKD is associated with significantly higher long-term risk of cardiovascular events and mortality in older hypertensive patients. By eGFR stratum, 5-year treatment with amlodipine or lisinopril was not superior to chlorthalidone in preventing cardiovascular events, mortality, or ESRD during 9-year follow-up. Because data on proteinuria were not available, these findings may not be extrapolated to proteinuric CKD.

Ruggenenti, P., A. Fassi, et al. (2011). "Effects of verapamil added-on trandolapril therapy in hypertensive type 2 diabetes patients with microalbuminuria: the BENEDICT-B randomized trial." Journal of Hypertension **29**(2): 207-216.

OBJECTIVES: To address whether nondihydropyridine calcium-channel blocker added-on angiotensin-converting-enzyme inhibitor therapy ameliorates albuminuria and cardiovascular outcomes in type 2 diabetes patients.

DESIGN: The Bergamo Nephrologic Diabetes Complications Trial-B was a multicentre, prospective, double-blind, parallel-group trial comparing renal and cardiovascular outcomes in 281 hypertensive type 2 diabetes patients with microalbuminuria randomized to at least 2-year VeraTran (verapamil/trandolapril 180 mg/2 mg daily) or trandolapril (2 mg daily, identical image) treatment. Main outcome was persistent macroalbuminuria (albuminuria >200 g/min in two consecutive visits). Treatment targets were SBP/DBP less than 120/80 mmHg and HbA1C less than 7%.

RESULTS: Over a median follow-up of 4.5 years, 18 patients (13%) on VeraTran vs. 15 (10.5%) on trandolapril [unadjusted hazard ratio (95% confidence interval [CI]) 1.07 (0.54-2.12), P = 0.852] progressed to macroalbuminuria, respectively; 62 (44.9%) vs. 71 (49.7%) [0.80 (0.57-1.12), P = 0.198] regressed to normoalbuminuria (urinary albumin excretion <20 g/min), and 20 (14.5%) vs. 21 (14.7%) [hazard ratio 0.93 (0.50-1.72), P = 0.816] had major cardiovascular events. BP and metabolic control were similar between groups. Patients with cardiovascular events were significantly less [13 (9.8%) vs. 28 (18.9%), hazard ratio: 0.37 (0.19-0.71), P = 0.003] among those regressing to normoalbuminuria than those without regression. Difference was independent of treatment allocation and was significant also after adjusting for baseline characteristics [0.40 (0.20-0.79), P = 0.009], follow-up SBP [0.40 (0.20-0.80), P = 0.010] or DBP [0.36 (0.18-0.73), P = 0.004] BP or HbA1C [0.43 (0.21-0.88), P = 0.021].

CONCLUSION: In hypertensive type 2 diabetes patients with microalbuminuria, verapamil added-on trandolapril did not improve renal or cardiovascular outcomes. Independent of verapamil, trandolapril normalized albuminuria in half of patients and this translated into significant cardioprotection.

Takano, H., H. Hasegawa, et al. (2012). "Effects of valsartan and amlodipine on home blood pressure and cardiovascular events in Japanese hypertensive patients: a subanalysis of the VART." Journal of Human Hypertension **26**(11): 656-663.

The Valsartan Amlodipine Randomized Trial (VART) was performed to compare the beneficial effects of valsartan and amlodipine on cardiovascular events in Japanese hypertensive patients. In this subanalysis of the VART, we assessed the relationship between home blood pressure (HBP) levels and cardiovascular events in the enrolled patients. We enrolled 1021 patients with mild-to-moderate hypertension in the VART. The participants were allocated randomly to either the valsartan group or the amlodipine group. The primary end point was a composite of all-cause death, sudden death, cerebrovascular events, cardiac events, vascular events and renal events. A total of 621 patients (valsartan group: 305 and amlodipine group: 316) completed the measurements of HBP (morning and evening) throughout the trial. Both the agents evenly and significantly lowered morning HBP and evening HBP throughout the trial. There was no significant difference in the primary end point between the two groups. However, we observed significant decreases in the left ventricular mass index and urinary albumin to creatinine ratio in the valsartan group but not in the amlodipine group. There were no significant differences in HBP levels and the main outcome of the cardiovascular events between the valsartan and amlodipine groups. However, in the valsartan group, significant improvements in left ventricular hypertrophy and microalbuminuria were observed.

Weber, M. A., G. L. Bakris, et al. (2010). "Cardiovascular events during differing hypertension therapies in patients with diabetes." Journal of the American College of Cardiology **56**(1): 77-85.

OBJECTIVES: The aim of this study was to determine which combination therapy in patients with hypertension and diabetes most effectively decreases cardiovascular events.

BACKGROUND: The ACCOMPLISH (Avoiding Cardiovascular Events Through COMbination Therapy in Patients Living With Systolic Hypertension) trial compared the outcomes effects of a renin-angiotensin system blocker, benazepril, combined with amlodipine (B+A) or hydrochlorothiazide (B+H). A separate analysis in diabetic patients was pre-specified.

METHODS: A total of 6,946 patients with diabetes were randomized to treatment with B+A or B+H. A subgroup of 2,842 diabetic patients at very high risk (previous cardiovascular or stroke events) was also analyzed, as were 4,559 patients without diabetes. The primary end point was a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for angina, resuscitated arrest, and coronary revascularization.

RESULTS: In the full diabetes group, the mean achieved blood pressures in the B+A and B+H groups were 131.5/72.6 and 132.7/73.7 mm Hg; during 30 months, there were 307 (8.8%) and 383 (11.0%) primary events (hazard ratio [HR]: 0.79, 95% confidence interval [CI]: 0.68 to 0.92, p = 0.003). For the diabetic patients at very high risk, there were 195 (13.6%) and 244 (17.3%) primary events (HR: 0.77, 95% CI: 0.64 to 0.93, p = 0.007). In the nondiabetic patients, there were 245 (10.8%) and 296 (12.9%) primary events (HR: 0.82, 95% CI: 0.69 to 0.97, p = 0.020). In the diabetic patients, there were clear coronary benefits with B+A, including both acute clinical events (p = 0.013) and revascularizations (p = 0.024). There were no unexpected adverse events.

CONCLUSIONS: In patients with diabetes and hypertension, combining a renin-angiotensin system blocker with amlodipine, compared with hydrochlorothiazide, was superior in reducing cardiovascular events and could influence future management of hypertension in patients with diabetes. (Avoiding Cardiovascular Events Through COMbination Therapy in Patients Living With Systolic Hypertension [ACCOMPLISH]; NCT00170950). Copyright (c) 2010 American College of Cardiology Foundation. Published by Elsevier Inc. All rights reserved.

Weber, M. A., K. Jamerson, et al. (2013). "Effects of body size and hypertension treatments on cardiovascular event rates: subanalysis of the ACCOMPLISH randomised controlled trial." Lancet **381**(9866): 537-545.

BACKGROUND: In previous clinical trials in high-risk hypertensive patients, paradoxically higher cardiovascular event rates have been reported in patients of normal weight compared with obese individuals. As a prespecified analysis of the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, we aimed to investigate whether the type of hypertension treatment affects patients' cardiovascular outcomes according to their body size.

METHODS: On the basis of body-mass index (BMI), we divided the full ACCOMPLISH cohort into obese (BMI >=30, n=5709), overweight (>=25 to <30, n=4157), or normal weight (<25, n=1616) categories. The ACCOMPLISH cohort had already been randomised to treatment with single-pill combinations of either benazepril and hydrochlorothiazide or benazepril and amlodipine. We compared event rates (adjusted for age, sex, diabetes, previous cardiovascular events, stroke, or chronic kidney disease) for the primary

endpoint of cardiovascular death or non-fatal myocardial infarction or stroke. The analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00170950.

FINDINGS: In patients allocated benazepril and hydrochlorothiazide, the primary endpoint (per 1000 patient-years) was 30.7 in normal weight, 21.9 in overweight, and 18.2 in obese patients (overall p=0.0034). However, in those allocated benazepril and amlodipine, the primary endpoint did not differ between the three BMI groups (18.2, 16.9, and 16.5, respectively; overall p=0.9721). In obese individuals, primary event rates were similar with both benazepril and hydrochlorothiazide and benazepril and amlodipine, but rates were significantly lower with benazepril and amlodipine in overweight patients (hazard ratio 0.76, 95% CI 0.59-0.94; p=0.0369) and those of normal weight (0.57, 0.39-0.84; p=0.0037).

INTERPRETATION: Hypertension in normal weight and obese patients might be mediated by different mechanisms. Thiazide-based treatment gives less cardiovascular protection in normal weight than obese patients, but amlodipine-based therapy is equally effective across BMI subgroups and thus offers superior cardiovascular protection in non-obese hypertension.

FUNDING: Novartis Pharmaceuticals.

Weir, M. R., G. L. Bakris, et al. (2012). "Renal outcomes in hypertensive Black patients at high cardiovascular risk." Kidney International **81**(6): 568-576.

The ACCOMPLISH trial (Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension) was a 3-year multicenter, event-driven trial involving patients with high cardiovascular risk who were randomized in a double-blinded manner to benazepril plus either hydrochlorothiazide or amlodipine and titrated in parallel to reach recommended blood pressure goals. Of the 8125 participants in the United States, 1414 were of self-described Black ethnicity. The composite kidney disease end point, defined as a doubling in serum creatinine, end-stage renal disease, or death was not different between Black and non-Black patients, although the Blacks were significantly more likely to develop a greater than 50% increase in serum creatinine to a level above 2.6 mg/dl. We found important early differences in the estimated glomerular filtration rate (eGFR) due to acute hemodynamic effects, indicating that benazepril plus amlodipine was more effective in stabilizing eGFR compared to benazepril plus hydrochlorothiazide in non-Blacks. There was no difference in the mean eGFR loss in Blacks between therapies. Thus, benazepril coupled to amlodipine was a more effective antihypertensive treatment than when coupled to hydrochlorothiazide in non-Black patients to reduced kidney disease progression. Blacks have a modestly higher increased risk for more advanced increases in serum creatinine than non-Blacks.

Appendix B: Abstracts from previous scans

Scan #4

Saruta, T., K. Hayashi, et al. (2009). "Effects of candesartan and amlodipine on cardiovascular events in hypertensive patients with chronic kidney disease: subanalysis of the CASE-J Study." Hypertension Research - Clinical & Experimental **32**(6): 505-12.

We examined the effects of candesartan and amlodipine on cardiovascular events in hypertensive patients with chronic kidney disease (CKD) using the data from the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial. CKD was defined as proteinuria and/or decreased GFR (<60 ml per min per 1.73 m(2)) at enrollment. Among 2720 subjects with CKD, there were 1376 and 1344 patients in the candesartan and the amlodipine group, respectively. During a 3.2-year follow-up, cardiovascular event rate did not differ in the two groups (7.2% for candesartan and 7.6% for amlodipine). In the subgroup analysis based on the CKD stage, there were no significant differences in the incidence rates of cardiovascular events between the two groups in stages 1+2 and 3 CKD. In stage 4 CKD, however, candesartan reduced the incidence of cardiovascular events (55% risk reduction), particularly of renal events (81% risk reduction), compared with amlodipine. Furthermore, composite cardiovascular events were increased as the CKD stage progressed, and this effect was exaggerated in the presence of proteinuria. Finally, the new onset of diabetes was less in the candesartan-based regimen in stage 3 CKD. In conclusion, candesartan protected hypertensive patients with CKD more potently against renal events, particularly in moderately-to-severely impaired CKD. Furthermore, candesartan prevented a new onset of diabetes in CKD, which would be favorable for the long-term management of CKD.

Scan #3

New trials

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

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

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

The present study was conducted to compare the renal and vascular protective effects of telmisartan and amlodipine in untreated hypertensive chronic kidney disease (CKD) patients with moderate renal insufficiency. Thirty hypertensive CKD patients were randomly assigned to receive telmisartan 40 mg (n = 15) or amlodipine 5 mg (n = 15) once daily for 12 months. Changes in blood pressure, serum creatinine, 24-h creatinine clearance (Ccr), proteinuria, brachial-ankle pulse wave velocity (baPWV), intima-media thickness (IMT), plasma interleukin-6 (IL-6), plasma matrix metalloproteinase (MMP)-9

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

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

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

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

BACKGROUND: Hypertensive haemodialysis patients may be at a high risk for cardiovascular events. This study was undertaken to ascertain whether the calcium channel blocker amlodipine reduces mortality and cardiovascular events in these high-risk patients. METHODS: We evaluated the effects of amlodipine on cardiovascular events in 251 hypertensive haemodialysis patients in an investigator-designed, prospective, randomized, double-blind, placebo-controlled, multicenter trial. One hundred and twenty-three patients were randomly assigned to amlodipine (10 mg once daily) and 128 to placebo. The primary endpoint was mortality from any cause. The secondary endpoint was a composite variable consisting of mortality from any cause or cardiovascular event. Analysis was by intention-to-treat. The trial was registered with

ClinicalTrials.gov (number NCT00124969). RESULTS: The median age of patients was 61 years (25% percentile - 75% percentile, 47-69), and the median follow-up was 19 months (8-30). Fifteen (12%) of the 123 patients assigned to amlodipine and 22 (17%) of the 128 patients assigned to placebo had a primary endpoint [hazard ratio 0.65 (95% CI 0.34-1.23); P = 0.19]. Nineteen (15%) of the 123 haemodialysis patients assigned to amlodipine and 32 (25%) of the 128 haemodialysis patients assigned to placebo reached the secondary composite endpoint [hazard ratio 0.53 (95% CI 0.31-0.93); P = 0.03]. CONCLUSION: Amlodipine safely reduces systolic blood pressure and it may have a beneficial effect on cardiovascular outcomes in hypertensive haemodialysis patients.

Publications of final outcomes from previous ongoing trials

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

The Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial was a comparative study of the angiotensin II receptor blocker (ARB), candesartan, and a calcium channel blocker (CCB), amlodipine, regarding the incidence of cardiovascular events in high-risk Japanese hypertensive patients. The study design was a prospective, multicenter, randomized, open-label, active-controlled, two-arm, parallel-group comparison study with a response-dependent dose titration and blinded assessment of the end point. The CASE-J trial enrolled 4728 patients, with a mean age of 63.8 years and a mean BMI of 24.6 kg/m(2), who were randomly assigned to either candesartan- or amlodipine-based treatment regimens. Blood pressure was well controlled to the level of less than 140/80 mmHg in both of the treatment regimens. During 3.2 years of follow-up, primary cardiovascular events occurred in 134 patients in each of the two treatment-based regimens, resulting in no significant difference in the incidence of cardiovascular events between them (hazard ratio: 1.01; 95% confidence interval: 0.79-1.28; p = 0.969). In 404 patients with left ventricular hypertrophy, a significantly larger decrease in left ventricular mass index 3 years after enrollment was observed in candesartan-based (n = 205) than amlodipine-based (n = 199) regimens (-22.9 vs -13.4 g/m(2), respectively; p = 0.023). Furthermore, new-onset diabetes occurred in fewer patients taking candesartan than in those taking amlodipine, resulting in a 36% relative risk reduction (p = 0.030). The CASE-J trial demonstrated that both an ARB, candesartan, and a CCB, amlodipine, equally suppressed the incidence of cardiovascular events. The ARB may confer more beneficial effects to hypertensive patients with left ventricular hypertrophy or for those at-risk of diabetes than CCB.

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

The Candesartan Antihypertensive Survival Evaluation in Japan Trial was designed to compare the long-term effects of the angiotensin II receptor blocker candesartan and the calcium channel blocker amlodipine on the incidence of cardiovascular events, represented as a composite of sudden death and cerebrovascular, cardiac, renal, and vascular events in high-risk Japanese hypertensive patients. We conducted a prospective, randomized, open-label study with blinded assessment of the end point in 4728 Japanese hypertensive patients (mean age: 63.8 years; mean body mass index: 24.6 kg/m(2)). Patients were followed for an average of 3.2 years. Blood pressure was well controlled with both treatment-based regimens (systolic blood pressure/diastolic blood pressure: 136.1/77.3 mm Hg for candesartan-based regimens and 134.4/76.7 mm Hg for amlodipine-based regimens after 3 years). Primary cardiovascular events occurred in 134 patients with both the candesartan- and amlodipine-based regimens. The 2 treatment-based regimens produced no significant differences in cardiovascular morbidity or mortality in the high-risk Japanese hypertensive patients (hazard ratio: 1.01; 95% CI: 0.79 to 1.28; P=0.969). In each primary end point category, there was no significant difference between the 2 treatment-based regimens. New-onset diabetes occurred in

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

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

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

New subgroup analyses from previously included trials

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

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

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

OBJECTIVE: Optimal initial antihypertensive drug therapy in people with the metabolic syndrome is unknown. RESEARCH DESIGN AND METHODS: We conducted a subgroup analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) to compare metabolic, cardiovascular, and renal outcomes in individuals assigned to initial hypertension treatment with a thiazide-like diuretic (chlorthalidone), a calcium channel blocker (CCB; amlodipine), or an ACE inhibitor (lisinopril) in nondiabetic individuals with or without metabolic syndrome. RESULTS: In participants with metabolic syndrome, at 4 years of follow-up, the incidence of newly diagnosed diabetes (fasting glucose >or=126 mg/dl) was 17.1% for chlorthalidone, 16.0% for amlodipine (P = 0.49, chlorthalidone vs. amlodipine) and 12.6% for lisinopril (P < 0.05, lisinopril vs. chlorthalidone). For those without metabolic syndrome, the rate of newly diagnosed diabetes was 7.7% for chlorthalidone, 4.2% for amlodipine, and 4.7% for lisinopril (P < 0.05 for both comparisons). There were no differences in relative risks (RRs) for outcomes with amlodipine compared with chlorthalidone in those with

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

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

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

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

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

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

BACKGROUND: Antihypertensive drugs with favorable metabolic effects are advocated for first-line therapy in hypertensive patients with metabolic/cardiometabolic syndrome (MetS). We compared outcomes by race in hypertensive individuals with and without MetS treated with a thiazide-type diuretic (chlorthalidone), a calcium channel blocker (amlodipine besylate), an alpha-blocker (doxazosin mesylate), or an angiotensin-converting enzyme inhibitor (lisinopril). METHODS: A subgroup analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a randomized, double-blind hypertension treatment trial of 42 418 participants. We defined MetS as hypertension plus at least 2 of the following: fasting serum glucose level of at least 100 mg/dL, body mass index (calculated as weight in kilograms divided by height in meters squared) of at least 30, fasting triglyceride levels of at least 150 mg/dL, and high-density lipoprotein cholesterol levels of less than 40 mg/dL in men or less than 50 mg/dL in women. RESULTS: Significantly higher rates of heart failure were consistent across all treatment comparisons in those with MetS. Relative risks (RRs) were 1.50 (95% confidence interval, 1.18-1.90), 1.49 (1.17-1.90), and 1.88 (1.42-2.47) in black participants and 1.25 (1.06-1.47), 1.20 (1.01-1.41), and 1.82 (1.51-2.19) in nonblack participants for amlodipine, lisinopril, and doxazosin comparisons with chlorthalidone, respectively. Higher rates for combined cardiovascular disease were observed with lisinopril-chlorthalidone (RRs, 1.24 [1.09-1.40] and 1.10 [1.02-1.19], respectively) and doxazosin-chlorthalidone comparisons (RRs, 1.37 [1.19-

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

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

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

Scan #2

Cooper-DeHoff, R. M., Q. Zhou, et al. (2007). "Influence of Hispanic ethnicity on blood pressure control and cardiovascular outcomes in women with CAD and hypertension: findings from **INVEST**." Journal of Women's Health **16**(5): 632-40.

BACKGROUND: Prospective data regarding blood pressure (BP) control and cardiovascular (CV) outcomes in Hispanic women are lacking. METHODS: We analyzed 5017 Hispanic and 4710 non-Hispanic white hypertensive women with coronary artery disease (CAD) in the INternational VErapamil SR/Trandolapril STudy (INVEST) to determine the impact of baseline characteristics and BP control on CV outcomes. RESULTS: At baseline, Hispanic women were younger and a had lower prevalence of most established CV risk factors than non-Hispanic white women. At 24 months, BP control (< 140/90 mm Hg) was achieved in 75% of Hispanic and 68% of non-Hispanic white women, ($p < 0.001$), with most women, regardless of ethnicity, requiring > or =2 antihypertensive agents. Following 26,113 patient-years of follow-up, the primary outcome (first occurrence of nonfatal myocardial infarction [MI], nonfatal stroke, or all cause death) occurred in 5.7% of Hispanic and 12.3% of non-Hispanic white women (adjusted HR = 0.84, 95% CI = 0.71-0.98, $p = 0.03$). There was no difference in outcome in either group of women comparing the randomized antihypertensive treatment strategies. CONCLUSIONS: Despite accounting for a lower risk profile, deployment of protocol-based antihypertensive treatment regimens resulted in superior BP control and fewer CV events in Hispanic women compared with non-Hispanic white women.

Ruilope, L. M., B.-A. Kirwan, et al. (2007). "Uric acid and other renal function parameters in patients with stable angina pectoris participating in the **ACTION** trial: impact of nifedipine GITS (gastro-intestinal therapeutic system) and relation to outcome." Journal of Hypertension **25**(8): 1711-8.

BACKGROUND: Little data is available concerning the prognostic implications of renal function abnormalities, their evolution over time and the effects of nifedipine on such abnormalities in patients with stable angina pectoris. METHODS: The previously published ACTION trial compared long-acting nifedipine GITS 60 mg once daily to placebo among 7,665 patients. Standard laboratory tests including creatinine and uric acid were assessed at baseline, after 6 months, 2 and 4 years, and at the end of follow-up. We assessed the impact of nifedipine on markers of renal dysfunction and determined whether evidence of renal failure alters the impact of nifedipine on the clinical outcome of patients with stable angina. RESULTS: Uric acid was not while creatinine level and estimated creatinine clearance were potent conditionally independent predictors of total mortality and of cardiovascular clinical events. Relative to placebo, nifedipine reduced 6-month uric acid levels by 3% ($P < 0.001$) of the baseline value. This difference was maintained during long-term follow-up, was present both in normotensives and in hypertensives, and was not explained by differences in diuretic therapy or allopurinol use. Nifedipine had no effect on the occurrence of clinical renal failure. Relative to placebo, the effects of nifedipine on cardiovascular death or myocardial infarction [hazard ratio (HR) = 1.01, 95% confidence interval (CI) 0.88-1.17], any stroke or transient ischaemic attack (HR = 0.73, 95% CI 0.60-0.88), new overt heart failure (HR = 0.72, 95% CI 0.55-0.95), and the need for any coronary procedure (HR = 0.81, 95% CI 0.75-0.88) were consistent across strata of markers of renal dysfunction. CONCLUSIONS: We conclude that, in patients with stable angina, nifedipine reduces uric acid levels and does not

affect other markers of renal dysfunction. Renal dysfunction does not alter the effects of nifedipine on clinical outcome.

Ruzyllo, W., M. Tendera, et al. (2007). "Antianginal efficacy and safety of ivabradine compared with amlodipine in patients with stable effort angina pectoris: a 3-month randomised, double-blind, multicentre, noninferiority trial." Drugs **67**(3): 393-405.

BACKGROUND AND OBJECTIVE: Current medical therapies for the symptoms of angina pectoris aim to improve oxygen supply and reduce oxygen demand in the myocardium. Not all patients respond to current antianginal monotherapy, or even combination therapy, and a new class of antianginal drug that complements existing therapies would be useful. This study was undertaken to compare the antianginal and anti-ischaemic effects of the novel heart-rate-lowering agent ivabradine and of the calcium channel antagonist amlodipine. PATIENTS AND METHODS: Patients with a >/=3-month history of chronic, stable effort-induced angina were randomised to receive ivabradine 7.5mg (n = 400) or 10mg (n = 391) twice daily or amlodipine 10mg once daily (n = 404) for a 3-month, double-blind period. Bicycle exercise tolerance tests were performed at baseline and monthly intervals. The primary efficacy criterion was the change from baseline in total exercise duration after 3 months of treatment. Secondary efficacy criteria included changes in time to angina onset and time to 1mm ST-segment depression, rate-pressure product at trough drug activity, as well as short-acting nitrate use and anginal attack frequency (as recorded in patient diaries). RESULTS: At 3 months, total exercise duration was improved by 27.6 +/- 91.7, 21.7 +/- 94.5 and 31.2 +/- 92.0 seconds with ivabradine 7.5 and 10mg and amlodipine, respectively, both ivabradine groups were comparable to amlodipine (p-value for noninferiority < 0.001). Similar results were observed for time to angina onset and time to 1mm ST-segment depression. Heart rate decreased significantly by 11-13 beats/min at rest and by 12-15 beats/min at peak of exercise with ivabradine but not amlodipine, and rate-pressure product decreased more with ivabradine than amlodipine (p-value vs amlodipine <0.001, at rest and at peak of exercise). Anginal attack frequency and short-acting nitrate use decreased substantially in all treatment groups with no significant difference between treatment groups. The most frequent adverse events were visual symptoms and sinus bradycardia with ivabradine (0.8% and 0.4% withdrawals, respectively) and peripheral oedema with amlodipine (1.5% withdrawals). CONCLUSIONS: In patients with stable angina, ivabradine has comparable efficacy to amlodipine in improving exercise tolerance, a superior effect on the reduction of rate-pressure product (a surrogate marker of myocardial oxygen consumption) and similar safety.

Scan #1

Active-Controlled Trials

Black HR, Elliott WJ, Grandits G, et al. Results of the Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints (CONVINCE) trial by geographical region. *Journal of Hypertension.* May 2005;23(5):1099-1106.

OBJECTIVE: To examine regional differences in the Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints (CONVINCE) trial. DESIGN: Double-blind, randomized, international clinical trial. SETTING: Six hundred and sixty-one clinical centers in 15 countries. PATIENTS: Hypertensive volunteers (n = 16,602) with > or =1 additional cardiovascular risk factor, grouped into four regions: USA (n = 8144), Canada (n = 3405), Western Europe (Spain, UK, Italy, Sweden, Germany; n = 2048) or 'other' (Bulgaria, Israel, Mexico, Czech Republic, Hungary, Poland, Slovakia, Brazil; n = 2879); subgroupings included country and state/province within the USA and Canada. INTERVENTIONS: Randomized to COER-verapamil or the investigator's choice of either atenolol or hydrochlorothiazide, titrated and additional drugs added as required. MAIN OUTCOME MEASURES: Baseline characteristics; blood pressure control, medication adherence and lost-to-follow-up at 2 years; and composite primary endpoint (stroke, myocardial infarction, cardiovascular death) by regional groupings. RESULTS: Regional differences were found at baseline for age, gender, blood pressure, percentage receiving antihypertensive drug therapy, initial choice of atenolol or hydrochlorothiazide, and risk factor profile. Blood pressure control rates increased markedly during follow-up in all regions, but varied significantly by region. Blood pressure control, medication adherence and lost-to-follow-up rates were poorest in the USA. After adjustment for baseline differences, the primary-event rate for each region was significantly lower than for the USA. Although baseline factors, blood pressure control and event rates varied by region, treatment differences did not. CONCLUSION: Despite differences in baseline and follow-up measures across geographical regions, the absence of treatment differences by region suggests that the overall findings of CONVINCE are robust.

Cooper-Dehoff R, Cohen JD, Bakris GL, et al. Predictors of development of diabetes mellitus in patients with coronary artery disease taking antihypertensive medications (findings from the INternational VErapamil SR-Trandolapril STudy [INVEST]). *American Journal of Cardiology.* Oct 1 2006;98(7):890-894.

Knowledge of predictors of diabetes mellitus (DM) development in patients with coronary artery disease (CAD) who use antihypertensive therapy could contribute to decreasing this adverse metabolic consequence. This is particularly relevant because the standard of care, beta blockers combined with diuretics, may contribute to adverse metabolic risk. The INternational VErapamil SR-trandolapril STudy compared a calcium antagonist-based (verapamil SR) and a beta-blocker-based (atenolol) strategy with trandolapril and/or hydrochlorothiazide added to control blood pressure (BP) in patients with CAD. The 16,176 patients without DM at entry were investigated with regard to newly diagnosed DM during follow-up. Newly diagnosed DM was less frequent in the verapamil SR

versus atenolol strategy (7.0% vs 8.2%, hazard ratio 0.85, 95% confidence interval 0.76 to 0.95, p <0.01). Characteristics associated with risk for newly diagnosed DM included United States residence, left ventricular hypertrophy, previous stroke/transient ischemic attack, Hispanic ethnicity, coronary revascularization, hypercholesterolemia, greater body mass index, and higher follow-up systolic BP. Addition of trandolapril to verapamil SR decreased DM risk and addition of hydrochlorothiazide to atenolol increased risk. In conclusion, clinical findings associated with more severe vascular disease and Hispanic ethnicity identify a group at high risk for developing DM, whereas lower on-treatment BP and treatment with verapamil SR-trandolapril attenuated this risk.

de Leeuw PW, Ruilope LM, Palmer CR, et al. Clinical significance of renal function in hypertensive patients at high risk: results from the INSIGHT trial.[see comment]. *Archives of Internal Medicine.* Dec 13-27 2004;164(22):2459-2464.

BACKGROUND: Increasing evidence suggests renal involvement in hypertension-related cardiovascular and cerebrovascular complications. To assess this role of renal function in more detail, we studied the evolution of renal function and the relationship of renal function with mortality and morbidity in the Intervention as a Goal in Hypertension Treatment (INSIGHT) study. METHODS: The INSIGHT study was a double-blind, randomized, multicenter trial in patients with hypertension and at least 1 additional cardiovascular risk factor. Treatment consisted of nifedipine gastrointestinal therapeutic system, 30 mg/d, or hydrochlorothiazide-amiloride (25 mg/d of hydrochlorothiazide and 2.5 mg/d of amiloride hydrochloride). Primary outcome was a composite of cardiovascular death, myocardial infarction, heart failure, and stroke. Renal function was assessed by measuring creatinine clearance, serum creatinine level, and serum uric acid level and by the presence of proteinuria. RESULTS: Creatinine clearance fell more in nifedipine recipients than in hydrochlorothiazide-amiloride recipients. Renal insufficiency developed in 2% of nifedipine recipients and 5% of hydrochlorothiazide-amiloride recipients. Primary outcomes occurred in 15% of patients with increased serum creatinine levels and 6% of patients with normal levels (odds ratio [OR] 2.89; 95% confidence interval [CI], 1.92-4.36; P<.001). Primary outcomes were more likely in patients with low creatinine clearance (<60 mL/min) than in those with higher clearances (9% vs 5%, respectively [OR, 1.51, 95%CI, 1.22-1.88; P<.001]). CONCLUSIONS: Renal function is an important predictor of risk in hypertensive patients at high risk. Antihypertensive treatment with a long-acting dihydropyridine calcium channel blocker may better preserve renal function than would treatment with diuretics.

Derosa G, Cicero AFG, Bertone G, et al. Comparison of the effects of telmisartan and nifedipine gastrointestinal therapeutic system on blood pressure control, glucose metabolism, and the lipid profile in patients with type 2 diabetes mellitus and mild hypertension: a 12-month, randomized, double-blind study. *Clinical Therapeutics.* Aug 2004;26(8):1228-1236.

BACKGROUND: Angiotensin receptor blockers (ARBs) provide effective blood pressure control. Whereas none of the ARBs appear to affect glucose homeostasis, some ARBs have been associated with a decrease in cholesterolemia. OBJECTIVE: This study was conducted to evaluate blood pressure control glucose homeostasis, and the plasma lipid profile in patients with type 2 diabetes mellitus and mild hypertension during 12 months

of treatment with the ARB telmisartan or nifedipine gastrointestinal therapeutic system (GITS). METHODS: In this double-blind trial, patients taking oral hypoglycemic agents were randomized to receive telmisartan 40 mg or nifedipine GITS 20 mg once daily for 12 months. At the time of enrollment, patients were given advice on diet (1400-1600 kcal/d) and exercise (stationary bicycle for > or =30 min, 4 d/wk). Assessments of systolic blood pressure (SBP), diastolic blood pressure, body mass index (BMI), fasting plasma glucose concentrations, glycosylated hemoglobin, fasting plasma insulin concentrations, the homeostasis model assessment of insulin resistance, and the lipid profile were performed at baseline and after 6 and 12 months of treatment. RESULTS: One hundred sixteen patients were divided into 2 age- and sex-matched treatment groups (58 men, 58 women; mean [SD] age, 52.5 [5] years). All patients were in good general health at baseline; had achieved adequate glycemic control with diet and oral hypoglycemic agents; were taking antihypercholesterolemic drugs; and had no evidence of macroangiopathy, microalbuminuria, or neuropathy. There were significant reductions from baseline in seated trough SBP after 12 months of treatment with both telmisartan and nifedipine GITS (from 139 [4] to 132 [4] mm Hg and from 140 [4] to 130 [4] mm Hg, respectively; both, P < 0.01). No change in BMI or glucose metabolism was observed with either treatment. After 12 months, there were significant improvements in concentrations of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) with telmisartan (-9% and -11.5%, respectively; both, P < 0.01) compared with nifedipine GITS (-2% and -1.5%). CONCLUSIONS: In this selected sample of patients with type 2 diabetes and mild hypertension, both telmisartan and nifedipine GITS produced significant reductions in blood pressure. Telmisartan was associated with a slight but statistically significant improvement in plasma TC and LDL-C concentrations compared with nifedipine GITS.

Frishman WH, Hainer JW, Sugg J, Group MFS. A factorial study of combination hypertension treatment with metoprolol succinate extended release and felodipine extended release results of the Metoprolol Succinate-Felodipine Antihypertension Combination Trial (M-FACT). *American Journal of Hypertension.* Apr 2006;19(4):388-395.

BACKGROUND: Many hypertensive patients require combination therapy to achieve target blood pressure (BP). beta-Blockers and dihydropyridine calcium channel blockers are effective as monotherapy in hypertensive patients and have complementary mechanisms for lowering BP. METHODS: This multicenter, randomized, placebo-controlled, unbalanced factorial study included a 4- to 5-week single-blind placebo, 9-week, double-blind treatment as well as a 2-week double-blind, down-titration period. Patients (N = 1092) were randomized to one of 16 treatment groups: extended-release (ER) metoprolol succinate (25, 100, or 400 mg), ER felodipine (2.5, 10, or 20 mg), ER felodipine/ER metoprolol succinate (2.5/25, 2.5/100, 2.5/400, 10/25, 10/100, 10/400, 20/25, 20/100, or 20/400 mg), or placebo. RESULTS: At baseline, treatment groups were well balanced; mean sitting BP was 152.6/99.9 mm Hg. Monotherapy with ER metoprolol succinate induced dose-related reductions in sitting systolic/diastolic BP (DBP) (mean 8.1/7.7 to 9.7/11.1 mm Hg) as did ER felodipine (mean 7.7/7.7 to 14.0/11.8) and the combinations reflected additive effects (mean 13.8/11.0 to 19.8/15.2). The decline in the placebo group was 2.1/4.0 mm Hg. All combinations were more effective than their components (P < .05 for all but ER metoprolol succinate 25/ER felodipine 20). When compared with the

highest doses of the individual agents (ER metoprolol succinate 400 mg; ER felodipine 20 mg), the low-dose combination ER metoprolol succinate 25/ER felodipine 2.5 was approximately as effective (differences in DBP <1 mm Hg). The most common adverse events leading to discontinuation were peripheral edema (4%), headache (2%), and fatigue (1%). Higher rates of peripheral edema and flushing were associated with high-dose ER felodipine, either alone or in combination. CONCLUSIONS: The antihypertensive effects of ER metoprolol succinate and ER felodipine are dose-related, and when given in combination, their BP-lowering effects are additive over a wide dose range. Low-dose combination therapy is comparable in effectiveness to high-dose monotherapy but is better tolerated.

Hemels MEW, Van Noord T, Crijns HJGM, et al. Verapamil versus digoxin and acute versus routine serial cardioversion for the improvement of rhythm control for persistent atrial fibrillation. *Journal of the American College of Cardiology.* Sep 5 2006;48(5):1001-1009.

OBJECTIVES: The VERDICT (Verapamil Versus Digoxin and Acute Versus Routine Serial Cardioversion Trial) is a prospective, randomized study to investigate whether: 1) acutely repeated serial electrical cardioversions (ECVs) after a relapse of atrial fibrillation (AF); and 2) prevention of intracellular calcium overload by verapamil, decrease intractability of AF. BACKGROUND: Rhythm control is desirable in patients suffering from symptomatic AF. METHODS: A total of 144 patients with persistent AF were included. Seventy-four (51%) patients were randomized to the acute (within 24 h) and 70 (49%) patients to the routine serial ECVs, and 74 (51%) patients to verapamil and 70 (49%) patients to digoxin for rate control before ECV and continued during follow-up (2 x 2 factorial design). Class III antiarrhythmic drugs were used after a relapse of AF. Follow-up was 18 months. RESULTS: At baseline, there were no significant differences between the groups, except for beta-blocker use in the verapamil versus digoxin group (38% vs. 60%, respectively, p = 0.01). At follow-up, no difference in the occurrence of permanent AF between the acute and the routine cardioversion groups was observed (32% [95% confidence intervals (CI)] 22 to 44) vs. 31% [95% CI 21 to 44], respectively, p = NS), and also no difference between the verapamil- and the digoxin-randomized patients (28% [95% CI 19 to 40] vs. 36% [95% CI 25 to 48] respectively, p = NS). Multivariate Cox regression analysis revealed that lone digoxin use was the only significant predictor of failure of rhythm control treatment (hazard ratio 2.2 [95% CI 1.1 to 4.4], p = 0.02). CONCLUSIONS: An acute serial cardioversion strategy does not improve long-term rhythm control in comparison with a routine serial cardioversion strategy. Furthermore, verapamil has no beneficial effect in a serial cardioversion strategy.

Inoue S, Tomino Y. Effects of calcium antagonists in hypertensive patients with renal dysfunction: a prospective, randomized, parallel trial comparing benidipine and nifedipine. *Nephrology.* Oct 2004;9(5):265-271.

BACKGROUND: Although calcium antagonists, derived from dihydropyridine (DHP), are important agents in achieving control in a majority of patients with high blood pressure and renal disease, there are no comparative data regarding their inhibitory effects on the progression of renal dysfunction in Japan. METHODS: Benidipine and nifedipine retard both calcium antagonists derived from DHP and were compared in terms of their

inhibitory effect on the progression of renal dysfunction in hypertensive patients. The primary end-points were defined as 1.5 times the serum creatinine value at baseline, progression to end-stage renal failure (ESRF) necessitating dialysis or renal transplantation, and death. RESULTS: During the study period, a significant decline in blood pressure was observed in the two groups, with no significant difference between them. The worsening of nephropathy was significantly inhibited in the benidipine group as compared with the nifedipine retard group (log-rank test: P = 0.014, Wilcoxon's test: P = 0.022). Among the subjects who reached a primary end-point, one (33%) in the benidipine group and five (50%) in the nifedipine retard group were placed on haemodialysis within 1 year. CONCLUSION: It appears that benidipine inhibits the progression of hypertensive renal diseases more effectively than nifedipine retard.

Investigators JE, Investigators JE. Effect of Losartan and Amlodipine on Left Ventricular Diastolic Function in Patients With Mild-to-Moderate Hypertension (J-ELAN): rationale and design. *Circulation Journal.* Jan 2006;70(1):124-128.

BACKGROUND: Hypertension is a major underlying disease that may cause left ventricular (LV) diastolic dysfunction, even without LV systolic dysfunction, and antihypertensive drugs could affect LV diastolic function. METHODS AND RESULTS: The Effect of Losartan and Amlodipine on Left Ventricular Diastolic Function in Patients With Mild-to-Moderate Hypertension (J-ELAN) study is a multicenter, prospective, randomized trial designed to assess the effects of losartan and amlodipine on LV diastolic function in hypertensive patients with LV diastolic dysfunction in the absence of systolic dysfunction. A total of 300 patients (150 patients in each group) will be enrolled. In addition to Doppler echocardiographic indices of LV diastolic function, changes in LV structure and atherosclerosis of the carotid arteries will be serially assessed. The maximum follow-up period is 18 months. CONCLUSIONS: This study will provide the characteristic differences in the effects of amlodipine and losartan on LV diastolic dysfunction in hypertensive patients.

Koylan N, Bilge AK, Adalet K, Mercanoglu F, Buyukozturk K, Group TTS. Comparison of the effects of trimetazidine and diltiazem on exercise performance in patients with coronary heart disease. The Turkish trimetazidine study (TTS). *Acta Cardiologica.* Dec 2004;59(6):644-650.

OBJECTIVE: A multicentre, double-blind comparative study was performed to compare the effects of trimetazidine with diltiazem on exercise performance in patients with stable angina pectoris. METHODS AND RESULTS: A total of 116 male patients with documented coronary artery disease at 11 centres were randomized into trimetazidine and diltiazem groups both including 58 men (mean age 55.1+/-8.6 years and 54.9+/-6.6 years, respectively) in a prospective, multicentre, double-blind active treatment trial.The study consisted of a two-week placebo washout period and a four-week active treatment phase. Clinical examinations and exercise tests were performed at the beginning (D0) and at the end (D28) of the active treatment. Laboratory investigations were also performed at the beginning of the washout period (D-14) and at D28. Holter recordings were done in the mid of the washout period (D-7) and D28. Both trimetazidine and diltiazem decreased the

number of anginal attacks per week ($p < 0.0001$ for both drugs) and weekly nitrate consumption ($p = 0.0008$ and $p < 0.0001$, respectively). Both trimetazidine and diltiazem improved the recovery of anginal pain ($p = 0.0188$ and $p = 0.0079$, respectively) and maximal ST-segment depression ($p = 0.0134$ and $p = 0.0214$, respectively) but none of the drugs significantly changed the time to 1 mm ST-segment depression and ST recovery time on exercise test. Diltiazem caused a slight prolongation of PR and QRS durations ($p = 0.039$) on ambulatory ECG whereas trimetazidine did not change these parameters significantly. CONCLUSION: This study suggests that trimetazidine is an effective and safe alternative for diltiazem in the treatment of patients with stable angina pectoris. Although several other trials have shown that this drug can be used in combination with other antianginal drugs or instead of beta blockers or nifedipine in the symptomatic treatment of stable anginal syndromes, this study suggests that trimetazidine can be used instead of diltiazem, a well-known powerful antianginal drug.

Leenen FHH, Nwachuku CE, Black HR, et al. Clinical events in high-risk hypertensive patients randomly assigned to calcium channel blocker versus angiotensin-converting enzyme inhibitor in the antihypertensive and lipid-lowering treatment to prevent heart attack trial.[see comment]. *Hypertension.* Sep 2006;48(3):374-384.

The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) provides a unique opportunity to compare the long-term relative safety and efficacy of angiotensin-converting enzyme inhibitor and calcium channel blocker-initiated therapy in older hypertensive individuals. Patients were randomized to amlodipine (n=9048) or lisinopril (n=9054). The primary outcome was combined fatal coronary heart disease or nonfatal myocardial infarction, analyzed by intention-to-treat. Secondary outcomes included all-cause mortality, stroke, combined cardiovascular disease (CVD), end-stage renal disease (ESRD), cancer, and gastrointestinal bleeding. Mean follow-up was 4.9 years. Blood pressure control was similar in nonblacks, but not in blacks. No significant differences were found between treatment groups for the primary outcome, all-cause mortality, ESRD, or cancer. Stroke rates were higher on lisinopril in blacks (RR=1.51, 95% CI 1.22 to 1.86) but not in nonblacks (RR=1.07, 95% CI 0.89 to 1.28), and in women (RR=1.45, 95% CI 1.17 to 1.79), but not in men (RR=1.10, 95% CI 0.92 to 1.31). Rates of combined CVD were higher (RR=1.06, 95% CI 1.00 to 1.12) because of higher rates for strokes, peripheral arterial disease, and angina, which were partly offset by lower rates for heart failure (RR=0.87, 95% CI 0.78 to 0.96) on lisinopril compared with amlodipine. Gastrointestinal bleeds and angioedema were higher on lisinopril. Patients with and without baseline coronary heart disease showed similar outcome patterns. We conclude that in hypertensive patients, the risks for coronary events are similar, but for stroke, combined CVD, gastrointestinal bleeding, and angioedema are higher and for heart failure are lower for lisinopril-based compared with amlodipine-based therapy. Some, but not all, of these differences may be explained by less effective blood pressure control in the lisinopril arm.

Mancia G, Ruilope L, Palmer C, et al. Effects of nifedipine GITS and diuretics in isolated systolic hypertension--a subanalysis of the INSIGHT study. *Blood Pressure.* 2004;13(5):310-315.

AIMS: This study tested the effects on cardiovascular outcomes of treatments based on nifedipine gastrointestinal therapeutic system (GITS) compared with the diuretic combination co-amilozide in a pre-specified subset of patients with isolated systolic hypertension (ISH) enrolled in the International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) study. MAJOR FINDINGS: Of 6321 randomized patients, 1498 (23.7%) had ISH with a baseline mean BP of 173/88 mmHg in both treatment groups. Mean BP fell by 29/10 mmHg in the nifedipine and 30/10 mmHg in the diuretic group to a mean BP of 144/78 mmHg and 143/79 mmHg, respectively, at endpoint. The percentage of primary outcomes in patients with ISH was not significantly different between the two treatment groups (nifedipine GITS 6.0%, co-amilozide 6.6%). The number of ISH patients with composite secondary outcomes was 90 (12.2%) in the nifedipine GITS group and 110 (14.5%) in the co-amilozide group (not significant). The incidence rates of primary and secondary outcomes were similar in patients without ISH. CONCLUSION: In patients with ISH, nifedipine GITS and co-amilozide had similar effects on clinical outcomes and BP lowering. They lend support to international guidelines for the treatment of hypertension recommending the use of long-acting dihydropyridine calcium-channel blockers as one treatment option for patients with ISH.

Messerli FH, Mancia G, Conti CR, et al. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Annals of Internal Medicine.* Jun 20 2006;144(12):884-893.

BACKGROUND: Because coronary perfusion occurs mainly during diastole, patients with coronary artery disease (CAD) could be at increased risk for coronary events if diastolic pressure falls below critical levels. OBJECTIVE: To determine whether low blood pressure could be associated with excess mortality and morbidity in this population. DESIGN: A secondary analysis of data from the International Verapamil-Trandolapril Study (INVEST), which was conducted from September 1997 to February 2003. SETTING: 862 sites in 14 countries. PATIENTS: 22 576 patients with hypertension and CAD. Interventions: Patients from INVEST were randomly assigned to a verapamil sustained-release- or atenolol-based strategy; blood pressure control and outcomes were equivalent. MEASUREMENTS: An unadjusted quadratic proportional hazards model was used to evaluate the relationship between average on-treatment blood pressure and risk for the primary outcome (all-cause death, nonfatal stroke, and nonfatal myocardial infarction [MI]), all-cause death, total MI, and total stroke. A second model adjusted for differences in baseline covariates. RESULTS: The relationship between blood pressure and the primary outcome, all-cause death, and total MI was J-shaped, particularly for diastolic pressure, with a nadir at 119/84 mm Hg. After adjustment, the J-shaped relationship persisted between diastolic pressure and primary outcome. The MI-stroke ratio remained constant over a wide blood pressure range, but at a lower diastolic blood pressure, there were substantially more MIs than strokes. An interaction between decreased diastolic pressure and history of revascularization was observed; low diastolic pressure was associated with a relatively lower risk for the primary outcome in patients with revascularization than in those without revascularization. LIMITATIONS: This is a post hoc analysis of hypertensive patients with CAD. CONCLUSIONS: The risk for the primary outcome, all-cause death, and MI, but not stroke, progressively increased with

low diastolic blood pressure. Excessive reduction in diastolic pressure should be avoided in patients with CAD who are being treated for hypertension.

Nissen SE, Tuzcu EM, Libby P, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial.[see comment]. *JAMA.* Nov 10 2004;292(18):2217-2225.

CONTEXT: The effect of antihypertensive drugs on cardiovascular events in patients with coronary artery disease (CAD) and normal blood pressure remains uncertain. OBJECTIVE: To compare the effects of amlodipine or enalapril vs placebo on cardiovascular events in patients with CAD. DESIGN, SETTING, AND PARTICIPANTS: Double-blind, randomized, multicenter, 24-month trial (enrollment April 1999-April 2002) comparing amlodipine or enalapril with placebo in 1991 patients with angiographically documented CAD (>20% stenosis by coronary angiography) and diastolic blood pressure <100 mm Hg. A substudy of 274 patients measured atherosclerosis progression by intravascular ultrasound (IVUS). INTERVENTIONS: Patients were randomized to receive amlodipine, 10 mg; enalapril, 20 mg; or placebo. IVUS was performed at baseline and study completion. MAIN OUTCOME MEASURES: The primary efficacy parameter was incidence of cardiovascular events for amlodipine vs placebo. Other outcomes included comparisons of amlodipine vs enalapril and enalapril vs placebo. Events included cardiovascular death, nonfatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina pectoris, hospitalization for congestive heart failure, fatal or nonfatal stroke or transient ischemic attack, and new diagnosis of peripheral vascular disease. The IVUS end point was change in percent atheroma volume. RESULTS: Baseline blood pressure averaged 129/78 mm Hg for all patients; it increased by 0.7/0.6 mm Hg in the placebo group and decreased by 4.8/2.5 mm Hg and 4.9/2.4 mm Hg in the amlodipine and enalapril groups, respectively (P<.001 for both vs placebo). Cardiovascular events occurred in 151 (23.1%) placebo-treated patients, in 110 (16.6%) amlodipine-treated patients (hazard ratio [HR], 0.69; 95% CI, 0.54-0.88 [P = .003]), and in 136 (20.2%) enalapril-treated patients (HR, 0.85; 95% CI, 0.67-1.07 [P = .16]. Primary end point comparison for enalapril vs amlodipine was not significant (HR, 0.81; 95% CI, 0.63-1.04 [P = .10]). The IVUS substudy showed a trend toward less progression of atherosclerosis in the amlodipine group vs placebo (P = .12), with significantly less progression in the subgroup with systolic blood pressures greater than the mean (P = .02). Compared with baseline, IVUS showed progression in the placebo group (P<.001), a trend toward progression in the enalapril group (P = .08), and no progression in the amlodipine group (P = .31). For the amlodipine group, correlation between blood pressure reduction and progression was r = 0.19, P = .07. CONCLUSIONS: Administration of amlodipine to patients with CAD and normal blood pressure resulted in reduced adverse cardiovascular events. Directionally similar, but smaller and nonsignificant, treatment effects were observed with enalapril. For amlodipine, IVUS showed evidence of slowing of atherosclerosis progression.

Ruggenenti P, Fassi A, Ilieva AP, et al. Preventing microalbuminuria in type 2 diabetes.[see comment]. *New England Journal of Medicine.* Nov 4 2004;351(19):1941-1951.

BACKGROUND: The multicenter double-blind, randomized Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) was designed to assess whether angiotensin-converting-enzyme inhibitors and non-dihydropyridine calcium-channel blockers, alone or in combination, prevent microalbuminuria in subjects with hypertension, type 2 diabetes mellitus, and normal urinary albumin excretion. METHODS: We studied 1204 subjects, who were randomly assigned to receive at least three years of treatment with trandolapril (at a dose of 2 mg per day) plus verapamil (sustained-release formulation, 180 mg per day), trandolapril alone (2 mg per day), verapamil alone (sustained-release formulation, 240 mg per day), or placebo. The target blood pressure was 120/80 mm Hg. The primary end point was the development of persistent microalbuminuria (overnight albumin excretion, > or =20 microg per minute at two consecutive visits). RESULTS: The primary outcome was reached in 5.7 percent of the subjects receiving trandolapril plus verapamil, 6.0 percent of the subjects receiving trandolapril, 11.9 percent of the subjects receiving verapamil, and 10.0 percent of control subjects receiving placebo. The estimated acceleration factor (which quantifies the effect of one treatment relative to another in accelerating or slowing disease progression) adjusted for predefined baseline characteristics was 0.39 for the comparison between verapamil plus trandolapril and placebo (P=0.01), 0.47 for the comparison between trandolapril and placebo (P=0.01), and 0.83 for the comparison between verapamil and placebo (P=0.54). Trandolapril plus verapamil and trandolapril alone delayed the onset of microalbuminuria by factors of 2.6 and 2.1, respectively. Serious adverse events were similar in all treatment groups. CONCLUSIONS: In subjects with type 2 diabetes and hypertension but with normoalbuminuria, the use of trandolapril plus verapamil and trandolapril alone decreased the incidence of microalbuminuria to a similar extent. The effect of verapamil alone was similar to that of placebo. Copyright 2004 Massachusetts Medical Society.

Vranic II, Matic M, Perunicic J, Simic T, Soskic L, Milic N. Adenosine cardioprotection study in clinical setting of paroxysmal supraventricular tachycardia. *Prostaglandins Leukotrienes & Essential Fatty Acids.* Jun 2006;74(6):365-371.

PSVT attack of >20min and frequency >160 is well-recognized model of myocardial dysfunction. We measured 6-keto-PGF1alpha and TXB(2) before and after adenosine administration to assess its cardioprotective potential. A total of 64 patients were randomly assigned as having acute episode of PSVT to adenosine or verapamil group. A bolus of 6mg of adenosine up to the maximum dose of 12 or 5mg of verapamil up to the maximum dose of 10mg were given, until the sinus rhythm was restored. The levels of PGI(2), TXA(2) and TAS were measured in three different time intervals. In adenosine group all parameters were normalized after 20min of conversion to sinus rhythm. The ratio of PGI(2)/TXA(2) increased after 5min of conversion to SR (P<0.01). Also, the ratio of TXA(2)/TAS was decreased for ADO (P<0.01). This is the first study to demonstrate that adenosine exerts cardioprotective effect.

Whelton PK, Barzilay J, Cushman WC, et al. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Archives of Internal Medicine.* Jun 27 2005;165(12):1401-1409.

BACKGROUND: Optimal first-step antihypertensive drug therapy in type 2 diabetes mellitus (DM) or impaired fasting glucose levels (IFG) is uncertain. We wished to determine whether treatment with a calcium channel blocker or an angiotensin-converting enzyme inhibitor decreases clinical complications compared with treatment with a thiazide-type diuretic in DM, IFG, and normoglycemia (NG). METHODS: Active-controlled trial in 31 512 adults, 55 years or older, with hypertension and at least 1 other risk factor for coronary heart disease, stratified into DM (n = 13 101), IFG (n = 1399), and NG (n = 17 012) groups on the basis of national guidelines. Participants were randomly assigned to double-blind first-step treatment with chlorthalidone, 12.5 to 25 mg/d, amlodipine besylate, 2.5 to 10 mg/d, or lisinopril, 10 to 40 mg/d. We conducted an intention-to-treat analysis of fatal coronary heart disease or nonfatal myocardial infarction (primary outcome), total mortality, and other clinical complications. RESULTS: There was no significant difference in relative risk (RR) for the primary outcome in DM or NG participants assigned to amlodipine or lisinopril vs chlorthalidone or in IFG participants assigned to lisinopril vs chlorthalidone. A significantly higher RR (95% confidence interval) was noted for the primary outcome in IFG participants assigned to amlodipine vs chlorthalidone (1.73 [1.10-2.72]). Stroke was more common in NG participants assigned to lisinopril vs chlorthalidone (1.31 [1.10-1.57]). Heart failure was more common in DM and NG participants assigned to amlodipine (1.39 [1.22-1.59] and 1.30 [1.12-1.51], respectively) or lisinopril (1.15 [1.00-1.32] and 1.19 [1.02-1.39], respectively) vs chlorthalidone. CONCLUSION: Our results provide no evidence of superiority for treatment with calcium channel blockers or angiotensin-converting enzyme inhibitors compared with a thiazide-type diuretic during first-step antihypertensive therapy in DM, IFG, or NG.

Kojima S, Shida M, Yokoyama H. Comparison between cilnidipine and amlodipine besilate with respect to proteinuria in hypertensive patients with renal diseases. *Hypertension Research - Clinical & Experimental.* Jun 2004;27(6):379-385.

Unlike other dihydropyridine calcium channel blockers (CCBs), cilnidipine has been reported to exert an N-type calcium-channel-blocking activity and to reduce sympathetic hyperactivity. This study compared cilnidipine and amlodipine with respect to their effects on renal function and proteinuria. Twenty-eight proteinuric hypertensive outpatients (13 men and 15 women, aged 62+/-2 years) who had been maintained on CCBs for more than 3 months were randomly assigned to a group receiving amlodipine besilate (14 patients) or a group receiving cilnidipine (14 patients). CCBs were increased in dosage or other drugs were added until blood pressure decreased below 140/90 mmHg, but no inhibitors of the renin-angiotensin (RA) system were added or changed in dosage. Before and at 6 and 12 months after randomization, the concentrations of urine protein, urine albumin, serum and urine creatinine (Cr), and serum beta2-microglobulin were determined. The amlodipine group showed a significant increase in proteinuria, while the increase was suppressed in the cilnidipine group. The rate of increase in proteinuria at 12 months was 87% (95% confidence interval (CI) -10 to 184) of the baseline value with amlodipine and 4% (95% CI -69 to 77) of baseline with cilnidipine, a significant intergroup difference ($p<0.05$). The mean blood pressure remained in the 96-99 mmHg range until 12 months after randomization, showing no significant difference between the two groups. The cilnidipine group showed an increase in serum Cr levels (baseline vs. 12

months, 1.36+/-0.20 vs. 1.50+/-0.23 mg/dl, p<0.01). Overall, an inverse correlation existed between the changes in Cr and proteinuria (r= -0.477, p<0.01). These results suggest that cilnidipine results in a greater suppression of the increase in proteinuria and greater reduction in glomerular filtration rate than amlodipine, and that these effects are similar between cilnidipine and RA inhibitors. However, additional large-cohort and longer-term studies will be needed to clarify whether cilnidipine is superior to other CCBs in maintaining renal function.

Vora A, Karnad D, Goyal V, et al. Control of rate versus rhythm in rheumatic atrial fibrillation: a randomized study.[see comment]. *Indian Heart Journal.* Mar-Apr 2004;56(2):110-116.

BACKGROUND: Patients with rheumatic heart disease and atrial fibrillation incur significant morbidity and mortality. It is not known which approach, rate control or maintenance of sinus rhythm might be most appropriate. The present study was undertaken to compare the strategy of ventricular rate control versus maintenance of sinus rhythm in rheumatic atrial fibrillation, and to evaluate the role of amiodarone in this patient population. METHODS AND RESULTS: We prospectively studied 144 patients with chronic rheumatic atrial fibrillation in a double-blind protocol-rhythm control (group I: 48 patients each with amiodarone -group Ia; and placebo -group Ib) and compared the effects with the ventricular rate control (group II) by diltiazem (n=48, open-label). Direct current cardioversion was attempted in group I. The mean age of the study population was 38.6+/-10.3 years, left atrial size was 4.7+/-0.6 cm, atrial fibrillation duration was 6.1+/-5.4 years, and 72.9% patients had undergone valvular interventions. At 1 year, 45 patients with sinus rhythm in group I compared to 48 patients in group II demonstrated significant increase in exercise to sinus rhythm time, had improvement in functional class and quality of life score. There was no difference in hospitalization rates, systemic bleeds or incidence of thromboembolism. Five patients died in group II but none in group I (p=0.02). In group I, 73/87 (83.9%) patients converted, and 45/86 (52.3%) patients maintained sinus rhythm at 1 year. Conversion rates were 38/43 (88.4%) with amiodarone versus 34/44 (77.3%) with placebo (p=0.49): corresponding rate for maintaining sinus rhythm was 29/42 (69.1%) versus 16/44 (36.4%), p=0.008 respectively. CONCLUSIONS: Maintenance of sinus rhythm appeared to be superior to ventricular rate control in patients with rheumatic atrial fibrillation in terms of an effect on mortality and morbidity. Sinus rhythm could be restored in the majority and amiodarone was superior to placebo in this regard.

Placebo-Controlled Trials

Liu L, Zhang Y, Liu G, et al. The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients.[see comment]. *Journal of Hypertension.* Dec 2005;23(12):2157-2172.

OBJECTIVE: To compare the incidence of stroke and other cardiovascular events in hypertensive patients receiving a low-dose diuretic and low-dose calcium antagonist combination with those receiving low-dose diuretic monotherapy, and assess the effects of a small blood pressure difference at achieved levels lower than those achieved in previous placebo-controlled trials. METHODS: The Felodipine Event Reduction

(FEVER) trial was an investigator-designed, prospective, multicentre, double-blind, randomized, placebo-controlled, parallel group trial. It enrolled 9800 Chinese patients, of either sex, aged 50-79 years, with one or two additional cardiovascular risk factors or disease, whose blood pressure, 6 weeks after switching from previous antihypertensive therapy to low-dose (12.5 mg a day) hydrochlorothiazide, was in the range 140-180 mmHg (systolic) or 90-100 mmHg (diastolic). These patients were randomly assigned either to low-dose felodipine extended release or placebo, and followed at 3-month intervals for an average of 40 months. RESULTS: The intention-to-treat analysis included 9711 randomly selected patients with only 30 (0.3%) lost to follow-up. A total of 31 842 patient-years of follow-up were accumulated, with 85.9% of patients remaining on blinded randomized treatment. Add-on therapy was given to 33.9% of the hydrochlorothiazide-felodipine patients and to 42.3% of the hydrochlorothiazide-placebo patients. In the felodipine group, systolic blood pressure (SBP)/diastolic blood pressure (DBP) decreased (from randomization to study end) from 154.2/91.0 to 137.3/82.5 mmHg, and in the placebo group from 154.4/91.3 to 142.5/85.0 mmHg, with an average difference throughout the trial of 4.2/2.1 mmHg. In the felodipine group, the primary endpoint (fatal and non-fatal stroke) was reduced by 27% (P = 0.001). Among secondary endpoints, all cardiovascular events were reduced by 27% (P < 0.001), all cardiac events by 35% (P = 0.012), death by any cause by 31% (P = 0.006), coronary events by 32% (P = 0.024), heart failure by 30% (P = 0.239), cardiovascular death by 33% (P = 0.019), cancer by 36% (P = 0.017) in the felodipine group. No significant differences were found in new-onset diabetes. Both treatments were very well tolerated. CONCLUSIONS: In moderately complicated hypertensive patients from China even a difference in SBP/DBP as small as 4/2 mmHg, such as that induced by adding low-dose felodipine to low-dose hydrochlorothiazide, is associated with very substantial reductions in the incidence of most types of cardiovascular events. As the SBP achieved in the felodipine group was below the recommended goal of less than 140 mmHg, and SBP in the placebo group was slightly above that level, FEVER provides the required evidence in support of the guidelines recommended goal, even for a hypertensive population not entirely consisting of patients with diabetes or previous cardiovascular events.

Lubsen J, Wagener G, Kirwan B-A, de Brouwer S, Poole-Wilson PA, investigators A. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with symptomatic stable angina and hypertension: the ACTION trial.[see comment]. *Journal of Hypertension.* Mar 2005;23(3):641-648.

OBJECTIVE: To examine the effects of nifedipine GITS on clinical outcome in patients with concurrent stable angina and hypertension. METHODS: Data from the double-blind placebo-controlled ACTION trial was stratified for hypertension (blood pressure > or = 140/90 mmHg), at baseline. RESULTS: A total of 52% of 7665 ACTION patients were hypertensive. Some 80% were on a beta blocker; hypertensives were more often treated with other blood pressure-lowering drugs. Mean baseline blood pressure was 122/74 mmHg among normotensives and 151/85 mmHg among hypertensives. Follow-up blood pressures were reduced by nifedipine (P < 0.001) on the average by 3.9/2.4 and 6.6/3.5 mmHg among normotensives and hypertensives, respectively. Nifedipine GITS significantly (P < 0.05) reduced the combined incidence of all-cause mortality, myocardial infarction, refractory angina, heart failure, stroke and peripheral

revascularization by 13% in hypertensives only. Nifedipine significantly reduced the incidence of any stroke or transient ischemic attack by almost 30% in both subgroups and the need for coronary angiography by 21% in normotensives and 16% in hypertensives. Among hypertensives, the incidence of new overt heart failure was significantly reduced by 38% and of debilitating stroke by 33%. Among normotensives, the need for coronary bypass grafting was significantly reduced by 32%. Nifedipine did not affect all-cause death, cardiovascular death and myocardial infarction in either normo- or hypertensives, but increased the need for peripheral revascularization. CONCLUSION: The salutary effects of the addition of nifedipine GITS to the basic regimen of patients with concurrent stable symptomatic coronary artery disease and hypertension emphasize the need for blood pressure control.