

Drug Class Review on ACE Inhibitors

Preliminary Scan Report 4

November 2013

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

Update scan prepared by Sujata Thakurta, MPA:HA

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

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

Oregon Health & Science University

Copyright © 2013 by Oregon Health & Science University
Portland, Oregon 97239. All rights reserved.



Copyright © 2013 by Oregon Health & Science University
Portland, Oregon 97239. All rights reserved.

OBJECTIVE

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

Date of Last Update

Update 2 June 2005 (searches through February 2005)

Date of Last Update Scans

Scan #1: February 2007

Scan #2: February 2008

Scan #3: November 2008

Scope and Key Questions

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

Key Questions

1. For adult patients with essential hypertension, heart failure, high cardiovascular risk factors, diabetic nephropathy, nondiabetic nephropathy, or recent myocardial infarction, do angiotensin converting enzyme (ACE) inhibitors differ in effectiveness?
2. For adult patients with essential hypertension, heart failure, high cardiovascular risk factors, diabetic nephropathy, nondiabetic nephropathy, or recent myocardial infarction, do ACE inhibitors differ in safety or adverse events?
3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one ACE inhibitor is more effective or associated with fewer adverse events?

Inclusion Criteria

Populations

Adult patients with any of the following indications:

- Hypertension without compelling indications. This refers to patients with hypertension who do not have any of the following indications:
 - a. a history of coronary heart disease (CHD)
 - b. other cardiovascular diseases (CVD), such as cerebrovascular (carotid) disease, peripheral vascular disease, or a history of stroke
 - c. other risk factors for CAD/CVD, such as diabetes, smoking or hyperlipidemia
 - d. renal insufficiency
- Hypertension with compelling indications. This refers to patients with hypertension who also have one of the conditions listed above.
- High cardiovascular risk. This group includes patients who have a history of CHD/CVD, or a combination of other risk factors for CHD/CVD, such as diabetes, smoking, and hyperlipidemia. These patients may or may not have hypertension as well.
- Recent myocardial infarction. This group includes patients who have had a recent myocardial infarction and who have normal left ventricular function or asymptomatic left ventricular dysfunction.
- Heart failure. This group includes patients who have symptomatic heart failure due to left ventricular systolic dysfunction, with or without hypertension.
- Diabetic nephropathy. This group includes patients with Type 1 or Type 2 diabetes who have laboratory evidence of nephropathy, such as albuminuria or decreased creatinine clearance.

Interventions

- benazepril
- captopril
- enalapril
- fosinopril
- lisinopril
- moexipril
- quinapril
- ramipril
- perindopril
- trandolapril

Effectiveness outcomes

Effectiveness measures varied according to the clinical condition:

Hypertension

- All-cause and cardiovascular mortality
- Cardiovascular events (stroke, myocardial infarction, or development of heart failure)
- End-stage renal disease (including dialysis or need for transplantation) or clinically significant and permanent deterioration of renal function (increase in serum creatinine or decrease in creatinine clearance)
- Quality-of-life

(Trials that focused on blood pressure reduction but not on any health outcomes were excluded from the effectiveness review)

High cardiovascular risk

- All-cause and cardiovascular mortality
- Cardiovascular events (stroke, myocardial infarction, or development of heart failure)

Recent myocardial infarction

- All-cause and cardiovascular mortality
- Cardiovascular events (usually, development of heart failure)

Heart failure

- All-cause or cardiovascular mortality
- Symptomatic improvement (heart failure class, functional status, visual analogue scores)
- Hospitalizations for heart failure

Diabetic nephropathy/non-diabetic nephropathy

- End-stage renal disease (including dialysis or need for transplantation)
- Clinically significant and permanent deterioration of renal function (increase in serum creatinine or decrease in creatinine clearance)

Safety outcomes

- Withdrawals
- Withdrawals due to adverse effects
- Specific adverse effects or withdrawals due to specific adverse events, for example, symptomatic hypotension

Study designs

1. Randomized controlled trials that compared one of the included ACE inhibitors to another.
2. Systematic reviews of the clinical effectiveness or adverse event rates of ACE inhibitors for included clinical conditions that reported an included outcome.
3. Large (> 100 patients) placebo-controlled trials for included clinical conditions that reported an included outcome.
4. Randomized controlled trials and large, good-quality observational studies that evaluated adverse event rates for one or more of the included ACE Inhibitors.

METHODS**Literature Search**

To identify relevant citations, we searched Ovid MEDLINE from October 2008 through October 2013, using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. We also searched FDA (<http://www.fda.gov/medwatch/safety.htm>) for identification of new drugs, indications, and safety alerts. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (<http://www.ahrq.gov/>) and the Canadian Agency

for Drugs and Technology in Health (<http://www.cadth.ca/>). All citations were imported into an electronic database (EndNote X3) and duplicate citations were removed.

Study Selection

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

RESULTS

New Drugs

New drugs identified in this Preliminary Update Scan

Epaned™ (enalapril maleate) oral solution approved on August 2013 is indicated for the treatment of hypertension, to lower blood pressure in adults and children older than one month.

New drugs identified in previous Preliminary Update Scan(s)

None identified.

New Indications

New indications identified in this Preliminary Update Scan

None identified.

Identified in previous Preliminary Update Scan(s)

New indication for perindopril in patients with stable coronary artery disease to reduce the risk of cardiovascular mortality or non-fatal myocardial infarction.

New Boxed Warnings

Identified in this Preliminary Update Scan

In January 2012, a new boxed warning was issued for Mavik® (trandolapril tablets). Similar boxed warnings were also issued for other included Ace Inhibitors including Accupril® (Quinapril), Altace®(Ramipril), Lotensin®(Benazepril) and Univas® (Moexipril) in 2012.

WARNING: FETAL TOXICITY

When pregnancy is detected, discontinue MAVIK as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus (See WARNINGS: Fetal Toxicity).

Identified in previous Preliminary Update Scan(s)

Prior to January 2012, for most Ace Inhibitors the black box warnings were directed against use of the drugs in second and third trimesters.

Comparative Effectiveness Reviews

Reviews identified in this Preliminary Update Scan

A guideline on the “Administration of Angiotensin Converting Enzyme Inhibitors Following Acute Myocardial Infarction” was produced by Canadian Agency for Drugs and Technologies in Health in May of 2010. The details of the guideline is included in Appendix A below.

Reviews identified in previous Preliminary Update Scan(s)

None

Overview

Medline searches resulted in 511 new citations. No relevant head to head trials comparing one ACE inhibitor against the other were found in this scan. There were 8 new potentially relevant placebo controlled trials (see Appendix B, attached) obtained from this scan and are shaded in table 1 below. There was 1 potentially relevant head to head trial and 16 placebo controlled trials that were found in previous scans (Appendix C). Cumulatively, 1 head to head trial and 24 placebo controlled trials that are available at this time. Majority of the trials focused on perindopril. Several of them were subgroup or secondary analyses of trials included in the DERP ACE Inhibitor report like EUROPA, PROGRESS, PEACE, GISSI.

Table 1. Potentially relevant trials of ACE Inhibitors

| Author, Year | Drugs | Population | Outcomes | NOTES |
|-------------------------------|--------------------------|---|--|----------|
| <i>Head to head trial</i> | | | | |
| Tumanan-Mendoza, 2007 | Elanalapril, Perindopril | Hypertension | Cough | |
| <i>Placebo control trials</i> | | | | |
| Arima, 2005 | Perindopril | Atrial Fibrillation and prior stroke, transient ischemic attack | Mortality, major vascular outcomes | PROGRESS |
| Arima, 2011 | Perindopril | Patients with diastolic hypertension | Major vascular events | PROGRESS |
| Bertrand, 2009 | Perindopril | Subpopulation of patients with a history of myocardial infarction and revascularization | composite of cardiovascular mortality, myocardial infarction and resuscitated cardiac arrest | EUROPA |
| Brugts, 2007 | Perindopril | Subgroup of patients with stable coronary artery disease | Cardiovascular death, nonfatal myocardial infarction, or resuscitated cardiac arrest | EUROPA |
| Coppo, 2007 | Benazepril | Nephropathy | Progression of kidney disease | |
| Daly, 2005 | Perindopril | Diabetes | Cardiovascular death, non-fatal myocardial infarction, and resuscitated cardiac arrest | EUROPA |
| Daly, 2005 | Perindopril | Coronary artery disease | Metabolic syndrome and its effect on cardiovascular morbidity and mortality | EOROPA |
| De Mello, 2008 | Enalapril | Type 2 diabetes with microalbuminuria | Urinary albumin excretion rate, blood pressure | |
| Deckers, 2006 | Perindopril | Coronary artery disease | Cardiovascular death, non-fatal myocardial infarction in male patients over 65 years | |
| Gianni, 2007 | Benazepril | Elderly patients | Cardiovascular death, srtoke, | |

| | | | | |
|---------------------|--------------|---|---|----------|
| | | with chronic stable vascular disease | myocardial infarction | |
| Hermida, 2009 | Ramipril | Hypertension | Blood pressure reduction | |
| Hou, 2006 | Benazepril | Renal insufficiency | Doubling of the serum creatinine level, end-stage renal disease, or death. | |
| Investigators, 2006 | Ramipril | Diabetes | Development of diabetes or death | |
| Jones-Burton 2010 | Enalapril | Hypertension in African American patients | Change in blood pressure | |
| Kostis, 2005 | Enalapril | Hypertension | Angioedema in black and older patients | |
| Luders, 2008 | Ramipril | High-normal blood pressure | Manifest hypertension, cerebrovascular and cardiovascular events | |
| Mauer, 2009 | Enalapril | Type 1 diabetes patients with nephropathy | Microalbuminuria | |
| Pedrazzini, 2008 | Lisinopril | Acute MI | Mortality up to 5 years | GISSI-3 |
| Potter, 2009 | Lisinopril | Patients with hypertension who had cerebral infarction and hemorrhage | Death and dependency at 2 weeks | CHHIPS |
| Ninomiya, 2008 | Perindopril | Chronic kidney disease | Recurrent stroke | PROGRESS |
| Rossignol, 2012 | Fosinopril | Hemodialysis patients | composite of cardiovascular death, nonfatal myocardial infarction, unstable angina, stroke, revascularization, hospitalization for heart failure, and resuscitated cardiac arrest. | |
| Rouleau, 2008 | Quinapril | Low-risk, post-CABG | Composite of cardiovascular death, resuscitated cardiac arrest, nonfatal myocardial infarction, coronary revascularization, unstable angina or heart failure requiring hospitalization, documented angina, and stroke | |
| Solomon, 2006 | Trandolapril | Chronic stable coronary disease | Mortality, reduced renal function | PEACE |
| Zannad, 2006 | Fosinopril | End stage renal disease | Combined fatal and nonfatal first major CVEs | |

Appendix A.

TITLE: Administration of Angiotensin Converting Enzyme Inhibitors Following Acute Myocardial Infarction: Guidelines

http://www.cadth.ca/media/pdf/k0187_ace_inhibitors_post-mi_management_htis1-5.pdf

DATE: 13 May 2010

RESEARCH QUESTION:

What are the guidelines for the administration of angiotension converting enzyme inhibitors following acute myocardial infarction?

OVERALL SUMMARY OF FINDINGS:

One systematic review¹ found that the use of ACE inhibitors in patients with acute MI improved both diastolic and systolic volumes over a term of six to twelve months. Another systematic review reported that in patients with a prior cardiovascular event or those who were at high risk of such an event, ACE inhibitors reduced the risk of all-cause mortality, cardiovascular mortality, acute MI, and stroke.

Several guidelines⁶⁻⁹ recommend that ACE inhibitors be offered to all patients presenting with acute MI or acute coronary syndrome. Others recommend the use of ACE inhibitors under more stringent conditions: ACE inhibitors are recommended as first-line therapy for hypertension in patients with recent MI; long-term management with ACE inhibitors should be used in patients with left ventricular dysfunction; ACE inhibitor use should be considered but not mandatory for patients presenting with ST elevation MI; ACE inhibitor dosages may have to be reduced or discontinued in patients with milder right ventricular dysfunction after MI.⁴ Most of the identified guidelines recommend angiotensin receptor blockers be used only when a patient is intolerant or allergic to ACE inhibitors.

Appendix B: Potentially relevant abstracts of trials from current scan 4

Arima, H., C. Anderson, et al. (2011). "Effects of blood pressure lowering on major vascular events among patients with isolated diastolic hypertension: the perindopril protection against recurrent stroke study (PROGRESS) trial." *Stroke* 42(8): 2339-2341.

BACKGROUND AND PURPOSE: Despite clear evidence that blood pressure (BP) lowering is effective for prevention of cardiovascular events among patients with isolated systolic hypertension and systolic-diastolic hypertension, there is ongoing uncertainty about its effects in those with isolated diastolic hypertension. The objective of the present analysis is to determine whether BP lowering provides benefits to patients with isolated diastolic hypertension.

METHODS: Patients with cerebrovascular disease and hypertension at baseline (n=4283) were randomly assigned to either active treatment (perindopril in all participants plus indapamide for those with neither an indication for nor a contraindication to a diuretic) or matching placebo(s). The primary outcome was total major vascular events.

RESULTS: There were 1923 patients with isolated systolic hypertension (systolic BP \geq 140 mm Hg and diastolic BP $<$ 90 mm Hg), 315 with isolated diastolic hypertension (systolic BP $<$ 140 mm Hg and diastolic BP \geq 90 mm Hg), and 2045 with systolic-diastolic hypertension (systolic BP \geq 140 mm Hg and diastolic BP \geq 90 mm Hg) at baseline. Active treatment reduced the relative risk of major vascular events by 27% (95% CI, 10% to 41%) among patients with isolated systolic hypertension, by 28% (-29% to 60%) among those with isolated diastolic hypertension, and by 32% (17% to 45%) among those with systolic-diastolic hypertension. There was no evidence of differences in the magnitude of the effects of treatment among different types of hypertension (P homogeneity=0.89).

CONCLUSIONS: BP lowering is likely to provide a similar level of protection against major vascular events for patients with isolated diastolic hypertension as for those with isolated systolic hypertension and systolic-diastolic hypertension. Clinical Trial Registration Information- This trial was not registered because patients were enrolled before July 1, 2005.

Bertrand, M. E., K. M. Fox, et al. (2009). "Angiotensin-converting enzyme inhibition with perindopril in patients with prior myocardial infarction and/or revascularization: a subgroup analysis of the EUROPA trial." *Archives of cardiovascular diseases* 102(2): 89-96.

BACKGROUND: The European trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease (EUROPA) demonstrated the benefits of perindopril with respect to secondary prevention of cardiovascular risk in patients with stable coronary artery disease.

AIMS: To describe the clinical effects of perindopril in a subpopulation of patients from EUROPA with a history of myocardial infarction and/or revascularization.

PATIENTS AND METHODS: Of the 12,218 patients in the EUROPA study, 10,962 had a history of myocardial infarction and/or revascularization. In this EUROPA subpopulation, 7910 patients had a history of myocardial infarction and 6709 had a history of revascularization. Patients were randomized to treatment with perindopril 8mg/day or placebo. The primary endpoint was a composite of cardiovascular mortality, myocardial infarction and resuscitated cardiac arrest.

RESULTS: After a mean follow-up of 4.2 years, treatment with perindopril 8mg/day was associated with a 22.4% reduction in the primary endpoint compared with placebo ($p < 0.001$) in patients with a history of myocardial infarction. Patients with a history of myocardial revascularization showed a 17.3% reduction in the primary endpoint with perindopril versus placebo ($p < 0.05$). In the combined population of patients with a history of myocardial infarction and/or revascularization, treatment with perindopril produced a 22.4% reduction in the primary endpoint compared with placebo ($p < 0.001$).

CONCLUSIONS: This study confirms the benefits of a high dose of angiotensin-converting enzyme inhibitor for the secondary prevention of cardiovascular risk among patients with a history of myocardial infarction and/or revascularization.

de Mello, V. D. F., T. Zelmanovitz, et al. (2008). "Long-term effect of a chicken-based diet versus enalapril on albuminuria in type 2 diabetic patients with microalbuminuria." *Journal of Renal Nutrition* 18(5): 440-447.

OBJECTIVE: In short-term studies, the replacement of red meat in the diet with chicken reduced the urinary albumin excretion rate (UAER) and improved lipid profile in type 2 diabetic patients with diabetic nephropathy. The present study sought to assess these effects over a long-term period, comparing the effects of a chicken-based diet (CD) versus enalapril on renal function and lipid profile in microalbuminuric type 2 diabetic patients.

DESIGN: This was a randomized, open-label, controlled clinical trial with a follow-up of 1 year.

SETTING: The trial involved outpatients with type 2 diabetes attending a clinic of the Division of Endocrinology at a tertiary-care hospital.

PATIENTS: Twenty-eight microalbuminuric patients completed the study and were evaluated.

INTERVENTIONS: Patients were randomized to an experimental diet (CD plus active placebo) or to treatment with enalapril (10 mg/day plus usual diet).

MAIN OUTCOME MEASURES: The main outcome measure was UAER (according to immunoturbidimetry). Blood pressure, anthropometric indices, and compliance were also evaluated monthly. The glomerular filtration rate ((⁵¹Cr-EDTA), and lipid, glycemic, and nutritional indices, were measured at baseline and quarterly.

RESULTS: The UAER was reduced after CD ($n = 13$; from 62.8 [range, 38.4 to 125.1] to 49.1 [range, 6.2 to 146.5] microg/min; $P < .001$) and after enalapril ($n = 15$; from 55.8 [range, 22.6 to 194.3] to 23.1 [range, 4.0 to 104.9] microg/min; $P < .001$), and this was already significant at month 4. The reduction in UAER after CD (32%; 95% confidence interval, 6.7% to 57.6%) and after enalapril treatment (44.7%; 95% confidence interval, 28.3% to 61.1%; $P = .366$) were not significantly different.

CONCLUSIONS: The CD and the angiotensin-converting enzyme inhibitor enalapril promoted a similar reduction of UAER in patients with type 2 diabetes and microalbuminuria in a 12-month follow-up period.

Hermida, R. C. and D. E. Ayala (2009). "Chronotherapy with the angiotensin-converting enzyme inhibitor ramipril in essential hypertension: improved blood pressure control with bedtime dosing." *Hypertension* 54(1): 40-46.

Clinical studies have demonstrated a different effect on blood pressure of some angiotensin-converting enzyme inhibitors when administered in the morning versus the evening. Their administration at bedtime resulted in a higher effect on nighttime blood pressure as compared with morning dosing. This study investigated the administration

time-dependent effects of ramipril on ambulatory blood pressure. We studied 115 untreated hypertensive patients, 46.7 \pm 11.2 years of age, randomly assigned to receive ramipril (5 mg/d) as a monotherapy either on awakening or at bedtime. Blood pressure was measured for 48 hours before and after 6 weeks of treatment. The blood pressure reduction during diurnal activity was similar for both treatment times. Bedtime administration of ramipril, however, was significantly more efficient than morning administration in reducing asleep blood pressure. The awake:asleep blood pressure ratio was decreased after ramipril on awakening but significantly increased toward a more dipping pattern after bedtime dosing. The proportion of patients with controlled ambulatory blood pressure increased from 43% to 65% (P=0.019) with bedtime treatment. Nocturnal blood pressure regulation is significantly better achieved at bedtime as compared with morning administration of ramipril, without any loss in efficacy during diurnal active hours. This might be clinically important, because nighttime blood pressure has been shown to be a more relevant marker of cardiovascular risk than diurnal mean values. The change in the dose-response curve, increased proportion of controlled patients, and improved efficacy on nighttime blood pressure with administration of ramipril at bedtime should be taken into account when prescribing this angiotensin-converting enzyme inhibitor for treatment of essential hypertension.

Jones-Burton, C., J. Rubino, et al. (2010). "Effects of the renin inhibitor MK-8141 (ACT-077825) in patients with hypertension." *Journal of the American Society of Hypertension* 4(5): 219-226.

The renin inhibitor MK-8141 (ACT-077825) demonstrates substantial immunoreactive active renin (ir-AR) increase (sevenfold) without a persistent plasma renin activity (PRA) decrease. The present study assessed the antihypertensive efficacy of MK-8141 in hypertensive patients. In this double-blind, placebo- and active comparator-controlled study, 195 patients with hypertension (trough sitting diastolic blood pressure \geq 92 to $<$ 105 mm Hg, trough sitting systolic blood pressure $<$ 170 mm Hg, and 24-hour mean diastolic blood pressure [DBP] \geq 80 mm Hg) were randomized to one of four treatments (stratified by race, black versus others): MK-8141 250 mg, MK-8141 500 mg, enalapril 20 mg, or placebo. Blood pressure was measured at trough and as 24-hour ambulatory blood pressure monitoring. The primary end point was change from baseline in 24-hour mean ambulatory DBP measured after 4 weeks. At week 4, the change from baseline in 24-hour mean (95% CI) ambulatory DBP compared with placebo was -1.6 mm Hg (-4.2, 1.1), -1.1 mm Hg (-3.9, 1.6), and -4.9 (-7.5, -2.2) for MK-8141 250 mg, MK-8141 500 mg, and enalapril 20 mg, respectively. Only mean ambulatory DBP-lowering with enalapril 20 mg was statistically significant. Enalapril, but not MK-8141, also significantly lowered 24-hour mean ambulatory systolic blood pressure (SBP) compared with placebo (-6.7 mm Hg [-10.5, -2.8]). Neither enalapril nor MK-8141 significantly lowered trough DBP and SBP compared with placebo. MK-8141 was generally well tolerated. In patients with hypertension, MK-8141 (ACT-077825) did not produce significant blood pressure-lowering efficacy despite a demonstrated effect of the drug on ir-AR, in the absence of durable PRA suppression. Copyright 2010 American Society of Hypertension. Published by Elsevier Inc. All rights reserved.

Mauer, M., B. Zinman, et al. (2009). "Renal and retinal effects of enalapril and losartan in type 1 diabetes." *New England Journal of Medicine* 361(1): 40-51.

BACKGROUND: Nephropathy and retinopathy remain important complications of type 1 diabetes. It is unclear whether their progression is slowed by early administration of drugs that block the renin-angiotensin system.

METHODS: We conducted a multicenter, controlled trial involving 285 normotensive patients with type 1 diabetes and normoalbuminuria and who were randomly assigned to receive losartan (100 mg daily), enalapril (20 mg daily), or placebo and followed for 5 years. The primary end point was a change in the fraction of glomerular volume occupied by mesangium in kidney-biopsy specimens. The retinopathy end point was a progression on a retinopathy severity scale of two steps or more. Intention-to-treat analysis was performed with the use of linear regression and logistic-regression models.

RESULTS: A total of 90% and 82% of patients had complete renal-biopsy and retinopathy data, respectively. Change in mesangial fractional volume per glomerulus over the 5-year period did not differ significantly between the placebo group (0.016 units) and the enalapril group (0.005, $P=0.38$) or the losartan group (0.026, $P=0.26$), nor were there significant treatment benefits for other biopsy-assessed renal structural variables. The 5-year cumulative incidence of microalbuminuria was 6% in the placebo group; the incidence was higher with losartan (17%, $P=0.01$ by the log-rank test) but not with enalapril (4%, $P=0.96$ by the log-rank test). As compared with placebo, the odds of retinopathy progression by two steps or more was reduced by 65% with enalapril (odds ratio, 0.35; 95% confidence interval [CI], 0.14 to 0.85) and by 70% with losartan (odds ratio, 0.30; 95% CI, 0.12 to 0.73), independently of changes in blood pressure. There were three biopsy-related serious adverse events that completely resolved. Chronic cough occurred in 12 patients receiving enalapril, 6 receiving losartan, and 4 receiving placebo.

CONCLUSIONS: Early blockade of the renin-angiotensin system in patients with type 1 diabetes did not slow nephropathy progression but slowed the progression of retinopathy. (ClinicalTrials.gov number, NCT00143949.) 2009 Massachusetts Medical Society

Potter, J. F., T. G. Robinson, et al. (2009). "Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial." *Lancet Neurology* 8(1): 48-56.

BACKGROUND: Raised blood pressure is common after acute stroke and is associated with an adverse prognosis. We sought to assess the feasibility, safety, and effects of two regimens for lowering blood pressure in patients who have had a stroke.

METHODS: Patients who had cerebral infarction or cerebral haemorrhage and were hypertensive (systolic blood pressure [SBP] >160 mm Hg) were randomly assigned by secure internet central randomisation to receive oral labetalol, lisinopril, or placebo if they were non-dysphagic, or intravenous labetalol, sublingual lisinopril, or placebo if they had dysphagia, within 36 h of symptom onset in this double-blind pilot trial. The doses were titrated up if target blood pressure was not reached. Analysis was by intention to treat. This trial is registered with the National Research Register, number N0484128008.

FINDINGS: 179 patients (mean age 74 [SD 11] years; SBP 181 [SD 16] mm Hg; diastolic blood pressure [DBP] 95 [SD 13] mm Hg; median National Institutes of Health stroke scale [NIHSS] score 9 [IQR 5-16] points) were randomly assigned to receive labetalol ($n=58$), lisinopril ($n=58$), or placebo ($n=63$) between January, 2005, and December, 2007. The primary outcome--death or dependency at 2 weeks--occurred in 61% (69) of the active and 59% (35) of the placebo group (relative risk [RR] 1.03, 95% CI 0.80-1.33; $p=0.82$).

There was no evidence of early neurological deterioration with active treatment (RR 1.22, 0.33-4.54; $p=0.76$) despite the significantly greater fall in SBP within the first 24 h in this group compared with placebo (21 [17-25] mm Hg vs 11 [5-17] mm Hg; $p=0.004$). No increase in serious adverse events was reported with active treatment (RR 0.91, 0.69-1.12; $p=0.50$) but 3-month mortality was halved (9.7% vs 20.3%, hazard ratio [HR] 0.40, 95% CI 0.2-1.0; $p=0.05$).

INTERPRETATION: Labetalol and lisinopril are effective antihypertensive drugs in acute stroke that do not increase serious adverse events. Early lowering of blood pressure with lisinopril and labetalol after acute stroke seems to be a promising approach to reduce mortality and potential disability. However, in view of the small sample size, care must be taken when these results are interpreted and further evaluation in larger trials is needed.

Rossignol, P., J. Criddig, et al. (2012). "Visit-to-visit blood pressure variability is a strong predictor of cardiovascular events in hemodialysis: insights from FOSIDIAL." *Hypertension* 60(2): 339-346.

Optimal blood pressure (BP) targets are still controversial in end-stage renal disease. Recent data have highlighted shortcomings of the usual BP hypothesis in other patient populations and emphasized the importance of visit-to-visit variability of BP in predicting cardiovascular events. The Fosinopril in Dialysis Study failed to demonstrate the efficacy of 2-year angiotensin-converting enzyme inhibition with fosinopril versus placebo in 397 hemodialysis patients with left ventricular hypertrophy but provided an opportunity to assess the influence of BP variability on cardiovascular events. The primary end point was the occurrence of a composite of cardiovascular death, nonfatal myocardial infarction, unstable angina, stroke, revascularization, hospitalization for heart failure, and resuscitated cardiac arrest. The variations in BP throughout the 17 visits were assessed by within-patient overall variability of systolic, diastolic, and pulse pressures between adjacent readings, by within-patient overall variability of systolic/diastolic/pulse pressures, and the residual of the linear fit. Compared with our previous predictive model of cardiovascular events occurrence based on stroke, peripheral arterial disease, coronary artery disease, diabetes mellitus, left ventricular mass, and age (which exhibited similar coefficients herein), the percentage of explained variance improved by 30.1% ($R(2)=0.141-0.183$) when adding the coefficient of variation of within-patient overall variability of systolic BP. Usual BP parameters were neither cardiovascular events predictors nor correlated to BP variability. Visit-to-visit BP variability was extremely high in hemodialysis patients compared with other populations and a major determinant of cardiovascular events. Such assessments should be prioritized for testing prevention strategies in end-stage renal disease.

Appendix C: Potentially relevant abstracts of trials from previous scans 1-3

Head to head trial

Tumanan-Mendoza, B. A., A. L. Dans, et al. (2007). "Dechallenge and rechallenge method showed different incidences of cough among four ACE-Is." *Journal of Clinical Epidemiology* 60(6): 547-553.

OBJECTIVE: To determine the incidence of cough secondary to (1) Cilazapril, (2) Enalapril, (3) Imidapril, and (4) Perindopril and their efficacy in the control of hypertension. **STUDY DESIGN AND SETTING:** Randomized double-blind study conducted in selected medical centers in the Philippines from the first quarter of 1999 to March, 2001. **RESULTS:** A total of 301 patients, aged 28-86 years with stage I or II hypertension were included. Patients were randomized to Cilazapril 2.5-5.0 mg/day (n=70), Enalapril 10-20 mg/day (n=82), Perindopril 4-8 mg/day (n=73), or Imidapril 10-20 mg/day (n=76). Hydrochlorothiazide 12.5 mg/day was added if needed. Using a dechallenge and rechallenge method, a strict criteria to attribute cough to angiotensin converting enzyme inhibitors (ACE-Is) not yet used in previous reports, the cough incidence were as follows: (1) Cilazapril--22.86% (16/70), (2) Enalapril--21.95% (18/82), (3) Perindopril--10.96% (6/73), and (4) Imidapril--13.16% (10/76) (P=0.041). Control of hypertension was significantly better with Enalapril during the first follow-up period.

CONCLUSION: Statistically significant differences in the incidence of cough among the studied ACE-Is were noted. Control of hypertension was observed to be better in those with a higher incidence of cough; however, the mean change of both systolic and diastolic blood pressure levels were not significantly different.

Placebo control trial

Arima, H., R. G. Hart, et al. (2005). "Perindopril-based blood pressure-lowering reduces major vascular events in patients with atrial fibrillation and prior stroke or transient ischemic attack." *Stroke* 36(10): 2164-2169.

BACKGROUND AND PURPOSE: Patients with atrial fibrillation have a high risk of stroke and other vascular events even if anticoagulated. The primary objective here is to determine whether routine blood pressure-lowering provides additional protection for this high-risk patient group. **METHODS:** This study was a subsidiary analysis of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS)--a randomized, placebo-controlled trial that established the beneficial effects of blood pressure--lowering in a heterogeneous group of patients with cerebrovascular disease. A total of 6105 patients were randomly assigned to either active treatment (2 to 4 mg perindopril for all participants plus 2.0 to 2.5 mg indapamide for those without an indication for or a contraindication to a diuretic) or matching placebo(s). Outcomes are total major vascular events, cause-specific vascular outcomes, and death from any cause. **RESULTS:** There were 476 patients with atrial fibrillation at baseline, of whom 51% were taking anticoagulants. In these patients, active treatment lowered mean blood pressure by 7.3/3.4 mm Hg and was associated with a 38% (95% confidence interval [CI], 6 to 59) reduction in major vascular events and 34% (95% CI, -13 to 61) reduction in stroke. The benefits of blood pressure-lowering in patients with atrial fibrillation were achieved irrespective of the use of anticoagulant therapy (P homogeneity=0.8) or the presence of hypertension (P homogeneity=0.4). **CONCLUSIONS:** For most patients with atrial fibrillation, routine blood pressure-lowering is likely to provide protection against major vascular events additional to that conferred by anticoagulation.

Brugts, J. J., E. Boersma, et al. (2007). "The cardioprotective effects of the angiotensin-converting enzyme inhibitor perindopril in patients with stable coronary artery disease are not modified by mild to moderate renal insufficiency: insights from the EUROPA trial." *Journal of the American College of Cardiology* 50(22): 2148-2155.

OBJECTIVES: This study sought to examine whether the cardioprotective effects of angiotensin-converting enzyme (ACE) inhibitor therapy by perindopril are modified by renal function in patients with stable coronary artery disease. **BACKGROUND:** A recent study reported that an impaired renal function identified a subgroup of patients with stable coronary artery disease more likely to benefit from ACE inhibition therapy. In light of the growing interest in tailored therapy for targeting medications to specific subgroups, remarks on the consistency of the treatment effect by ACE inhibitors are highly important. **METHODS:** The present study involved 12,056 patients with stable coronary artery disease without heart failure randomized to perindopril or placebo. Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease equation. Cox regression analysis was used to estimate

multivariable-adjusted hazard ratios. RESULTS: The mean eGFR was 76.2 (+/-18.1) ml/min/1.73 m². During follow-up, the primary end point (cardiovascular death, nonfatal myocardial infarction, or resuscitated cardiac arrest) occurred in 454 of 5,761 patients (7.9%) with eGFR \geq 75 and in 631 of 6,295 patients (10.0%) with eGFR $<$ 75. Treatment benefits of perindopril were apparent in both patient groups either with eGFR \geq 75 (hazard ratio 0.77; 95% confidence interval 0.64 to 0.93) or eGFR $<$ 75 (hazard ratio 0.84; 95% confidence interval 0.72 to 0.98). We observed no significant interaction between renal function and treatment benefit ($p = 0.47$). Using different cutoff points of eGFR at the level of 60 or 90 resulted in similar trends. CONCLUSIONS: The treatment benefit of perindopril is consistent and not modified by mild to moderate renal insufficiency.

Coppo, R., L. Peruzzi, et al. (2007). "IgACE: a placebo-controlled, randomized trial of angiotensin-converting enzyme inhibitors in children and young people with IgA nephropathy and moderate proteinuria.[see comment]." *Journal of the American Society of Nephrology* 18(6): 1880-1888.

This European Community Biomedicine and Health Research-supported, multicenter, randomized, placebo-controlled, double-blind trial investigated the effect of an angiotensin-converting enzyme inhibitor (ACE-I) in children and young people with IgA nephropathy (IgAN), moderate proteinuria (>1 and <3.5 g/d per 1.73 m²) and creatinine clearance (CrCl) >50 ml/min per 1.73 m². Sixty-six patients who were 20.5 yr of age (range 9 to 35 yr), were randomly assigned to Benazepril 0.2 mg/kg per d (ACE-I) or placebo and were followed for a median of 38 mo. The primary outcome was the progression of kidney disease, defined as $>30\%$ decrease of CrCl; secondary outcomes were (1) a composite end point of $>30\%$ decrease of CrCl or worsening of proteinuria until ≥ 3.5 g/d per 1.73 m² and (2) proteinuria partial remission (<0.5 g/d per 1.73 m²) or total remission (<160 mg/d per 1.73 m²) for >6 mo. Analysis was by intention to treat. A single patient (3.1%) in the ACE-I group and five (14.7%) in the placebo group showed a worsening of CrCl $>30\%$. The composite end point of $>30\%$ decrease of CrCl or worsening of proteinuria until nephrotic range was reached by one (3.1%) of 32 patients in the ACE-I group, and nine (26.5%) of 34 in the placebo group; the difference was significant (log-rank $P = 0.035$). A stable, partial remission of proteinuria was observed in 13 (40.6%) of 32 patients in the ACE-I group versus three (8.8%) of 34 in the placebo group (log-rank $P = 0.033$), with total remission in 12.5% of ACE-I-treated patients and in none in the placebo group (log-rank $P = 0.029$). The multivariate Cox analysis showed that treatment with ACE-I was the independent predictor of prognosis; no influence on the composite end point was found for gender, age, baseline CrCl, systolic or diastolic BP, mean arterial pressure, or proteinuria.

Daly, C. A., K. M. Fox, et al. (2005). "The effect of perindopril on cardiovascular morbidity and mortality in patients with diabetes in the EUROPA study: results from the PERSUADE substudy.[see comment]." *European Heart Journal* 26(14): 1369-1378.

AIMS: The aim of this study was to assess the effect of the angiotensin converting enzyme inhibitor perindopril on cardiovascular events in diabetic patients with coronary artery disease. METHODS AND RESULTS: A total of 1502 diabetic patients with known coronary artery disease and without heart failure of 12 218 overall in the European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery

(EUROPA) disease were randomized in a double-blinded manner to perindopril 8 mg once daily or placebo. Follow-up was for a median of 4.3 years. The primary end point was cardiovascular death, non-fatal myocardial infarction, and resuscitated cardiac arrest. Perindopril treatment was associated with a non-significant reduction in the primary endpoint in the diabetic population, 12.6 vs. 15.5%, relative risk reduction 19% [(95% CI, -7 to 38%), P=0.13]. This was of similar relative magnitude to the 20% risk reduction observed in the main EUROPA population. CONCLUSION: Perindopril tends to reduce major cardiovascular events in diabetic patients with coronary disease in addition to other preventive treatments and the trend towards reduction was of a similar relative magnitude to that observed the general population with coronary artery disease.

Daly, C. A., P. Hildebrandt, et al. (2007). "Adverse prognosis associated with the metabolic syndrome in established coronary artery disease: data from the EUROPA trial." *Heart* 93(11): 1406-1411.

OBJECTIVE: To assess the prevalence of metabolic syndrome, and its effect on cardiovascular morbidity and mortality in patients with established coronary disease and to explore the inter-relationships between metabolic syndrome, diabetes, obesity and cardiovascular risk. **METHODS:** The presence of metabolic syndrome was determined in 8397 patients with stable coronary disease from the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease, with mean follow-up of 4.2 years. Metabolic syndrome was defined using a modified version of the National Cholesterol Education Programme criteria. **RESULTS:** Metabolic syndrome was present in 1964/8397 (23.4%) of the population and significantly predicted outcome; relative risk (RR) of cardiovascular mortality = 1.82 (95% CI 1.40 to 2.39); and fatal and non-fatal myocardial infarction RR = 1.50 (95% CI 1.24 to 1.80). The association with adverse outcomes remained significant after adjustment, RR of cardiovascular mortality after adjustment for conventional risks and diabetes = 1.39 (95% CI 1.03 to 1.86). In comparison with normal weight subjects without diabetes or metabolic syndrome, normal weight dysmetabolic subjects (with either diabetes or metabolic syndrome) were at substantially increased risk of cardiovascular death (RR = 4.05 (95% CI 2.38 to 6.89)). The relative risks of cardiovascular death for overweight and obese patients with dysmetabolic status were nominally lower (RR = 3.01 (95% CI 1.94 to 4.69) and RR = 2.35 (95% CI 1.50 to 3.68), respectively). **CONCLUSIONS:** Metabolic syndrome is associated with adverse cardiovascular outcome, independently of its associations with diabetes and obesity. A metabolic profile should form part of the risk assessment in all patients with coronary disease, not just those who are obese.

Deckers, J. W., D. M. Goedhart, et al. (2006). "Treatment benefit by perindopril in patients with stable coronary artery disease at different levels of risk." *European Heart Journal* 27(7): 796-801. **AIMS:** Patients with stable coronary artery disease (CAD) are at increased risk. Estimation of individual risk is difficult. We developed a cardiovascular risk model based on the EUROPA study population and investigated whether benefit of long-term administration of the angiotensin-converting enzyme (ACE)-inhibitor perindopril was modified by risk level. **METHODS AND RESULTS:** A total of 12 218 patients with stable CAD were treated with 8 mg perindopril or placebo. Baseline patient characteristics were assessed for association with 1091 cardiovascular deaths or non-fatal myocardial infarction (MI). Risk factors were age over 65 years, male gender [hazard

ratio (HR) 1.2], previous MI (HR 1.5), previous stroke and/or peripheral vascular disease (HR 1.7), diabetes, smoking, angina (all HR 1.5), and high serum cholesterol and systolic blood pressure. Treatment benefit by perindopril was consistent among high, intermediate, and low risk patients (HRs 0.88, 0.68, and 0.83, respectively). Risk reduction was thus not modified by absolute risk level. **CONCLUSION:** Risk factors such as age, male gender, smoking, total cholesterol, and blood pressure continue to play an important role once clinical sequelae of coronary heart disease have developed. Patients at moderate-to-high risk because of uncontrolled risk factors and those with other indications for ACE-inhibitors have the most to gain from ACE-inhibition.

Gianni, M., J. Bosch, et al. (2007). "Effect of long-term ACE-inhibitor therapy in elderly vascular disease patients.[see comment]." *European Heart Journal* 28(11): 1382-1388.

AIMS: Cardiovascular (CV) disease is the leading cause of death in the elderly. The use of ACE-inhibitors in elderly patients with chronic stable vascular disease has not been previously reported. **METHODS AND RESULTS:** The HOPE trial evaluated the effects of ramipril and vitamin E in high-risk vascular disease patients. We report the effects of ramipril in the elderly HOPE study patients, defined as those \geq 70 years of age. A total of 2755 elderly patients with vascular disease or diabetes and at least one additional CV risk factor and without heart failure or low ejection fraction were randomized to ramipril 10 mg daily or placebo. Those assigned to ramipril had fewer major vascular events compared to those assigned to placebo [18.6 vs. 24.0%, hazard ratio (HR) = 0.75, $P = 0.0006$], CV deaths (9.3 vs. 13.0%, HR = 0.71, $P = 0.003$), myocardial infarctions (12.0 vs. 15.6%, HR = 0.75, $P = 0.006$), and strokes (5.4 vs. 7.7%, HR = 0.69, $P = 0.013$). Treatment was safe and generally well tolerated. **CONCLUSION:** Ramipril reduces the risk of major vascular events in elderly patients with vascular disease and is safe and well tolerated by most.

Hou, F. F., X. Zhang, et al. (2006). "Efficacy and safety of benazepril for advanced chronic renal insufficiency.[see comment]." *New England Journal of Medicine* 354(2): 131-140.

BACKGROUND: Angiotensin-converting-enzyme inhibitors provide renal protection in patients with mild-to-moderate renal insufficiency (serum creatinine level, 3.0 mg per deciliter or less). We assessed the efficacy and safety of benazepril in patients without diabetes who had advanced renal insufficiency. **METHODS:** We enrolled 422 patients in a randomized, double-blind study. After an eight-week run-in period, 104 patients with serum creatinine levels of 1.5 to 3.0 mg per deciliter (group 1) received 20 mg of benazepril per day, whereas 224 patients with serum creatinine levels of 3.1 to 5.0 mg per deciliter (group 2) were randomly assigned to receive 20 mg of benazepril per day (112 patients) or placebo (112 patients) and then followed for a mean of 3.4 years. All patients received conventional antihypertensive therapy. The primary outcome was the composite of a doubling of the serum creatinine level, end-stage renal disease, or death. Secondary end points included changes in the level of proteinuria and the rate of progression of renal disease. **RESULTS:** Of 102 patients in group 1, 22 (22 percent) reached the primary end point, as compared with 44 of 108 patients given benazepril in group 2 (41 percent) and 65 of 107 patients given placebo in group 2 (60 percent). As compared with placebo, benazepril was associated with a 43 percent reduction in the risk of the primary end point in group 2 ($P=0.005$). This benefit did not appear to be attributable to blood-pressure control. Benazepril therapy was associated with a 52 percent reduction in the level of

proteinuria and a reduction of 23 percent in the rate of decline in renal function. The overall incidence of major adverse events in the benazepril and placebo subgroups of group 2 was similar. CONCLUSIONS: Benazepril conferred substantial renal benefits in patients without diabetes who had advanced renal insufficiency. (ClinicalTrials.gov number, NCT00270426.) Copyright 2006 Massachusetts Medical Society.

Investigators, D. T., J. Bosch, et al. (2006). "Effect of ramipril on the incidence of diabetes.[see comment]." *New England Journal of Medicine* 355(15): 1551-1562.

BACKGROUND: Previous studies have suggested that blockade of the renin-angiotensin system may prevent diabetes in people with cardiovascular disease or hypertension. **METHODS:** In a double-blind, randomized clinical trial with a 2-by-2 factorial design, we randomly assigned 5269 participants without cardiovascular disease but with impaired fasting glucose levels (after an 8-hour fast) or impaired glucose tolerance to receive ramipril (up to 15 mg per day) or placebo (and rosiglitazone or placebo) and followed them for a median of 3 years. We studied the effects of ramipril on the development of diabetes or death, whichever came first (the primary outcome), and on secondary outcomes, including regression to normoglycemia. **RESULTS:** The incidence of the primary outcome did not differ significantly between the ramipril group (18.1%) and the placebo group (19.5%; hazard ratio for the ramipril group, 0.91; 95% confidence interval [CI], 0.81 to 1.03; P=0.15). Participants receiving ramipril were more likely to have regression to normoglycemia than those receiving placebo (hazard ratio, 1.16; 95% CI, 1.07 to 1.27; P=0.001). At the end of the study, the median fasting plasma glucose level was not significantly lower in the ramipril group (102.7 mg per deciliter [5.70 mmol per liter]) than in the placebo group (103.4 mg per deciliter [5.74 mmol per liter], P=0.07), though plasma glucose levels 2 hours after an oral glucose load were significantly lower in the ramipril group (135.1 mg per deciliter [7.50 mmol per liter] vs. 140.5 mg per deciliter [7.80 mmol per liter], P=0.01). **CONCLUSIONS:** Among persons with impaired fasting glucose levels or impaired glucose tolerance, the use of ramipril for 3 years does not significantly reduce the incidence of diabetes or death but does significantly increase regression to normoglycemia. (ClinicalTrials.gov number, NCT00095654 [ClinicalTrials.gov].). Copyright 2006 Massachusetts Medical Society.

Kostis, J. B., H. J. Kim, et al. (2005). "Incidence and characteristics of angioedema associated with enalapril." *Archives of Internal Medicine* 165(14): 1637-1642.

BACKGROUND: Angioedema is a rare but potentially serious adverse event of angiotensin-converting enzyme inhibitor therapy. However, no prospective, controlled studies have reported on its incidence and clinical characteristics. **METHODS:** We studied the occurrence of angioedema in a randomized, double-blind, controlled trial of 12 557 persons with hypertension treated with enalapril maleate, 5 to 40 mg/d, using a prospective ascertainment and adjudication of angioedema by an expert committee. **RESULTS:** Angioedema occurred in 86 (0.68%) of the subjects. Stepwise logistic regression identified black race (odds ratio [OR], 2.88; 95% confidence interval [CI], 1.72-4.82), history of drug rash (OR, 3.78; 95% CI, 1.80-7.92), age greater than 65 years (OR, 1.60; 95% CI, 1.02-2.53), and seasonal allergies (OR, 1.79; 95% CI, 1.06-3.00) as independent risk factors for angioedema. The incidence of angioedema was higher after initiation of therapy (3.6/1000 patients per month) and declined to 0.4/1000 patients per month. Treatment was not given in 44 (51%) of the cases; antihistamines were

administered in 35 (41%); corticosteroids, in 20 (23%); and epinephrine, in 1 (1%). Two patients were hospitalized but none had airway compromise. **CONCLUSIONS:** Enalapril-related angioedema is uncommon. Although it is most likely to occur early after initiation of therapy, it may occur at any time. It is more likely to occur in black patients, those older than 65 years, and those with a history of drug rash or seasonal allergies. Fatal angioedema or angioedema requiring airway protection did not occur in this study.

Luders, S., J. Schrader, et al. (2008). "The PHARAO study: prevention of hypertension with the angiotensin-converting enzyme inhibitor ramipril in patients with high-normal blood pressure: a prospective, randomized, controlled prevention trial of the German Hypertension League." *Journal of Hypertension* 26(7): 1487-96.

BACKGROUND: The prevention of hypertension with the angiotensin-converting enzyme inhibitor ramipril in patients with high-normal blood pressure study addresses the issue of whether progression to manifest hypertension in patients with high-normal blood pressure can be prevented with treatment. **METHODS:** A total of 1008 participants with high-normal office blood pressure were randomized to ramipril treatment group (n = 505) and a control group (n = 503). The patients were followed up for 3 years. Primary endpoint was to prevent or delay the progression to manifest hypertension. Secondary endpoints were reduction in the incidence of cerebrovascular and cardiovascular events, as well as the development of hypertension as defined by ambulatory blood pressure monitoring. **FINDINGS:** One hundred and fifty-five patients (30.7%) in the ramipril group, and 216 (42.9%) in the control group reached the primary endpoint (relative risk reduction 34.4%, P = 0.0001). Ramipril also proved to be more effective in reducing the incidence of manifest office hypertension in patients with baseline ambulatory blood pressure monitoring high-normal blood pressure. The incidence of cerebrovascular and cardiovascular events showed no statistically significant differences between the two groups. Cough was more frequent in the ramipril group (4.8 vs. 0.4%).

INTERPRETATION: There is now good clinical evidence that patients with high-normal blood pressure (prehypertension) are more likely to progress to manifest hypertension than patients with optimal or normal blood pressure. Additional ambulatory blood pressure monitoring seems to be essential to achieve correct diagnosis. Treatment of patients with high-normal office blood pressure with the angiotensin-converting enzyme inhibitor was well tolerated, and significantly reduced the risk of progression to manifest hypertension.

Ninomiya, T., V. Perkovic, et al. (2008). "Lower blood pressure and risk of recurrent stroke in patients with chronic kidney disease: PROGRESS trial." *Kidney International* 73(8): 963-70.

Recent epidemiological studies have shown a J-shaped association between the risk of stroke and systolic blood pressure (SBP) levels in people with chronic kidney disease (CKD). The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was a randomized, placebo-controlled trial demonstrating that perindopril-based blood pressure (BP) lowering reduced the risk of stroke in 6105 participants with prior cerebrovascular disease. We estimated the effects of therapy on the risk of recurrent stroke in 1757 of these participants with stage 3 or greater CKD according to baseline BP and the relationship between achieved follow-up BP and the risk of stroke. Active therapy produced comparable and significant reductions in the risk of stroke across all baseline

SBP levels. The age- and gender-adjusted incidence of stroke increased significantly in a log-linear relationship for achieved SBP levels and strokes per 1000 person-years. This association persisted after adjusting for potential confounding factors. We found that perindopril-based BP lowering effectively prevented recurrent stroke in people with CKD, across a wide range of BP levels, without evidence of an increased risk of stroke in people with low BP levels.

Pedrazzini, G., E. Santoro, et al. (2008). "Causes of death in patients with acute myocardial infarction treated with angiotensin-converting enzyme inhibitors: findings from the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto (GISSI)-3 trial." *American Heart Journal* 155(2): 388-94.

BACKGROUND: The causes of death occurring in clinical trials of myocardial infarction (MI) are scarcely reported in the literature. The present analysis is aimed to describe the in-hospital causes of death in patients with acute MI stratified to angiotensin converting enzyme (ACE) inhibitor treatment/no treatment, as described in the GISSI-3 trial. Furthermore, the 5-year survival analysis of GISSI-3 patients is reported. **METHODS AND RESULTS:** An independent committee assigned the definition of causes of death of GISSI-3 based on clinical and/or anatomical data. Univariate and multivariable analyses were performed to identify the predictors of early and late deaths. Kaplan-Meier mortality curves were used to describe the effects of ACE-I treatment on mortality on a median follow-up period of 56 months. Patients receiving lisinopril had fewer in-hospital cardiac deaths than patients allocated to the no-lisinopril group (4.7% vs 5.3%, $P = .052$), corresponding to a 12% relative risk reduction. The risk of dying from cardiac rupture was reduced by 39% by lisinopril treatment. The improvement in survival associated with the lisinopril treatment was mainly due to a reduction in cardiac rupture, electromechanical dissociation, and pump failure occurring early (within 4 days) from the onset of MI symptoms. The beneficial effects of lisinopril observed at 6 weeks (8 fewer deaths per 1000 treated patients) were maintained up to nearly 5 years (10 fewer deaths per 1000). **CONCLUSIONS:** Early administration of ACE inhibitors in unselected patients with acute MI should be considered standard therapy to reduce early deaths, specifically those due to cardiac rupture. The early beneficial effect persisted up to nearly 5 years.

Rouleau, J. L., W. J. Warnica, et al. (2008). "Effects of angiotensin-converting enzyme inhibition in low-risk patients early after coronary artery bypass surgery.[see comment]." *Circulation* 117(1): 24-31.

BACKGROUND: Early after coronary artery bypass surgery (CABG), activation of numerous neurohumoral and endogenous vasodilator systems occurs that could be influenced favorably by angiotensin-converting enzyme inhibitors. **METHODS AND RESULTS:** The Ischemia Management with Accupril post-bypass Graft via Inhibition of the coNverting Enzyme (IMAGINE) trial tested whether early initiation (< or = 7 days) of an angiotensin-converting enzyme inhibitor after CABG reduced cardiovascular events in stable patients with left ventricular ejection fraction > or = 40%. The trial was a

double-blind, placebo-controlled study of 2553 patients randomly assigned to quinapril, target dose 40 mg/d, or placebo, who were followed up to a maximum of 43 months. The mean (SD) age was 61 (10) years. The incidence of the primary composite end point (cardiovascular death, resuscitated cardiac arrest, nonfatal myocardial infarction, coronary revascularization, unstable angina or heart failure requiring hospitalization, documented angina, and stroke) was 13.7% in the quinapril group and 12.2% in the placebo group (hazard ratio 1.15, 95% confidence interval 0.92 to 1.42, $P=0.212$) over a median follow-up of 2.95 years. The incidence of the primary composite end point increased significantly in the first 3 months after CABG in the quinapril group (hazard ratio 1.52, 95% confidence interval 1.03 to 2.26, $P=0.0356$). Adverse events also increased in the quinapril group, particularly during the first 3 months after CABG. **CONCLUSIONS:** In patients at low risk of cardiovascular events after CABG, routine early initiation of angiotensin-converting enzyme inhibitor therapy does not appear to improve clinical outcome up to 3 years after CABG; however, it increases the incidence of adverse events, particularly early after CABG. Thus, early after CABG, initiation of angiotensin-converting enzyme inhibitor therapy should be individualized and continually reassessed over time according to risk.

Solomon, S. D., M. M. Rice, et al. (2006). "Renal function and effectiveness of angiotensin-converting enzyme inhibitor therapy in patients with chronic stable coronary disease in the Prevention of Events with ACE inhibition (PEACE) trial.[see comment]." *Circulation* 114(1): 26-31.

BACKGROUND: Patients with reduced renal function are at increased risk for adverse cardiovascular outcomes. In the post-myocardial infarction setting, angiotensin-converting enzyme (ACE) inhibitors have been shown to be as effective in patients with impaired renal function as in those with preserved renal function. **METHODS AND RESULTS:** We assessed the relation between renal function and outcomes, the influence of ACE inhibition on this relation, and whether renal function modifies the effectiveness of ACE inhibition in patients with stable coronary artery disease and preserved systolic function enrolled in the Prevention of Events with ACE inhibition trial (PEACE). Patients ($n=8290$) were randomly assigned to receive trandolapril (target, 4 mg/d) or placebo. Clinical creatinine measures were available for 8280 patients before randomization. The estimated glomerular filtration rate (eGFR) was calculated with the 4-point Modification of Diet in Renal Disease equation. Renal function was related to outcomes, and the influence of ACE-inhibitor therapy was assessed with formal interaction modeling. The mean eGFR in PEACE was 77.6 ± 19.4 , and 1355 (16.3%) patients had reduced renal function (eGFR <60 mg.mL(-1).1.73 m(-2)). We observed a significant interaction between eGFR and treatment group with respect to cardiovascular and all-cause mortality ($P=0.02$). Trandolapril was associated with a reduction in total mortality in patients with reduced renal function (adjusted HR, 0.73; 95% CI, 0.54 to 1.00) but not in patients with preserved renal function (adjusted HR, 0.94; 95% CI, 0.78 to 1.13). **CONCLUSIONS:** Although trandolapril did not improve survival in the overall PEACE cohort, in which mean eGFR was relatively high, trandolapril reduced mortality in patients with reduced eGFR. These data suggest that reduced renal function may define a subset of patients most likely to benefit from ACE-inhibitor therapy for cardiovascular protection.

Zannad, F., M. Kessler, et al. (2006). "Prevention of cardiovascular events in end-stage renal disease: results of a randomized trial of foscinopril and implications for future studies." *Kidney International* 70(7): 1318-1324.

Cardiovascular events (CVEs) are the leading cause of death in chronic hemodialysis patients. Results of trials in non-end-stage renal disease (ESRD) patients cannot be extrapolated to patients with ESRD. It is critical to test cardiovascular therapies in these high-risk patients who are usually excluded from major cardiovascular trials. The study objective was to evaluate the effect of foscinopril on CVEs in patients with ESRD. Eligible patients were randomized to foscinopril 5 mg titrated to 20 mg daily (n=196) or placebo (n=201) plus conventional therapy for 24 months. The primary end point was combined fatal and nonfatal first major CVEs (cardiovascular death, resuscitated death, nonfatal stroke, heart failure, myocardial infarction, or revascularization). No significant benefit for foscinopril was observed in the intent to treat analysis (n=397) after adjusting for independent predictors of CVEs (RR=0.93, 95% confidence interval (CI) 0.68-1.26, P=0.35). The per protocol secondary supportive analysis (n=380) found a trend towards benefit for foscinopril (adjusted RR=0.79 (95% CI 0.59-1.1, P=0.099)). In the patients who were hypertensive at baseline, systolic and diastolic blood pressures were significantly decreased in the foscinopril as compared to the placebo group. After adjustment for risk factors, trends were observed suggesting foscinopril may be associated with a lower risk of CVEs. These trends may have become statistically significant had the sample size been larger, and these findings warrant further study.

Appendix B: Abstracts of potentially relevant new trials of ACE Inhibitors