Overview of clinical trials to improve endothelial function

Content Points:

- During the past few years a number of clinical studies have focused on reducing cardiovascular events and atherosclerosis by treating the underlying endothelial pathology.

- This presentation will review the current understanding of how risk factors lead to endothelial dysfunction and CV disease.

- Types of treatment and the rationale for their use will be discussed. Clinical trials regarding the use of two classes of pharmacological agents, HMG-CoA reductase inhibitors and ACE inhibitors, will be covered in this curriculum update.
Content outline

Content Points:

The following topics will be addressed in this curriculum update:

- Role of hypertension in endothelial impairment
- Effect of dyslipidemia on endothelial function
- Vasculoprotective effects of ACE inhibitors and HMG-CoA reductase inhibitors
- Recent clinical trials on the benefits of improving endothelial function
Endothelium and hypertension

**Endothelial cell**
- Structural and biochemical changes to intima
- ↑ Cell replication
- Alterations in cell size, shape and cytoplasm
- ↑ Adhesion of monocytes, accelerated atherosclerosis

**Vascular smooth muscle cell**
- Hypertrophy
- Hyperplasia (?)
- ↑ Vasoconstriction, impaired vasodilatory response

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**Endothelium and hypertension**

**Content Points:**

- In people with high blood pressure, a number of changes occur within the vascular endothelium.¹

- The intima undergoes structural and biochemical changes. Endothelial cells proliferate while undergoing alterations to their size, shape and cytoplasm.

- Monocytes adhere more readily to the endothelium.

- Atherosclerotic plaques form.

- Vascular smooth muscle cells also undergo change. These cells tend to hypertrophy and develop abnormal vasomotor tone, leading to heightened constriction.

- Smooth muscle cells may undergo hyperplasia, although this response has not been well documented.
Endothelial function in patients with and without dyslipidemia

Content Points:

• This study by Creager et al demonstrates some of the abnormalities that occur in the endothelium in people with dyslipidemia.¹

• As shown, blood vessels in individuals with normal lipid levels relax in a dose dependent manner when treated with methacholine.

• But, in subjects with dyslipidemia, the blood vessels do not dilate normally in response to methacholine. This lack of dilation leads to significantly lower maximal forearm blood flow as compared with control subjects ($P < 0.05$).
Vasculoprotective effects of ACE inhibition

Content Points:

• ACE inhibitors protect the vasculature in a number of different ways, presumably by blocking both circulating and tissue RAS in addition to preventing bradykinin degradation.³

• First, ACE inhibitors limit migration and proliferation of smooth muscle cells, and inhibit migration of inflammatory cells. These are angiotensin II-mediated processes important in atherosclerotic lesion development.

• Second, ACE inhibitors improve or restore endothelial function. This may be mediated by a reduction in angiotensin II-induced endothelin production or by enhanced bradykinin-induced production of NO and prostacyclin. NO and prostacyclin facilitate local vasodilation and inhibit platelet aggregation, whereas endothelin promotes these effects.

• Third, ACE inhibitors reduce production and secretion of PAI-1, which may improve endogenous fibrinolytic function, and thereby reduce risk for ischemic events.

• Fourth, ACE inhibitors reduce elevated blood pressure, and they improve arterial compliance and tone. These effects reduce the impact of hypertension on atherosclerosis progression.

• Based on experimental evidence from animal models, ACE inhibitors may have a direct antiatherogenic effect. These models mimic cholesterol-mediated endothelial injury, mechanical endothelial injury after balloon angioplasty and immune-mediated endothelial damage. In addition, ACE inhibitors may promote plaque stabilization and thereby protect against plaque rupture. This may result from inhibition of angiotensin II-induced vasoconstriction, reduction of endothelin production or increased serum or tissue magnesium levels. However, these 2 beneficial effects have not yet been demonstrated conclusively in man.

Vasculoprotective effects of lipid lowering with statin therapy

- Endothelial normalization
- Anti-inflammatory effects
- Depletion and physicochemical stability of lipid core
- Strengthening of fibrous cap
- Inhibition of platelet thrombus formation and deposition
- Reduction of thrombogenic response


Vasculoprotective effects of lipid lowering with statin therapy

Content Points:

- Clinical trials with statins, or HMG-CoA reductase inhibitors, demonstrate an improvement in cardiovascular end points and coronary atherosclerosis that can not fully be explained by their efficacy in lipid reduction.4

- Some of these additional effects include improvement in endothelial function, reduction of inflammation, beneficial effects on atherosclerotic plaques and inhibition of thrombosis.
Aggressive LDL-C reduction benefits patients with other CV risk factors: Post-CABG trial

Content Points:

• A number of studies have demonstrated a beneficial influence of lipid lowering with statin agents on endothelial function. A few of these trials will be highlighted in this presentation.

• The effect of aggressive lipid lowering on 5 risk factors—smoking, diabetes, hypertension, HDL-C < 40 mg/dL and triglycerides = 145 mg/dL—was investigated in this analysis from the Post-CABG trial.5

• The influence of aggressive lowering of LDL-C to 93-97 mg/dL was compared with moderate lowering to 132-136 mg/dL on atherosclerosis progression in saphenous vein grafts that had been placed 1-11 years previously. A total of 1351 patients were followed for a mean of 4.3 years.

• Relative to moderate LDL-C lowering, aggressive lowering reduced risk for atherosclerosis progression to a similar degree in patients with or without CV risk factors. This benefit was especially evident in those with 2 or ≥3 risk factors, where aggressive lowering significantly reduced risk by 54% ($P < 0.0001$) and 51% ($P = 0.0001$), respectively. The 22% risk reduction in patients with 0-1 risk factors did not achieve statistical significance ($P = 0.12$).

• This analysis demonstrates that aggressive LDL-C lowering reduces progression of atherosclerosis.
**Statin therapy improves endothelial function within months in patients with CAD**

**Content Points:**

- The effect of statin therapy on endothelial function was evaluated in 23 patients who were undergoing coronary angioplasty. In this double-blind study, patients with total serum cholesterol of 160-300 mg/dL were randomized to receive lovastatin 40 mg twice daily or placebo in addition to the American Heart Association (AHA) step 1 diet.

- Endothelial function was assessed 12 days after randomization and again 5.5 months later. The ability of the endothelium to mediate vasodilation in response to serial intracoronary infusions of acetylcholine was determined by quantitative angiography, and expressed as the percentage change in coronary artery diameter.

- In this slide, the solid lines depict the endothelial responses of each patient, and the dashed lines show the mean responses of the treatment groups. At the initial assessment, endothelial function was similar in the 2 groups. After 5.5 months, statin therapy significantly improved the endothelial response to acetylcholine, whereas there was no change in endothelial function in the placebo group ($P = 0.004$).

- These results demonstrate that statin therapy significantly improves endothelial function in coronary arteries of atherosclerosis patients.
Treatment with a statin and an antioxidant improves endothelial function and reduces LDL-C oxidation

Content Points:

• The relationship between endothelial function and oxidized LDL-C was evaluated in 23 hypercholesterolemic patients in a 1-year study. Nine patients were randomized to receive lovastatin and probucol, 7 to lovastatin and cholestyramine and 7 to an AHA step 1 diet.

• Endothelial function in response to serial intracoronary infusions of acetylcholine was determined by quantitative coronary angiography. After 1 year of treatment, endothelial function significantly improved in both lovastatin groups relative to the diet group ($P < 0.01$).

• The susceptibility of LDL-C to oxidation was determined from the lag phase of Cu$^{2+}$-induced conjugated diene formation. The lag time was significantly longer in the group treated with lovastatin and probucol than in the other 2 groups ($P < 0.0001$). This finding indicates that lovastatin and probucol treatment reduced LDL-C oxidation.

• As shown in this slide, a univariate analysis demonstrated that endothelial function and the lag time were significantly correlated ($r = 0.62, P = 0.002$). In contrast, total cholesterol, LDL-cholesterol, HDL-cholesterol, apolipoprotein B, triglycerides or the LDL-C:apolipoprotein B ratio did not correlate significantly with endothelial function.

• These results demonstrate that endothelial function is related to the susceptibility of LDL-C to oxidation in hypercholesterolemic patients. This finding is consistent with the role of oxidative stress in causing endothelial dysfunction.

Reducing blood pressure and improving endothelial function

A number of studies have demonstrated that tissue ACE inhibition improves endothelial function and reduces blood pressure.

Reducing blood pressure and improving endothelial function

Content Points:

• The results of a number of recent clinical studies demonstrate that inhibition of tissue ACE improves endothelial function and reduces hypertension. These studies will be discussed in the following slides.
Endothelial function and ACE inhibition: TREND results

Content Points:

- The TREND (Trial on Reversing ENdothelial Dysfunction) study was designed to ascertain if ACE inhibition with quinapril could improve endothelial dysfunction in normotensive patients with CAD. In this double-blind study, 105 patients randomized to once daily treatment with quinapril 40 mg or placebo were restudied after 6 months.

- Endothelial function in response to intracoronary infusions of acetylcholine ($10^{-6}$ and $10^{-4}$ mol/L) was determined by quantitative coronary angiography.

- At baseline, endothelial function in the target artery segment was similar in the placebo and quinapril groups.

- The endothelial response to acetylcholine, expressed as the net change from baseline (primary endpoint), significantly improved with quinapril treatment relative to placebo ($P < 0.002$). The net change with quinapril was $4.5 \pm 3.0\%$ and $12.1 \pm 3.0\%$ at the two acetylcholine doses, respectively. In contrast, endothelial responses in the placebo group did not change from baseline: $-0.1 \pm 2.8\%$ and $-0.8 \pm 2.9\%$ at the 2 acetylcholine doses, respectively.

- At the higher acetylcholine dose, the difference between quinapril and placebo was highly significant ($P < 0.0003$).
TREND: Endothelium-dependent microvascular response

Content Points:

- Coronary blood flow (CBF) was measured by intracoronary Doppler techniques in a subgroup of patients enrolled in the TREND study.9

- CBF was measured after intracoronary infusion of acetylcholine and then again after intracoronary infusion of adenosine. The acetylcholine/adenosine CBF ratio reflects the endothelium-dependent blood flow response as a function of the maximal flow response.

- Thirteen patients - 8 randomized to placebo and 5 to quinapril - had CBF measured at baseline and after 6 months of treatment. The CBF responses at baseline did not differ between groups.

- After 6 months of treatment, there was a trend for the endothelium-dependent blood flow response to increase in the quinapril group, but remain unchanged in the placebo group. The mean change in the acetylcholine/adenosine ratio over the 6-month treatment period with quinapril was 48% ($P = 0.38$) and was similar in direction and magnitude to the diameter responses observed in the larger coronary arteries.

- These results demonstrate that endothelial function improved with quinapril treatment. However, the limited number of patients in this pilot substudy precluded a demonstration of statistical significance relative to placebo. A study involving a larger number of patients is warranted.
**BANFF trial: Absolute changes in flow-mediated vasodilation**

**Content Points:**

- The BANFF trial compared the effects of two ACE inhibitors (quinapril and enalapril), an angiotensin receptor blocker (losartan) and a calcium channel blocker (amlodipine) on endothelial function in patients with documented CAD.\(^\text{10}\)

- Flow-mediated vasodilation in the brachial artery, a measure of endothelial function, was determined by high resolution ultrasound. This assessment was made before and after 8 weeks of treatment with quinapril, enalapril, losartan and amlodipine.

- At baseline, these CAD patients had significantly impaired flow-mediated dilation, which reflected the presence of endothelial dysfunction.

- Quinapril significantly improved flow-mediated dilation by 1.8 ± 1.0% \((P < 0.02)\), whereas none of the other treatments provided significant improvement.

\(^*P < 0.02\)  

BANFF trial: Summary and conclusions

Content Points:

• Significantly impaired flow-mediated dilation (FMD) in CAD patients vs normals

• Quinapril was associated with significant improvement in FMD; enalapril, losartan and amlodipine were not

• Some antihypertensive agents appear to be more effective than others at improving endothelial function

QUO VADIS: Effects of ACE inhibition on ischemia

Content Points:

- QUO VADIS (effects of QUinapril On Vascular ACE and Determinants of Ischemia Study) was a randomized, double-blind, placebo controlled study that was designed to evaluate the effect of ACE inhibition with quinapril on ischemia in patients who underwent CABG.¹¹

- A total of 149 patients who were scheduled to undergo CABG were randomized 27 ± 1 days before surgery to receive once daily treatment with quinapril 40 mg or placebo. Treatment started at randomization and continued for up to 1 year after the CABG procedure.

- The effect of treatment on ischemia was determined by exercise testing, 48-hour Holter monitoring and the occurrence of clinical ischemic events.

- Similar improvements in exercise duration and ischemic ST-segment changes were found in both the quinapril and placebo groups (data not shown). Overall, total exercise duration increased by 77 ± 7 seconds after 1 year. Ischemic ST-segment changes, which were present in all patients at randomization, were found in only 33% of patients at the 1-year evaluation.

- The 48-hour Holter monitoring revealed that 20% of patients in the placebo group and 13% of patients in the quinapril group had 1 or more ischemic episodes. This difference between treatments did not achieve statistical significance (odds ratio: 0.63 [0.21-1.90]).

- In contrast, the percentage of patients who experienced a clinical ischemic event was significantly lower with quinapril treatment than with placebo (odds ratio: 0.2 [0.04-0.96]; P = 0.03). Clinical ischemic events included recurrence of angina pectoris, myocardial infarction, ischemic stroke or transient ischemic attack. Overall, 18% of patients in the placebo group and 4% of those in the quinapril group had a clinical ischemic event within 1 year after the CABG procedure.
**QUO VADIS: Conclusion**

- 1 year after CABG, total exercise duration was comparable between quinapril and placebo patients.
- Within 1 year after CABG, treatment with quinapril associated with a significant reduction in clinical ischemic events.
- This suggests ACE inhibition may improve vascular disease outcome post-CABG.


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**QUO VADIS: Conclusion**

**Content Points:**

- In QUO VADIS, exercise testing and 48-hour Holter monitoring did not reveal significant differences between quinapril and placebo at 1 year after CABG.\(^\text{11}\)

- However, long-term treatment with quinapril provided a statistically significant and clinically relevant reduction in clinical ischemic events within this time period.

- These results suggest that ACE inhibition with quinapril may improve vascular disease outcomes after CABG.
Effect of ACE inhibition on FDD in patients with CHF

Content Points:

• Chronic heart failure (CHF) is associated with endothelial dysfunction, including impaired flow-dependent dilation (FDD).

• In this study, 40 patients with NYHA class III heart failure and radiologic and electrocardiographic signs of cardiomegaly and hypertrophy were randomized to receive intra-arterial infusions of quinaprilat (n = 15), enalaprilat (n = 15) or placebo (n = 10).12

• Flow-dependent dilation in the radial artery was determined by high-resolution ultrasound under control conditions (at rest) and following reactive hyperemia (causing endothelium-mediated dilation) both before and after administration of N-monomethyl-L-arginine (L-NMMA), an inhibitor of endothelial cell NO synthesis.

• Quinaprilat (1.6 µg/min) improved flow-dependent dilation by more than 40% relative to control levels - 10.2 ± 0.6% vs 6.9 ± 0.6%; $P < 0.01$. In contrast, enalaprilat (5 µg/min) and placebo did not have a significant effect.

• After administration of L-NMMA, flow-dependent dilation was reduced similarly in all 3 groups of patients under control conditions.

Effect of ACE inhibition on NO-mediated endothelial dysfunction

Content Points:

- This slide shows the change in flow-dependent dilation that is inhibited by L-NMMA under control conditions and after administration of quinaprilat, enalaprilat or placebo. These histograms represent the component of flow-dependent dilation that is mediated by NO.

- Quinaprilat significantly increased the NO-mediated component of flow-dependent dilation by more than 100% (5.6 ± 0.5% vs 2.5 ± 0.5%; \(P < 0.01\)). Enalaprilat and placebo did not have a significant effect.

- These results indicate that quinaprilat improves flow-dependent dilation by increasing endogenous NO levels in CHF patients by a mechanism that is largely dependent on NO production.

- Based on the study findings, the authors concluded that ACE inhibitors work by differing mechanisms. ACE inhibitors with high tissue affinity appear to have stronger effects on endothelial-mediated vasodilation.

- Data from this study supports findings from TREND and BANFF regarding the beneficial effect of quinapril on the endothelium.
Increasing dosages of enalaprilat did not affect FDD

**Content Points:**

- The effect of increasing enalaprilat doses on flow-dependent dilation of the radial artery was evaluated in 5 CHF patients.\textsuperscript{12}

- Enalaprilat was infused at doses ranging from 5 to 30 µg/min. Even at high doses, enalaprilat did not significantly increase flow-dependent dilation relative to saline (control) infusion.

- This study demonstrates that quinaprilat, which has high affinity for tissue ACE, significantly improves endothelial function in CHF patients, whereas enalaprilat, which has low affinity for tissue ACE, does not do so, even at high doses.
Multitrial analysis: ACE inhibition reduces death in acute MI patients

Content Points:

• The ACE Inhibitor Myocardial Infarction Collaborative Group evaluated data from all randomized trials that included more than 1000 patients in which ACE inhibitor treatment was started during the acute phase (0-36 hours) of a myocardial infarction and continued for 4 to 6 weeks. Included were 4 trials (CONSENSUS-II, GISSI-3, ISIS-4 and CCS-1) that involved approximately 100,000 patients. Captopril was used in 2 of these studies, and enalapril and lisinopril were used in the other 2 trials.

• Overall, there were 239 fewer deaths in patients treated with ACE inhibitors than in those receiving control treatments. This corresponds to a savings of 4.8 lives per 1000 patients treated with ACE inhibitors.

• Approximately 80% of the deaths were avoided during the first week of treatment - 96 in the first day and 104 between days 2 and 7 after the myocardial infarction. During this first week, ACE inhibitor treatment provided an 8 ± 3% reduction (95% CI, 3-14%) in mortality and resulted in a savings of 4.0 lives per 1000 patients treated.

• Overview of these 4 major randomized clinical trials indicates that very early (within hours) treatment with ACE inhibitors following MI improves initial (within a week) clinical outcomes.
Multitrial analysis: Effect of ACE inhibition on 30-day mortality

Content Points:

- Overall, there were 3501 deaths among 49,214 patients given ACE inhibitors (incidence, 7.11%) and 3740 deaths among 49,269 patients allocated to control treatments (incidence, 7.59%) in the 30-day period following an acute myocardial infarction.\(^{13}\)

- The results of the 4 studies-CONSENSUS-II with enalapril, GISSI-3 with lisinopril, and ISIS-4 and CCS-1 with captopril-were consistent. A test for heterogeneity indicated that there was no statistical difference in effects among the 4 trials.

- The cumulative 30-day mortality was significantly reduced by 7% (95% CI, 2-11%; \(P = 0.004\)) in the ACE-inhibitor group relative to control treatment.

- These results support the very early use of ACE inhibitors in the treatment of acute myocardial infarction.
Studies of ACE inhibition in endothelial dysfunction

Content Points:

- This slide and the following one summarize the results of some of the clinical studies that have evaluated the ability of ACE inhibitors to improve endothelial function.

- Of 5 studies conducted with ACE inhibitors in patients with hypertension, only 2 provided evidence for a significant improvement in endothelial function. Of these, both were acute studies and neither was placebo-controlled. Captopril, but not nifedipine, improved the forearm vasodilatory response to acetylcholine in 7 hypertensive subjects in the study by Hirooka et al. Similarly, perindoprilat restored cold pressor test-induced and flow-mediated coronary artery dilation in 10 hypertensive patients in the study by Antony et al.

- A study by Strikwerda et al was conducted in patients with CAD. In this placebo-controlled trial, cilazapril did not significantly improve endothelial function.
Studies of ACE inhibition in endothelial dysfunction (cont’d)

Content Points:

• Three additional studies considered the effect of ACE inhibitors on endothelial function in CAD patients. In each, an ACE inhibitor was shown to have a significant benefit. In two of these studies, which were discussed previously - the TREND trial by Mancini et al.⁸ and the study by Anderson et al.⁷ - quinapril significantly improved endothelial function in CAD patients. In the study by Prasad et al, enalaprilat improved endothelial function.

• ACE inhibitors were also shown to significantly improve endothelial function in 2 studies involving healthy individuals. In the study by Lyons et al, quinapril was significantly more effective than enalapril and placebo, whereas in the study by Hornig et al, quinaprilat provided improvement over baseline levels.¹⁹,²⁰

• This summary indicates that all ACE inhibitors are not equally effective in reducing endothelial dysfunction; rather, some, such as quinapril, appear to provide greater benefit than others. This suggests that differences in efficacy among ACE inhibitors may reflect differences in their mechanism of action.

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Studies of ACE inhibition in endothelial dysfunction (cont’d)

<table>
<thead>
<tr>
<th>ACE-I</th>
<th>PC</th>
<th>N</th>
<th>Disease</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinapril⁷</td>
<td>Yes</td>
<td>105</td>
<td>CAD</td>
<td>Improvement (P &lt; 0.002 vs PL)</td>
<td>Mancini, 1996</td>
</tr>
<tr>
<td>Enalaprilat</td>
<td>No</td>
<td>36</td>
<td>CAD</td>
<td>Improvement (P &lt; 0.02 vs before)</td>
<td>Prasad, 1996</td>
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<tr>
<td>Quinapril⁷</td>
<td>Yes</td>
<td>8</td>
<td>Healthy</td>
<td>Improvement Q vs E (P = 0.006)</td>
<td>Lyons, 1997</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Yes</td>
<td>8</td>
<td>Healthy</td>
<td>Improvement Q vs PL (P = 0.01)</td>
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<tr>
<td>Quinaprilat</td>
<td>No</td>
<td>10</td>
<td>Healthy</td>
<td>Improvement (P &lt; 0.001 vs before)</td>
<td>Hornig, 1997</td>
</tr>
<tr>
<td>Quinapril</td>
<td>No</td>
<td>56</td>
<td>CAD</td>
<td>Improvement (P &lt; 0.02 vs before)</td>
<td>Anderson, 1998</td>
</tr>
</tbody>
</table>

Enalapril | No  | 55| CAD     | NS                             |                |
Losartan  | No  | 38| CAD     | NS                             |                |
Amlodipine| No  | 45| CAD     | NS                             |                |

*All forearm brachial artery except Mancini and Prasad (coronary arteries) and Hornig (radial artery). †Acute study.
ACE-I = angiotensin-converting enzyme inhibitor; CAD = coronary artery disease; NS = difference not significant; PC = placebo controlled; E = enalapril; PL = placebo; Q = quinapril
New clinical trials of ACE inhibition in patients with CAD: Morbidity and mortality outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>ACE inhibitor</th>
<th>Duration of follow-up</th>
<th>Number of patients</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>QUIET</td>
<td>Quinapril</td>
<td>3 years</td>
<td>1750</td>
<td>Cardiac ischemia endpoints (CV death, nonfatal MI, unstable angina, need for revascularization)</td>
</tr>
<tr>
<td>HOPE</td>
<td>Ramipril (± vitamin E)</td>
<td>≤ 4 years</td>
<td>9541</td>
<td>CV disease events; MI, stroke, CV death</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>Lisinopril (± pravastatin)</td>
<td>6 years</td>
<td>40 000</td>
<td>CV death; nonfatal MI; fatal MI all-cause mortality</td>
</tr>
<tr>
<td>PEACE</td>
<td>Trandolapril</td>
<td>5.5 years</td>
<td>8100</td>
<td>CV death, nonfatal MI, PTCA, CABG</td>
</tr>
</tbody>
</table>

Joel Vetter, MD. Personal communication.

**New clinical trials of ACE inhibition in patients with CAD: Morbidity and mortality outcomes**

**Content Points:**

- A number of clinical studies are underway or recently completed that examine the effects of ACE inhibitors on morbidity and mortality in CAD patients. Three of the studies shown—HOPE (Heart Outcomes and Prevention Evaluation), ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial) and PEACE (Prevention of Events with Angiotensin-Converting Enzyme inhibition)—are currently in progress, whereas QUIET (Quinapril Ischemic Event Trial) is the only completed moderately sized morbidity and mortality outcome study.21

- QUIET followed 1750 low-risk patients for 3 years and used an aggregate ischemic event outcome measure.21 These patients had controlled hypertension, average lipid levels, single- or double-vessel disease and had undergone successful coronary angioplasty.

- HOPE randomized 9541 patients to treatment with ramipril or placebo with or without added vitamin E.21,22 HOPE includes a broad range of high-risk patients, including those with CAD, peripheral vascular disease, previous stroke and diabetes. Patients are being followed for up to 4 years. The ACE inhibitor arm was terminated in 1999 due to significant benefit. The vitamin E arm is continuing.

- ALLHAT is a practice-based 6-year study involving 40 000 hypertensive patients.21,23 Four different antihypertensive agents are being evaluated including the ACE inhibitor lisinopril. Embedded within ALLHAT is an open-label lipid-lowering trial involving 20 000 patients who are being randomized to pravastatin or placebo.

- PEACE is evaluating the benefit of adding trandolapril to standard therapy in patients with CAD and preserved left ventricular function.21 The study is designed to enroll 8100 patients and continue for 5.5 years.24

- It is hoped that these moderate to large scale investigations will expand knowledge of the effectiveness of ACE inhibitors to reduce CV events in CAD patients.
Recent and ongoing clinical trials of ACE inhibition in patients with CAD: Surrogate outcomes

Content Points:

- Several recent and ongoing clinical trials are evaluating the effect of short-term (6 months) and long-term (3-5 years) treatment with ACE inhibitors on surrogate outcome measures. Each of these studies involve more than 100 patients.
- TREND is the only one of these studies that has been completed. The results, which were discussed in earlier slides, showed that quinapril significantly improved endothelial dysfunction in normotensive patients with CAD.8
- QUASAR (QUinapril Anti-ischemia and Symptoms of Angina Reductio) is a surrogate outcomes study that is designed to ascertain if quinapril has anti-ischemic effects.21 In this 6-month study, approximately 400 patients with exercise-induced or daily life ischemia will be randomized to quinapril or placebo. Ischemia will be assessed by ambulatory ECG monitoring and exercise tolerance testing.
- Two 3-4 year studies-SECURE (Study to Evaluate Carotid Ultrasound changes with Ramipril and vitamin E) and PART-2 (Prevention of Atherosclerosis with Ramipril Therapy)-are using B-mode ultrasound to evaluate the effect of ramipril on the intimal-medial thickness of the carotid artery, a measure of atherosclerosis. SECURE is a substudy of HOPE and will include 732 high-risk patients, whereas PART-2 will include 600 patients with a history of CAD, transient cerebral ischemia or peripheral vascular disease.21,25
- SCAT (Simvastatin Coronary Atherosclerosis Trial) is a 5-year study that evaluated the effect of enalapril with or without simvastatin on the progression of coronary atherosclerosis in 468 patients with documented CAD.21,26 Quantitative coronary angiography was used to define the extent of atherosclerosis. The results were presented at the meeting and showed that the ACE-I was associated with a decrease in clinical events while the statin was associated with less CAD progression.
- Information gained from these new studies may build on existing data regarding the mechanisms by which ACE inhibitors alter endothelial function.
Content Points:

- As discussed previously, quinapril reduces endothelial dysfunction, an underlying condition in CVD. Angiogenesis is beneficial in some forms of CVD, such as ischemia. Therefore, an experimental rabbit model of chronic hindlimb ischemia was used to explore whether quinapril has beneficial effects on angiogenesis.27

- Baseline endothelial responsiveness to acetylcholine was determined on day 10, and then the animals were randomized to receive an intra-arterial injection of vascular endothelial growth factor (VEGF) or daily injections of quinapril or captopril. Control animals did not receive any treatment.

- Treatment with quinapril and captopril was continued until day 35, and then 5 days later (on day 40), endothelial responsiveness to acetylcholine was again tested.

- Quinapril and VEGF significantly and similarly increased endothelial responsiveness to acetylcholine, as reflected by greater increases in the percentage of basal flow relative to day 10 ($P < 0.01$). In contrast, the responses to acetylcholine in the captopril and control groups did not differ significantly from the day 10 responses.

- These results suggest that quinapril improved endothelial cell function, resulting in improved blood flow responses.
Effect of VEGF & ACE inhibition on calf blood pressure

Content Points:

• In the rabbit model of chronic hindlimb ischemia, endothelial function was also assessed by measuring the calf blood pressure index (BPI). This parameter is the ratio of blood pressure in the ischemic limb relative to the healthy limb.

• Quinapril and VEGF significantly and similarly increased calf BPI relative to baseline values on day 10 ($P < 0.01$). In contrast, the BPI was not increased significantly in the captopril or control groups.

• These results provide additional evidence that quinapril improves blood pressure beyond the occluded iliac artery in the ischemic limb.
Comparisons of angiogram scores and capillary density

Content Points:

• Quinapril significantly increased angiographic score and capillary density in the rabbit model of chronic hindlimb ischemia. Moreover, these effects were similar in magnitude to that provided by VEGF.

• The angiographic score on day 40 was significantly higher than on day 10 in the quinapril and VEGF groups ($P < 0.01$), but not in the captopril or control groups.

• Similarly, capillary density, expressed as the number of capillaries per mm$^2$, was significantly higher after treatment with quinapril or VEGF ($P < 0.01$), but not after treatment with captopril.

• These results indicate that angiogenesis is stimulated by ACE inhibition with quinapril, but not captopril. Thus, the improvement in endothelial cell function by quinapril is associated with the development of new/enlarged microvessels and contributes to improved perfusion of the ischemic limb.