Advancing our Understanding of RAAS Modulation in High-Risk Patients
The prevalence of diabetes in the United States has increased from 6.7 million persons in 1990 to 14.7 million in 2004, an increase of 119%.

During the same period, hospital discharges for cardiovascular (CV) disease (CVD) also increased. In 2003, CVD was the most common disease category in hospital discharges.

Due to the combined prevalence of both CVD and diabetes, these increases are projected to continue.
Continued increase in CVD and diabetes is predicted in US

- Narayan and colleagues at the Centers for Disease Control and Prevention forecast that by 2050 there will be 48.3 million Americans with diagnosed diabetes.

- Heart disease and stroke account for ~65% of deaths in people with diabetes, suggesting that by 2050 diabetes will account for an estimated 31.4 million deaths from CVD.¹

¹ AHA. Circulation. 2006;113:e85-151.
Discharge ACEI post-MI remains suboptimal

- CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse End points with Early Implementation of the ACC/AHA Guidelines) is a national quality improvement initiative.

- The ACC/AHA guidelines for discharge therapy following non-ST-segment acute coronary syndromes (ACS) give angiotensin-converting enzyme (ACE) inhibitors (ACEIs) a class IA recommendation for patients with diabetes, hypertension, left ventricular (LV) dysfunction, or heart failure.¹

- However, data from 393 participating CRUSADE hospitals show that in the first quarter of 2006, these drugs were prescribed in only 65% of cases.

MI = myocardial infarction
TC = total cholesterol

AHA/ACC secondary prevention guidelines: ACEIs and ARBs

ACEIs
- All patients with LVEF ≤40%, hypertension, diabetes, or chronic kidney disease (IA)
- Consider for all other patients (IB)
- Optional: Lower-risk, post-revascularization patients with normal LVEF and well-controlled risk factors (IIaB)

ARBs
- ACEI-intolerant patients with HF or post-MI LVEF ≤40% (IA)
- Consider in other ACEI-intolerant patients (IB)
- Consider use in combination with ACEIs in systolic dysfunction HF (IIbB)


• Preventing CV events remains an important healthcare goal. The role of renin-angiotensin-aldosterone system (RAAS) modulation with ACEIs and angiotensin-receptor blockers (ARBs) was recognized in secondary-prevention guidelines issued earlier this year. Additional data on prevention of CV events in high-risk patients are presented elsewhere in this slide kit.

• The potential role of RAAS modulation in diabetes prevention and glycemic control is also examined in this curriculum.
Critical Role of RAAS in Vasculoprotection: New Science
New aspects of RAAS

- ACE homologues
  - ACE2
  - Soluble ACE

- ACE substrates
  - Ang (1–7)
  - Ang (1–9)
  - N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP)
  - Amyloid β-protein

- Formation of Ang II by non-ACE peptidases

- ACE signal transduction pathway

RAAS = renin-angiotensin-aldosterone system


A number of advances have been made in our understanding of RAAS.

- ACE homologues include ACE2 (which shares ~42% of the catalytic domain of ACE) and a soluble form of ACE (a product of metalloprotease-catalyzed cleavage between residues Arg and Ser).

- In addition to angiotensin (Ang) I and bradykinin, newly identified substrates for ACE include:
  - The peptides Ang (1–7) and Ang (1–9), which may contribute to CV homeostasis
  - N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP), an inhibitor of hematopoietic stem cell proliferation
  - Amyloid β-protein, which has been implicated in Alzheimer’s disease

- A number of other peptidases have also been identified that catalyze the conversion of Ang I to Ang II (slide to follow).

- Finally, there is evidence suggesting that ACE may act as a signal transduction molecule.
This slide summarizes the roles of ACE2, the additional peptidases that convert Ang I to Ang II, and the substrates for ACE and ACE2.

ACE2 converts Ang I to Ang (1–9) and Ang II to Ang (1–7). Ang I may also be converted to Ang (1–7) through the action of neutral endopeptidases (NEP).

The importance of ACE2, NEP, and their products are incompletely understood. Ang (1–7) has attracted interest since it may oppose many Ang II actions, through one or both of its receptors.

In addition, at the tissue level Ang I may be converted to Ang II via non-ACE pathways.

ACEIs were the first RAAS modulators to become clinically available, followed by ARBs and, most recently, by renin inhibitors. Evidence for interactions among the different pathways of the RAAS suggests that the net effect of these RAAS modulators may differ.
Impact of ACEI on ACE signaling pathway

- In endothelial cells, one of the serine residues located at the extreme COOH-terminal end of ACE is phosphorylated by casein kinase 2 (CK2). This phosphorylation, activated by ACEI binding, stabilizes the enzyme in the cell membrane.

- Mitogen-activated protein kinase kinase 7 (MKK7) and c-Jun NH$_2$-terminal kinase (JNK) become associated with the intracellular domain of the enzyme. Phosphorylated c-Jun translocates to the nucleus, with eventual increased expression of genes for ACE and cyclooxygenase-2 (COX-2).

- The clinical significance of this signaling pathway is under investigation.
ACE metabolism

• Initially, kininase II, the enzyme of the kallikrein-kinin system (KKS) that converts bradykinin to inactive metabolites, bradykinin (1–7) and the dipeptide Phe-Arg, was thought to have no relation to ACE.

• However, ACE was subsequently found to have two active domains with different substrate affinities and it is now accepted that these two enzymes are one and the same.
ACEI mechanism of benefit: Reduction in clinical events

- ACEIs favorably modify vascular homeostasis principally by lowering Ang II levels and raising bradykinin levels, although there is evidence that other pathways may also contribute.

- The effect of ACEIs on bradykinin differentiates these agents from other modulators of RAAS.

- Whatever the exact mechanism, a substantial body of data exists demonstrating that ACEIs have favorable effect on atherosclerosis beyond blood pressure (BP) reduction. Evidence discussed in this slide kit suggests that these agents may improve glucose metabolism in selected subgroups.
Aliskiren, a human renin inhibitor, is being evaluated as a potential new antihypertensive therapy in clinical trials. To evaluate its effects on hypertension-associated target organ damage, Pilz et al administered aliskiren to rats transgenic for human renin and human angiotensinogen. These animals rapidly develop hypertension and severe target organ damage, dying at approximately 6–8 weeks.

Six-week-old animals were randomized into 5 groups of 19 rats each. They received aliskiren (0.3 or 3 mg/kg per day), valsartan (1 or 10 mg/kg per day), or vehicle for 3 weeks. Since untreated animals would die before study end, the low-dose valsartan group was intended to serve as control.

Aliskiren (both doses) lowered BP to a similar extent as high-dose valsartan, reduced albuminuria, and normalized serum creatinine (data not shown).

As shown, equipotent antihypertensive doses of aliskiren and valsartan reduced LV hypertrophy (LVH) as measured by LV thickness and cardiac hypertrophy index.
Demonstrated benefits of AT₁R blockade

- ARBs effectively reduce BP, improve heart failure symptoms, blunt progression of diabetic renal disease, and prevent stroke.
- However, trials of ARBs in high-risk patients have generally demonstrated a neutral effect on myocardial infarction (MI).
AT$_1$R blockade upregulates both Ang II levels and AT$_2$R expression

Both physiologic and pathologic effects have been proposed for AT$_2$R stimulation

- The role of AT$_2$ receptors (AT$_2$R) in adults is still unclear. It was thought that this receptor was limited to embryogenesis and early development. More recently, researchers have proposed that increased levels of Ang II resulting from AT$_1$R blockade lead to upregulation of AT$_2$R.
- Both positive (pathophysiologic) and negative (pathologic) effects have been linked to AT$_2$R.
- Thus, the net clinical effect of chronic AT$_1$ receptor blockade remains controversial.
Postulated role of AT$_2$R and MMP-1 in plaque destabilization

- AT$_1$R blockade with ARBs lead to elevated levels of Ang II and upregulation of AT$_2$R in atherosclerotic plaque.

- Ang II, via AT$_2$R, stimulates monocyte production of matrix metalloproteinase-1 (MMP-1), one of a family of MMPs that are produced by monocytes/macrophages and other cells.$^1$ MMP-1 is a collagenase that cleaves fibrillar collagens.

- Degradation of the fibrous cap by increased MMP-1 levels may eventually lead to mechanical failure of the plaque, contact between blood and the plaque contents, and formation of an occlusive thrombus.

AT$_2$R mediates cardiac myocyte enlargement during pressure overload

- Senbonmatsu et al used aortic constriction to induce pressure overload-related LV hypertrophy in wild-type mice.
- However, this effect was not seen in AT$_2$R-deficient mice, where cardiac function remains normal.
- This finding implicates the AT$_2$R in LV hypertrophy due to elevated systolic BP.
Brown et al. looked at the effects of ACE inhibition versus AT₁ receptor blockade on plasminogen-activator inhibitor-1 (PAI-1) in insulin-resistant hypertensive patients, who have elevated levels of this enzyme. To further elevate baseline PAI-1, patients were treated with hydrochlorothiazide (HCTZ) 12.5 mg.

Subjects were then randomized to receive ramipril (n = 9) or losartan (n = 11) for 6 weeks. The dose of each medication was increased every 5 to 7 days (up to 10 mg ramipril or 100 mg losartan) to achieve diastolic BP <90 mm Hg.

After 1 week, both treatments significantly decreased PAI-1 antigen levels from baseline (P = 0.046).

After 3 weeks, PAI-1 antigen levels returned to baseline in the losartan group but remained significantly decreased in the ramipril group. After 6 weeks, PAI-1 antigen levels were still significantly decreased from baseline in the ramipril group.

Thus, both ACE inhibition and AT₁ receptor blockade decrease PAI-1, but only ACE inhibition provides a sustained effect (P = 0.043).
ACEIs and bradykinin oppose Ang II effects

- Ang II effects are proatherogenic and are mediated principally through its AT₁R.
- Bradykinin is associated with a number of vasculoprotective effects, including stimulating synthesis and release of nitric oxide (NO), prostacyclin, and endothelium-derived hyperpolarizing factor (EDHF). Bradykinin also stimulates endothelial release of tissue plasminogen activator (tPA). These effects are mediated by the B₂ receptor.
- Since ACE degrades bradykinin to the inactive fragment bradykinin (1–5), ACEIs increase levels of bradykinin.
- ACEIs also have direct positive effects on the B₂ receptor. They inhibit B₂ receptor sequestration within caveolae (which desensitizes the receptor) and enhance the effect of bradykinin on the receptor.
Ang II effect in target organ damage

- In summary, RAAS activation is implicated in the altered structure and function of several organ systems. These effects are mediated by Ang II, the principal effector molecule of the RAAS.
- Renin converts angiotensinogen to Ang I, which in turn is converted to Ang II by ACE.
- Intervention at multiple targets in this system has favorable effects on target organ structure and function.
Potential role of RAAS activation in metabolic syndrome and diabetes

• Local RAAS has been identified in adipose tissue and pancreatic beta cells, where they are believed to contribute to development of metabolic syndrome (MetS) and type 2 diabetes (T2DM).

• For example, Ang II plays a role in adipose cell maturation and growth. Fatty acids also activate angiotensinogen gene expression in adipocytes.

• The pancreatic RAAS appears to regulate pancreatic and islet blood flow as well as secretion of pancreatic hormones.

• RAAS activation also appears to diminish skeletal muscle glucose uptake.
RAAS activation in obesity

Engeli S et al measured levels of RAAS components in 19 obese (mean BMI 37.6 kg/m²) and 19 lean (mean BMI 23.5 kg/m²) menopausal women.

As shown, circulating levels of renin, ACE, and aldosterone were significantly higher in the obese group.

Levels of Ang II were also higher, but the difference did not reach statistical significance.
RAAS activation contributes to obesity-related hypertension

- Data from Engeli et al and others point to a role for adipose tissue RAAS activation in obesity-related hypertension.¹
- Overexpression of angiotensinogen in adipose tissue results in release of this molecule into the circulation, which contributes to the circulating pool of Ang II, thereby raising BP.

ACEIs: Potential mechanisms of improved glucose metabolism

- Two mechanisms have been proposed for ACEI-related enhanced glucose uptake in skeletal muscle tissue.
- The first involves bradykinin B₂ receptor–mediated increase in NO and blunting of Ang II-mediated vasoconstriction, both of which improve skeletal-muscle blood flow.
- The second involves enhanced skeletal-muscle glucose disposal.
Role of Ang II in insulin resistance: Focus on signaling pathways

- Glucose enters cells through a family of glucose transporters (GLUT).\(^1\) GLUT-4 mediates insulin-stimulated glucose uptake by adipocytes and muscle.

- Insulin binding to its receptor results in formation of an active complex between insulin receptor substrate-1 (IRS-1) and phosphatidyl inositol-3 kinase (PI3-K), which in turn triggers a cascade resulting in translocation of GLUT-4 to the sarcolemmal membrane.

- Bradykinin, via the B\(_2\) receptor, enhances IRS-1 and PI3-K activity, thereby promoting translocation of GLUT-4.

- Ang II inhibits PI3-K, blunting insulin-mediated glucose entry into cells.

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ACEIs improve glucose uptake in peripheral tissue

- Shiuchi et al measured glucose uptake in peripheral tissues of a diabetic mouse model (a cross between glucose-intolerant black KK female mice and male yellow obese Ay mice).
- This slide shows uptake of tritiated deoxy-d-glucose (2-[\(^3\)H]DG) in the soleus muscle.
- ACE inhibition (temocapril) administration enhanced glucose uptake. This effect was attenuated by concomitant administration of the bradykinin B\(_2\) receptor blocker HOE 140 or the NO synthase inhibitor L-NAME.
- The investigators concluded that ACEI improves glucose uptake, in part, through enhancement of the bradykinin-NO pathway.
RAAS Modulation in High-Risk Patients
ACEIs: Evolution of benefits

- ACEIs were developed as antihypertensive agents. However, a subsequent series of major trials demonstrated beneficial cardiac (myocardial), vascular (antiatherosclerotic), and renal effects.
- In addition, results from recent clinical trials have suggested improved glycemic control with these agents.
- The preceding slides provide a physiologic rationale for these clinical findings. The slides in this section summarize clinical data.
Abuissa et al conducted a meta-analysis of 12 randomized trials (N = 116,220) of ACEIs (5 trials) and ARBs (7 trials) that reported the incidence of new-onset diabetes.

- ACEIs were associated with a 27% relative risk reduction (RRR) in diabetes; ARBs were associated with a 23% RRR.
- Only two of these trials included new-onset diabetes as a prespecified end point.
HOPE, EUROPA, PEACE: Reduction in new-onset diabetes (placebo-controlled trials)

- Although new-onset diabetes was not a pre-specified end point, three trials showed a consistently lower rate of incidence:
  - HOPE (Heart Outcomes Prevention Evaluation)
  - EUROPA (EURopean trial On reduction of cardiac events with Perindolpril in stable coronary Artery disease)
  - PEACE (Prevention of Events with Angiotensin-Converting Enzyme inhibition).
- Overall, ACEI treatment provided a 14% RRR in the onset of diabetes (P = 0.0023).
- Use of agents that adversely affect glucose metabolism (such as diuretics and beta-blockers) was comparable between the active treatment and placebo groups. Thus, the data suggest a small but favorable affect of ACEIs.
• The thiazolidinediones (TZDs) are a family of antidiabetic agents that are agonists of peroxisome proliferator-activator receptor-gamma (PPARγ).

• TZD effects include improving insulin sensitivity and preserving pancreatic β-cell function, as well as improvements in a number of traditional and new CV risk factors.¹

• The Diabetes Prevention Program (DPP) included 2343 subjects at high-risk of diabetes, as measured by elevated fasting and postload glucose concentrations.

• Patients were randomized to troglitazone 400 mg/day (n = 585), metformin 850 mg bid (n = 587), intensive lifestyle modification (≥7% weight loss plus ≥150 min/wk physical activity;² n = 589), or placebo (n = 582).

• This slide summarizes cumulative incidence of diabetes by subgroup for the 1.5 years before early termination of the troglitazone arm due to concerns of possible liver toxicity.

• Compared with placebo, troglitazone reduced the development of diabetes by 75%, lifestyle intervention by 58%, and metformin by 44%.

DPP: Long-term benefit of lifestyle intervention or metformin on diabetes prevention

- When the trial was completed (average follow-up, 2.8 years), the benefit of lifestyle intervention remained greater than that of metformin.

- Incidence of diabetes was reduced by 58% with diet and exercise and by 31% with metformin as compared with placebo.

- Moderate lifestyle intervention was particularly effective as a means of preventing diabetes—an estimated 1 case of diabetes would be prevented per 6.9 persons treated for 3 years.
DREAM: Background

- Prevalence of T2DM continues to rise
- Persons with diabetes are at risk for macro- and microvascular complications
- Current options for diabetes prevention include:
  - Lifestyle intervention: ≥50%
  - Acarbose, metformin: ≥25%–30%
- New approaches are needed


DREAM: Background

- The Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial provides important new information on potential strategies for diabetes prevention and improving glucose metabolism.
- By the time diabetes is diagnosed, patients have been at increased CV risk for years. Thus, prevention of diabetes is a logical strategy for reducing the high CV morbidity and mortality associated with the disease.
- Lifestyle modification (weight loss plus physical activity) has been shown to reduce new-onset diabetes by more than 50% in high-risk individuals. However, patient adherence tends to be poor.¹
- Some glucose-lowering therapies (metformin, acarbose) are demonstrated to prevent new-onset diabetes, but their effect is less effective than lifestyle intervention.
- ACEIs have attracted interest as potential new approaches to diabetes prevention because of their documented benefits in reduction of CVD and renal disease and because of intriguing evidence in prevention of new-onset diabetes.

DREAM: Study design

- The DREAM trial assessed treatment with rosiglitazone and/or ramipril in 5269 multi-ethnic adult patients (ages ≥30 years) with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG) but without diabetes. Follow-up was 3 to 5 years.

- The 2 × 2 factorial trial design compared ramipril and/or rosiglitazone vs placebo (slide to follow).

- The primary end point was new-onset diabetes or all-cause mortality.

- The secondary end points were as follows:
  - CV events: MI, stroke, CV death, revascularization, heart failure, angina, or ventricular arrhythmia requiring resuscitation
  - Renal events: progression of normo- or microalbuminuria to micro- or macroalbuminuria, or a 30% decrease in creatinine clearance
  - Glycemic status: Glucose levels and conversion to normoglycemia (defined as fasting glucose <110 mg/dL and 2-hour glucose <140 mg/dL\(^1\))

- The DREAM population was obese (mean BMI, 30 kg/m\(^2\)) and middle-aged (mean, 54.7 years). BP and glucose were not markedly elevated.

**DREAM: 2 × 2 factorial design**

N = 5269 with IFG and/or IGT

- Ramipril: 5 mg × 2 months; 10 mg × 10 months; 15 mg thereafter
- Rosiglitazone: 4 mg × 2 months; 8 mg thereafter

The 2 × 2 factorial design randomized subjects to the following groups:
- Rosiglitazone 8 mg plus ramipril 15 mg
- Rosiglitazone 8 mg plus placebo
- Ramipril 15 mg plus placebo
- Placebo plus placebo

Rosiglitazone was initiated at 4 mg daily, with titration to 8 mg at 2 months. Ramipril was started at 5 mg daily, with titration to 10 mg at 2 months, and to 15 mg at 1 year.

Clinical outcomes in DREAM were assessed by masked adjudication with prespecified diagnostic criteria.*

In the case of heart failure, these included overnight hospitalization or attendance in an acute care setting for two out of the following three criteria:
- Signs or symptoms of heart failure
- Radiologic evidence of heart failure
- Need for intravenous or oral diuretic, vasodilator, and/or inotrope therapy

DREAM: Ramipril effect on new-onset diabetes or death

- The primary end point (diabetes or death) occurred in 18.1% and 19.5% of the ramipril and placebo groups, respectively, a 9% RRR (hazard ratio [HR] 0.91; 95% confidence interval [CI], 0.81–1.03; P = 0.15).
  - Diabetes occurred in 17.1% and 18.5% of participants, respectively, a 9% RRR (HR 0.91; 95% CI, 0.80–1.03).
  - Death occurred in 1.2% of each group (HR 0.98; 95% CI, 0.60–1.60).
- The Kaplan-Meier curves appeared to diverge late in the trial, suggesting that benefit may have been demonstrated with longer follow-up. However, the DREAM investigators noted that this divergence may have been due to chance.

Hazard rate = cumulative daily risk of having an outcome
Regression to normoglycemia (fasting plasma glucose <110 mg/dL and 2-hour glucose <140 mg/dL) was observed in 42.5% and 38.2% of participants receiving ramipril vs placebo, respectively—a 16% relative increase in the likelihood of this end point (HR 1.16; 95% CI, 1.07–1.27; P = 0.001).

Overall, there were fewer patients with dysglycemia in the ramipril group than in the placebo group, supporting the hypothesis that ACE inhibition may have a favorable effect on glucose metabolism.
DREAM: Rosiglitazone effect on primary end point

- The primary end point occurred in 11.6% and 26.0% of the rosiglitazone and placebo groups, respectively, a 60% RRR (HR 0.40; 95% CI, 0.35–0.46; P < 0.0001).
  - Diabetes occurred in 10.6% and 25% of participants, respectively, a 62% RRR (HR 0.38; 95% CI, 0.33–0.44; P < 0.0001).
  - Death occurred in 1.1% and 1.3% of participants, respectively, a 9% RRR (HR 0.91; 95% CI, 0.55–1.49; P = 0.70).
- The effect of rosiglitazone on the primary end point was observed across all geographic regions studied and among participants of all ethnic, gender, and age groups. Benefit was also independent of weight or fat distribution.
DREAM: Conversion to normoglycemia with rosiglitazone

- Conversion to normoglycemia (fasting plasma glucose <110 mg/dL and 2-hour glucose <140 mg/dL) was observed in 50.5% and 30.3% of rosiglitazone- and placebo-treated participants, respectively—a 71% relative increase in this end point (HR 1.71; 95% CI, 1.57–1.87; P < 0.0001).
DREAM: Safety

Ramipril vs placebo
- No adverse hepatic effects
  - Alanine aminotransferase (ALT) levels ↓1.1 U/L at 1 year (P = 0.004)

Rosiglitazone vs placebo
- Increased incidence of HF* (0.5% vs 0.1%, P = 0.01)
  - No cases of fatal HF
  - No difference for other CV events
- Increased incidence of peripheral edema (6.8% vs 4.9%, P = 0.003)
- 4.9-lb weight gain (P < 0.0001)
  - Increased hip circumference (0.71 in, P < 0.0001)
  - No difference in waist circumference
  - Decreased waist-hip ratio (P < 0.0001)
- No adverse hepatic effects
  - ALT levels ↓4.2 U/L at 1 year (P < 0.0001)

*Adjudicated

Overall, CV event rates were similar between the rosiglitazone and placebo groups. The CV events composite outcome occurred in 2.9% and 2.1% of participants in the rosiglitazone and placebo groups, respectively (HR 1.37; 95% CI, 0.97–1.94; P = 0.08). Other than heart failure, there were no significant differences in CV event rates between the groups.

Adjudicated nonfatal heart failure was reported in 14 patients (0.5%) and 2 patients (0.1%) in the rosiglitazone and placebo groups, respectively (HR 7.03; 95% CI, 1.60–30.9; P = 0.01). There were no cases of fatal heart failure.

Peripheral edema occurred more frequently in the rosiglitazone group (6.8% vs 4.9%, P = 0.003).

There were no adverse hepatic effects associated with either treatment.
DREAM: Clinical implications

Ramipril
- No significant effect on new-onset diabetes
  - Improved glucose metabolism; further research is needed
  - Routine use for diabetes prevention cannot be recommended
- When ACEIs are indicated, improved glucose metabolism may be additional benefit

Rosiglitazone
- Provides evidence that pharmacologic intervention is an option for treatment of prediabetes
- Benefit/risk: Of 1000 individuals treated for 3 years, ~144 cases of new-onset diabetes could be prevented with excess of 4–5 HF cases

In summary, ramipril was associated with a nonsignificant 9% RRR in new-onset diabetes or death in participants with IFG or IGT and without CVD. However, significantly more participants achieved normoglycemia with ramipril versus placebo. Ramipril also significantly reduced BP versus placebo (P < 0.001).

Rosiglitazone substantially reduced the risk of diabetes or death and was associated with a significantly greater likelihood of conversion to normoglycemia. Benefit was consistent across a number of prespecified subgroups. Rosiglitazone was also associated with a modest but significant reduction in BP versus placebo.

The DREAM results do not extend the benefits of ACEIs to diabetes prevention. The trial raised the hypothesis that ACEIs may improve glucose metabolism, but this needs to be tested in clinical trials. If this is confirmed, improved glucose metabolism would be an additional benefit of ACEIs in patients with existing indications for these agents (ie, patients at high CV risk).

Based on the DREAM results, rosiglitazone, with a favorable benefit/risk ratio, appears to be a novel approach for treatment of dysglycemia.

Evolution of ACE inhibition for treating patients with CHD

- Outcomes trials of ACEIs were conducted in patients with heart failure or LV dysfunction. Meta-analysis of some of these early studies suggested a reduction in MI,\(^1\) which prompted evaluation of these agents in patients with CAD but without heart failure or LV dysfunction.

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Meta-analyses show consistency of ACEI benefit in preventing CV events

Randomized, placebo-controlled trials in patients with CAD without HF or LV dysfunction

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<td>Al-Mallah, 2006</td>
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<tr>
<td>Dagenais, 2006</td>
<td>3</td>
<td>29,805</td>
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- Three meta-analyses of ACEI trials in patients with CAD and preserved LV function have been recently published. While differing in selection criteria (and, hence, in number of trials included), the results of these analyses are consistent, eg, similar reductions in CV death and MI.

- However, 4 of the 7 trials in the meta-analyses were small, enrolling <2000 patients each. The remaining 3 trials—HOPE, EUROPA, and PEACE—comprise the bulk of the evidence (ie, these trials account for 88% of all patients studied).
EUROPA, HOPE, PEACE, QUIET: Treatment effect on CV end points

- In EUROPA, perindopril 8 mg demonstrated a 20% reduction in the primary outcome.
- In HOPE, ramipril 10 mg reduced the primary outcome by 15% after 1 year and 22% at the end of the study.¹
- Thus, HOPE and EUROPA demonstrated comparable benefits with long-term treatment.
- In contrast, PEACE results demonstrated a neutral effect with trandolapril 4 mg on the primary outcome (21.9% vs 22.5%, trandolapril vs placebo, respectively).
- Various reasons have been suggested for the difference in the PEACE outcome.¹
  - Better risk factor control at baseline in PEACE.
  - The trandolapril dose was not adequate to obtain the same vascular effects as ramipril or perindopril.
  - Trandolapril was uptitrated to its target dose too slowly.
  - A greater number of PEACE patients were lost to follow-up than in the other trials.
  - The study was underpowered to provide evidence of a reduction in hard end points such as MI and CV death.
- QUIET randomized 1750 patients who had undergone coronary angioplasty or atherectomy to quinapril 20 mg or placebo. Study results demonstrated a nonsignificant 13% relative reduction in risk of the secondary end point (CV death, MI, or resuscitated cardiac arrest).

¹ Fox K et al. Eur Heart J. 2006;27:2154-7.
HOPE, EUROPA, PEACE: Overview

- HOPE studied the effects of ramipril 10 mg in 9297 high-risk patients (ages ≥55 years) with vascular disease (80% with coronary heart disease [CAD]) or with diabetes plus ≥1 other CV risk factors, but without LV dysfunction or heart failure. Primary end point was CV death, MI, and stroke.

- EUROPA studied the effects of perindopril 8 mg in 12,218 lower-risk patients (ages ≥18 years) with CAD and without heart failure. Primary end point was CV death, MI, and cardiac arrest.

- PEACE, a somewhat smaller trial, studied the effect of trandolapril 4 mg in 8290 patients (ages ≥50 years) with stable CAD and preserved LV function. Originally, the primary end point of PEACE was CV death or nonfatal MI, but the trial was not powered to determine this end point. After randomizing 1584 patients, the steering committee decided that recruiting the necessary 14,100 patients was not feasible. At this point, the sample size was reduced to 8100 and the primary end point expanded to include coronary revascularization.
Dagenais et al conducted a meta-analysis of these three trials (N = 29,805).

Reduction in all-cause mortality was significant in HOPE (17%, P < 0.005).

The odds ratios favored ACEIs in EUROPA and PEACE, although the confidence intervals overlapped with unity.

However, pooling the results yielded a significant 14% reduction (P = 0.0004).
HOPE, EUROPA: Benefit consistent across ancillary therapy

- Pooled data from HOPE and EUROPA showed benefits in patients taking beta-blockers, lipid-lowering agents, and antiplatelet therapy, or patients who underwent revascularization.

HOPE, EUROPA: Benefit of ACEIs consistent across baseline combinations

- Dagenais et al also analyzed the results according to different combinations of baseline therapies in HOPE and EUROPA patients. Again, they observed consistent benefit with ACEIs.

- Patients receiving ancillary therapy, alone or in combination, resulted in consistent benefits, which suggest that the apparently neutral results of PEACE were not due to the background therapies used.
Benefit of ACEIs in patients with/without LVD or HF

- When pooled data from HOPE, EUROPA, and PEACE were compared with similar data from trials of higher-risk patients with LV dysfunction (LVD) or heart failure (HF), ACEIs were beneficial in all cases.
- This analysis included patients representing a fourfold range in baseline risk.
EUROPA: Consistent risk reduction regardless of baseline risk

- In a post hoc analysis, Deckers et al assessed whether the benefit observed with long-term administration of perindopril in the overall EUROPA population was consistent among patients at all baseline risk levels.
- To make this determination, they developed a CV risk–scoring system according to the association of baseline patient characteristics with subsequent events. These characteristics included:
  - Traditional CV risk factors: Age >65 years, male gender, high serum cholesterol, hypertension, smoking, obesity, family history of CAD
  - Comorbidities: Previous MI, stroke, and/or peripheral vascular disease; symptomatic CAD, diabetes
- Risk scores developed in this manner identified patients at low, intermediate, and high risk, with risk scores/yearly event rates as follows:

<table>
<thead>
<tr>
<th>Risk</th>
<th>Score</th>
<th>Yearly event rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt;4</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Medium</td>
<td>4–9</td>
<td>1%–3%</td>
</tr>
<tr>
<td>High</td>
<td>≥10</td>
<td>&gt;3%</td>
</tr>
</tbody>
</table>

- Whereas only 5% of patients were at low risk, ~30% of patients were at high risk.
- Treatment benefit was consistent among high, intermediate, and low risk patients; the test for heterogeneity of treatment effect was negative (P = 0.15), indicating that the relative treatment benefit was not modified by risk level.
HOPE, EUROPA, PEACE: Benefit of ACEIs across broad spectrum of risk

• To further analyze the potential effect of baseline risk, Dagenais et al classified HOPE and EUROPA patients according to low, medium, or high risk, based on annual event rates in the placebo groups.

<table>
<thead>
<tr>
<th>Risk</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOPE</td>
<td>2.17</td>
<td>3.58%</td>
<td>5.98%</td>
</tr>
<tr>
<td>EUROPA</td>
<td>1.40</td>
<td>2.41%</td>
<td>4.0%</td>
</tr>
</tbody>
</table>

• Treatment benefit in EUROPA was consistent among high-, intermediate-, and low-risk patients; the test for heterogeneity of treatment effect was negative (P = 0.15), indicating that the relative treatment benefit was not modified by risk level.

• For the composite end point of CV death, MI, or stroke, investigators compared the risk reductions in HOPE and EUROPA across low/medium/high-risk categories versus trials with patients at much higher risk because of HF or LV dysfunction (an end point of total mortality, instead of CV death, was used in these trials).

• Again, investigators found consistent benefit with ACEIs regardless of baseline risk, suggesting that the apparently neutral results of PEACE were not due to inclusion of a population at lower risk than in HOPE and EUROPA.
ACEIs in vascular disease: Conclusions

- ACEIs reduce mortality, MI, HF, and stroke in patients with vascular disease with/without LVSD or HF
- Benefit in addition to antiplatelet agents, β-blockers, and lipid-lowering agents
  - Combining ACEIs with these agents provides greatest benefit
- Benefit in patients across a broad range of risk for CV events
  - Annual rate in placebo groups of 1.4%–22.6%

Consider ACEIs in all patients with vascular disease
- Assess risk/benefits and tolerability
- Use doses proven in clinical trials


ACEIs in vascular disease: Conclusions

- Dagenais et al concluded that ACEIs:
  - Should be considered in all patients with vascular disease who can tolerate them if the absolute risk reduction is judged to be valuable.
  - Should be used in combination with other proven therapies (such as antiplatelet agents, beta-blockers, and lipid-lowering agents)
  - Provide benefit in a broad range of patients

- Additionally, Fox et al concluded that only agents and doses proven in clinical trials to provide vasculoprotection should be used.
ACEIs and elevated serum creatinine in renal insufficiency

- Creatinine elevations are modest and self-limiting
  - ≤30% above baseline
  - Stabilize within 2 to 4 weeks
  - If BP is controlled, elevation after 4 weeks is unlikely

- Causes
  - Effective circulating volume (most common)
  - Bilateral renal stenosis

- Withdraw ACEI only if creatinine is >30% above baseline or K ≥21.9 mg/dL (5.6 mmol/L)


- Often, there is reluctance to use ACEIs in patients with renal insufficiency because elevations in serum creatinine can occur.

- Bakris and Weir reviewed 12 randomized clinical trials of ACEIs in patients with renal insufficiency at baseline. Their findings are as follows:
  - Any elevations that may occur in patients treated with ACEIs are generally ≤30% above baseline, tend to occur within the first 2 weeks of therapy, and stabilize by week 4 of therapy.
  - The most common cause is a decrease in effective arterial blood volume secondary to aggressive diuresis or to heart failure.
  - Bilateral renal stenosis is a rare cause of serum creatinine elevation and should be suspected if rehydration fails to normalize serum creatinine levels.

- The investigators suggest that ACEI therapy be reduced or stopped only in cases of a creatinine elevation >30% above baseline or if serum potassium levels are ≥21.9 mg/dL.
Mann et al analyzed the HOPE data to assess if ramipril would reduce CV events in patients with renal insufficiency (serum creatinine ≥1.4 mg/dL).

As shown, ramipril was associated with similar reductions in risk for the primary end point (CV death, MI, or stroke) and for MI in patients with and without renal insufficiency (Table).

<table>
<thead>
<tr>
<th></th>
<th>Renal insufficiency</th>
<th>Normal renal function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary end point</strong></td>
<td>0.80 (0.59–1.09)</td>
<td>0.79 (-0.70–0.88)</td>
</tr>
<tr>
<td><strong>Fatal/nonfatal MI</strong></td>
<td>0.78 (0.54–1.11)</td>
<td>0.81 (0.70–0.93)</td>
</tr>
</tbody>
</table>
Meta-analysis of trials comparing ARB vs placebo, non-ACEI comparators, or ACEI

9 of 11 trials show excess MI for ARB

<table>
<thead>
<tr>
<th>Trial</th>
<th>ARB n/N (MI)</th>
<th>Control n/N (MI)</th>
<th>Favors ARB</th>
<th>Favors control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELITE</td>
<td>3/352</td>
<td>4/370</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DETAIL</td>
<td>9/120</td>
<td>6/130</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELITE II</td>
<td>31/1576</td>
<td>28/1574</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDNT</td>
<td>39/579</td>
<td>66/1136</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHARM-Alt</td>
<td>75/1013</td>
<td>48/1015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCOPE</td>
<td>70/2477</td>
<td>63/2460</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RENAAL</td>
<td>50/751</td>
<td>68/762</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIFE</td>
<td>198/4605</td>
<td>188/4588</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VALUE</td>
<td>369/7649</td>
<td>313/7596</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPTIMAAL</td>
<td>384/2744</td>
<td>379/2733</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VALIANT</td>
<td>587/4909</td>
<td>559/4909</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>26,777</td>
<td>27,273</td>
<td>1.08 (1.01–1.16)</td>
<td></td>
</tr>
</tbody>
</table>


Meta-analysis of trials comparing ARB vs placebo, non-ACEI comparators, or ACEI

- Strauss and Hall conducted a meta-analysis of 11 trials that compared an ARB with placebo, a non-ACEI comparator, or an ACEI. Trials which permitted concomitant nonstudy ACEI or <6 months duration were excluded.
- In the majority of the trials, more MIs were reported in the ARB versus the control groups.
- Pooled analysis yielded an odds ratio (OR) in favor of control (OR 1.08; 95% CI, 1.01–1.16; P = 0.03).
Meta-analysis of ACEI and ARB trials

- Three other meta-analyses evaluated the effects of ARBs on clinical outcomes. Their findings with regards to MI and CV death are compared with those of Strauss and Hall.
  - Tsuyuki and McDonald: any controlled trials of ARBs (N = 68,711; 25 trials)
  - Volpe et al: trials with MI as specified end point or prespecified event (N = 56,254; 11 trials, 10 included in the Strauss and Hall analysis)
  - Verdecchia et al: trials with MI as a prespecified end point, had follow-up ≥1 years, and included ≥500 patients (N = 64,381; 11 trials)
- Increased risk for MI was consistently noted in all four analyses, although only Strauss and Hall results found it statistically significant (agent vs all comparators):
  - Strauss and Hall: ACEIs, OR 0.86 (95% CI, 0.82–0.90); ARBs, OR 1.08 (95% CI, 1.01–1.16)
  - Tsuyuki and McDonald: ARBs, RR 1.03 (95% CI, 0.93–1.13)
  - Volpe: ARBs, 1.036 (95% CI, 0.97–1.11)
  - Verdecchia: ARBs, OR 1.02 (95% CI, 0.96–1.09)
- Tsuyuki and McDonald, Volpe et al, and Verdecchia et al concluded that their findings do not support the hypothesis that ARBs increase risk of MI. Conversely, Strauss and Hall concluded their data show ARBs do not reduce risk of MI.
- Strauss and Hall also conducted a meta-analysis of 23 ACEI trials of 68,631 patients. They found a 14% RRR for MI (P < 0.00001) and a 12% RRR for CV death (P < 0.0005). Importantly events rates for these end points in comparator groups were similar in the ACEI vs ARB trials, respectively: MI 5.8% vs 6.3%; CV death 8.4% vs 9.2%.
ACEIs vs ARBs: Comparative effects on stroke, HF, and CHD

- The Blood Pressure Lowering Treatment Trialists’ Collaboration (BPLTTC) conducted a meta-regression analysis of 21 randomized trials (N = 137,356) that compared ACEI versus ARB.

- The BPLTTC concluded there were no differences in risk reduction between the two classes with respect to stroke and heart failure. However, there was a significant risk reduction in favor of ACEI with respect to MI and CV death (RRR 15%, P = 0.001).

- Compared with BP lowering alone, ACEIs were associated with a 9% RRR and ARBs were associated with a 7% relative increase in CHD risk.
**EPHESUS: New subgroup analysis**

<table>
<thead>
<tr>
<th></th>
<th>Eplerenone better</th>
<th>Placebo better</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>●</td>
<td>●</td>
<td>0.001</td>
</tr>
<tr>
<td>CV mortality/hospitalization</td>
<td>●</td>
<td>●</td>
<td>0.002</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>●</td>
<td>●</td>
<td>0.022</td>
</tr>
<tr>
<td>History of diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>●</td>
<td>●</td>
<td>0.127</td>
</tr>
<tr>
<td>CV mortality/hospitalization</td>
<td>●</td>
<td>●</td>
<td>0.03</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>●</td>
<td>●</td>
<td>0.641</td>
</tr>
<tr>
<td>LVEF ≤30%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>●</td>
<td>●</td>
<td>0.012</td>
</tr>
<tr>
<td>CV mortality/hospitalization</td>
<td>●</td>
<td>●</td>
<td>0.001</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>●</td>
<td>●</td>
<td>0.01</td>
</tr>
</tbody>
</table>

The Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) was a placebo-controlled evaluation of the aldosterone blocker eplerenone 50 mg in 6632 patients with acute MI, LVEF ≤40%, and signs of heart failure. All patients also received standard medical therapy. Patients were followed for up to 2.5 years (mean, 16 months).

- There was a 15% RRR in the primary outcome of all-cause mortality (P = 0.008). Significant reductions in other end points (ie, CV mortality and/or hospitalization, sudden cardiac death) were also observed.
- An analysis of eplerenone effects in high-risk subgroups enrolled in EPHESUS is summarized on the slide. Patients with diabetes appeared to obtain less benefit than those with hypertension or severe LV systolic dysfunction.
Role of RAAS modulation continues to evolve

- Several major ongoing trials are assessing the effects of RAAS modulation on CV events and diabetes. Results are anticipated beginning in 2007.
ONTARGET: Study design

- The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) randomized 25,620 high-risk patients to telmisartan 80 mg, ramipril 10 mg, or their combination. Eligible subjects were ≥55 years of age with coronary, cerebrovascular, or peripheral vascular disease, or with diabetes plus evidence of end-organ damage.

- The primary end point is a composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for congestive heart failure. New-onset diabetes is one of the secondary end points. Patients will be followed for up to 5.5 years. Recruitment ended in 2003.
The Telmisartan Randomized AssessmeNt study in aCE iNtolerant subjects with cardiovascular Disease (TRANSCEND) used the same entry criteria as ONTARGET, with the addition that patients enrolled in this trial had to be intolerant of ACEIs.

The projected enrollment is 6000 patients. Length of follow-up and the primary end point are the same as in ONTARGET. Recruitment ended in 2004.
### ONTARGET/TRANSCEND: Baseline medical conditions vs HOPE

- In general, patients enrolled in ONTARGET and TRANSCEND have similar characteristics as those in HOPE, except for a higher proportion of hypertension and cerebrovascular disease at baseline.
### ONTARGET/TRANSCEND: Baseline medications vs HOPE

<table>
<thead>
<tr>
<th>Medications (%)</th>
<th>ONTARGET</th>
<th>TRANSCEND</th>
<th>HOPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEIs</td>
<td>57.5</td>
<td>58.1</td>
<td>11.6</td>
</tr>
<tr>
<td>ARBS</td>
<td>8.6</td>
<td>29.9</td>
<td>–</td>
</tr>
<tr>
<td>β-blockers</td>
<td>56.9</td>
<td>57.9</td>
<td>39.5</td>
</tr>
<tr>
<td>Statins</td>
<td>60.7</td>
<td>54.5</td>
<td>28.9</td>
</tr>
<tr>
<td>Aspirin</td>
<td>75.6</td>
<td>74.7</td>
<td>73.6</td>
</tr>
<tr>
<td>CCBs</td>
<td>33.5</td>
<td>41.1</td>
<td>47.6</td>
</tr>
<tr>
<td>Nitrates</td>
<td>29.2</td>
<td>33.9</td>
<td>31.1</td>
</tr>
<tr>
<td>Oral hypoglycemics</td>
<td>25.0</td>
<td>23.8</td>
<td>21.8</td>
</tr>
<tr>
<td>Insulin</td>
<td>10.4</td>
<td>7.2</td>
<td>11.7</td>
</tr>
</tbody>
</table>


- Use of antiplatelet therapy is similar across ONTARGET, TRANSCEND, and HOPE; but a higher percentage of patients in ONTARGET and TRANSCEND receive beta-blockers and statins.
NAVIGATOR: Study design

• The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial enrolled 9150 subjects aged ≥50 years with IGT and prior CV disease or ≥55 years with CVD risk factors.

• Using a 2×2 factorial design, subjects were randomized to the insulin secretagogue nateglinide vs placebo or valsartan vs placebo.

• The primary end points are CV events and new-onset diabetes. The trial is expected to conclude in 2008.
The Effect of Eplerenone in Chronic Systolic Heart Failure (EMPHASIZE-HF) study is being conducted in 2584 stable patients with New York Heart Association (NYHA) class II chronic systolic heart failure.

- Study subjects were randomized to eplerenone or placebo added to standard therapy.
- The primary end point is a composite of CV death or hospitalization for heart failure. Patients will be followed for 4 years.
- Results are anticipated in 2010.
**TOPCAT: Study design**

- The Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial is being conducted in ~4500 patients with heart failure and with preserved LV systolic function (LVEF >45%).
- Study subjects were randomized to spironolactone or placebo.
- The primary end point is a composite of CV death or hospitalization for heart failure. Patients will be followed for at least 2 years.
- Results are anticipated in 2011.
RAAS modulation in high-risk patients: Summary

- Opportunity for greater use of RAAS modulation in patients at high risk for CV events

- ACEIs reduce CV death, MI, HF, and stroke across a broad range of patients with vascular disease
  - With/without LVSD or HF
  - With/without other proven CV therapies
  - Annual event rates of 1.4%–22.6% in untreated groups

- ARBs reduce HF and stroke

- ACEIs may be considered in all patients with vascular disease
  - ARBs are an alternative in ACEI-intolerant patients


• Opportunity exists for expanded use of ACEIs and ARBs in high-risk patients.
• ACEIs have documented benefits in reduction of CV death, MI, heart failure, and stroke.
• While the ability of ARBs to reduce MI is unproven at present, there is substantial documentation that they reduce heart failure and stroke.
• Dagenais et al concluded from their meta-analysis of major ACEI trials that these agents may be considered in all patients with vascular disease who can tolerate them.
• Smith et al stated that, in ACEI-intolerant patients, ARBs appear to be an effective alternative.