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Scientific Update™

ACE Inhibition and Cardiovascular Protection
The Impact of Emerging Data on Micro and Macrovascular Disease Management

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Angiotensin II plays a pivotal role in the pathogenesis of cardiovascular disease (CVD). There is increasing evidence to show that interruption of the renin-angiotensin system (RAS) results in improved cardiovascular outcomes, not only for patients following myocardial infarction (MI) or with congestive heart failure (CHF), but also for those at high risk of life-threatening vascular disease (eg, diabetics) or with peripheral and cerebrovascular disease. Recent evidence indicates that the angiotensin-converting enzyme (ACE) inhibitors have multiple beneficial effects on the vasculature, including arterial remodeling, reducing inflammation, and improving the balance of thrombosis and thrombolysis, vasodilatation, and vascular compliance. This issue of *Cardiology Scientific Update* will discuss the potentially expanded role of ACE inhibitors and the accumulating evidence demonstrating that their benefit extends beyond the relatively short period of observation in clinical trials.

Glucose intolerance and CVD

Although age-adjusted mortality from CVD has fallen over the past 30-40 years, there is evidence to suggest that mortality rates have recently reached a plateau and may actually be increasing. It is estimated that the prevalence of diabetes will increase by 50% over the next 10 years and double within the next 25 years. Since 70%-80% of diabetics die from cardiovascular complications, diabetes is likely to become one of the important causes of the reversed trend in cardiovascular mortality. With the increasing prevalence of diabetes, there will be greater numbers of patients with impaired glucose tolerance (IGT) without the current criteria for the diagnosis of diabetes. Can we arrest this new epidemic of CVD by preventing diabetes and improving glucose metabolism?

Diabetes is currently defined biochemically by measuring fasting blood glucose levels or the blood glucose response to a standardized glucose load. Many years ago, the glucose thresholds for diabetes were determined from their association with the development of microvascular disease. Today, it is recognized that coronary vascular disease is common in patients with abnormal glucose metabolism (IGT) or mildly elevated fasting glucose levels, yet without the criteria for a diabetes diagnosis. In a recent study of patients admitted to a coronary care unit with acute coronary syndromes (ACS), IGT was observed in 69%. The increase in abdominal obesity, decreased physical activity, and the ageing of the population will most likely result in a markedly increased prevalence of IGT and consequently, a substantial increase in the number of patients at very high risk for cardiovascular events.

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Table 1: Prevention of diabetes	
Study	**Intervention**
Finnish DP[6]	Lifestyle
Chinese	Diet and exercise
US DPP[1]	Metformin, diet and exercise
STOP-NIDDM[4]	Acarbose
XEndo[2]	Orlistat
TRIPOD	Troglitazone
WOSCOP	Pravastatin
HOPE[3] CAPP[7] ALLHAT[9] SOLVD[8]	Ramipril vs placebo Captopril vs placebo Lisinopril vs amlodipine vs thiazide Enalapril vs placebo
LIFE[10]	Losartan vs atenolol
CHARM[12,13]	Candesartan vs placebo

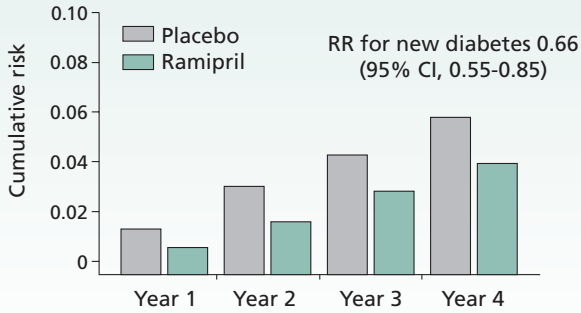
Prevention of diabetes (Table 1)

Diet, weight loss, and exercise have been shown to prevent overt diabetes in patients with IGT.[1] Treatment with orlistat, a weight reduction medication, is also associated with a reduction in the development of diabetes.[2] ACE inhibition has been associated with a higher probability of remaining free from diabetes in trials of heart failure, hypertension, and vascular protection.[3] The angiotensin-receptor blocker (ARB), losartan, given to patients for hypertension control, is associated with less diabetes than the comparator, atenolol. Acarbose, an alpha-glucosidase inhibitor, improves sensitivity to insulin and reduces the incidence of diabetes by 25%.[4,5] Subsequent retrospective analysis indicate that in IGT patients, the prevention of diabetes with acarbose was associated with a 49% reduction in cardiovascular events and the incidence of hypertension.[6] This is the first clinical trial to demonstrate that treatment of post-prandial hyperglycemia was associated with a reduction in cardiovascular events.

Renin-angiotensin inhibition and the prevention of diabetes

The Captopril Prevention Project (CAPPP)[7] was the first controlled trial to demonstrate that an ACE inhibitor reduces the development of new-onset type 2 diabetes in hypertensive patients. The Heart Outcomes Prevention Evaluation (HOPE) study observed a reduction in the diagnosis of new diabetes in patients with vascular disease receiving the ACE inhibitor ramipril over 4 years of treatment (RR 0.66; 95% CI, 0.51-0.85, $p<0.001$; Figure 1).[3] Ramipril reduced cardiovascular events (cardiovascular mortality, MI, or stroke) by 22% in patients with vascular disease or diabetes. Furthermore, diabetic patients in the HOPE study had an enhanced benefit from ramipril, ie, a 37% reduction in cardiovascular mortality over the 4 years of treatment. It is likely that patients with IGT and hyperinsulinemia have similar enhanced vasculoprotective benefits from ramipril, as well as reduced progression to diabetes. Ongoing studies such as the Diabetes Reduction Assessment with Ramipril and Roziglitazone Medication (DREAM) study will confirm this hypothesis.

Figure 1: HOPE Study: Reduction in new diabetes over 4 years of treatment with ramipril[3]



Recently, a retrospective analysis of the SOLVD trial showed that progression to diabetes was reduced by 74% in patients receiving enalapril compared to those taking placebo.[8] In patients enrolled in ALLHAT receiving lisinopril,[9] new-onset diabetes occurred 22% less frequently compared to the metabolically inactive agent, amlodipine, and almost 40% less frequently compared to chlorthalidone, a drug known to be associated with diabetes provocation. In the CAPP study, patients randomized to captopril had less new-onset diabetes than those receiving either a beta-adrenergic blocker or a thiazide diuretic.[7]

ARBs have recently been reported to be associated with a lower incidence of new diabetes. The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study compared the outcomes of patients randomized to losartan 50 mg daily or atenolol 50 mg daily as initial treatment for moderately severe hypertension associated with left ventricular hypertrophy.[10] Patients randomized to losartan had a 25% reduction in the diagnosis of new-onset diabetes compared to the group treated with atenolol.[11] Unfortunately, it is not clear whether this was a benefit of losartan or a hazard of beta-blockade, which is known to be associated with an increase in new cases of diabetes.[2] The Candesartan in Heart Failure – Assessment of Reduction in Mortality and Morbidity

Table 2: Mechanisms for ACE inhibition and the prevention of diabetes	
Reduced angiotensin II	**Increased bradykinin**
Decreased muscular artery vasoconstriction	Vasodilatation and increased skeletal blood flow
Increased pancreatic blood flow	Increased NO availability, and improved endothelial function
Decreased K^+ loss	Enhanced insulin-mediated vasodilatation
Decreased lipolysis and FFA	Reduced inflammation
Reduced norepinephrine	

NO = nitric oxide, FFA = free fatty acid

(CHARM) study is a heart failure study investigating the value of the ARB, candesartan, alone (in patients intolerant of ACE inhibition), or in combination with an ACE inhibitor.[12,13] The studies recently published in *Lancet* and presented at the European Society of Cardiology Congress in September, show that candesartan reduces the incidence of new diabetes by 22% (HR 0.78; 95% CI, 0.68-0.90). In this arm of the study, candesartan also reduced the primary endpoint of CV death, and heart failure hospitalization (HR 0.77; 95% CI, 0.69-0.89).[12]

The ACE inhibitor, ramipril, prevents cardiovascular events and may reduce new diabetes in patients at risk. Whether the vascular and diabetic protective mechanisms are linked is uncertain. ACE inhibitors may prevent the progression of glucose intolerance by several possible mechanisms, both consequent to a reduction of angiotensin II and an increase in available bradykinin (Table 2).

The DREAM study will test whether ramipril and/or roziglitazone reduces the onset of type 2 diabetes in high risk individuals. Five thousand people have been recruited and enrollment is now complete. Baseline characteristics include mild impairment of glucose tolerance (mean elevation of fasting glucose 5.8 mmol/L), a history of hypertension in 43% (although mean entry blood pressure is 130/85 mm Hg); and obesity is common (an average BMI of 30.5 kg/m^2). The DREAM study will complete the vascular and diabetic protective link. The HOPE study revealed that treating diabetics with ramipril prevented adverse cardiovascular outcomes and, if the DREAM study confirms that ramipril also prevents diabetes, the association between the treatment of dysglycemia and the prevention of cardiovascular events will be strengthened. There will then exist a multipurpose medication for a preventative therapy that could restore metabolic homeostasis and limit the cardiovascular consequences of IGT and hyperinsulinaemia.

Prolonged life expectancy after MI

ACE inhibition with ramipril reduces mortality in patients with heart failure following acute MI. The AIRE (Acute Infarction Ramipril Efficacy) study[14] demonstrated that ramipril reduced all-cause mortality from 22.6% in the placebo group to 16.9% in the ramipril group (RRR 27%; 95% CI, 11%-40%, $p = 0.002$) after an average follow-up of 15 months. The reduction in mortality was consistent across a range of subgroups, including age and sex. After 5 years of follow-up, the benefits of the 13-month treatment with ramipril were maintained (absolute risk reduction 11.4%, RRR 36%, $p = 0.002$), yet there was no further widening of the survival curves after 24 months.[15]

The AIREX extension study (also presented at the recent European Society of Cardiology meeting) followed the original patients for 10 years from the close of the study. As of March 2003, death from all causes had occurred in 189/301 (63%) of the placebo and 174/302 (58%) of ramipril-treated patients (absolute risk reduction 5%, RRR 18%, $p = 0.059$). Consequently, there are 5 additional 10-year survivors for every 100 patients treated. The median survival time for patients in the placebo group versus the ramipril group was 8.4 years and 9.85 years, respectively. Thus, ramipril, given for an average of 13 months to patients with heart failure after an acute MI resulted in a median extension of life of 1.45 years. When deaths were ranked according to when they occurred and which treatment had been administered, a delay in the mortality/time relationship was observed in the ramipril group, with a maximal median extension of life of 3.01 years. This maximal extension of life occurred during the treatment period and subsequently declined with a median value for the whole cohort of 1.45 years as noted above. Hence, it is possible that more prolonged treatment with ramipril may have maintained this large, early treatment benefit.

When treatment benefit was examined according to the cause of death as recorded on the death certificate, a reduction in mortality with ramipril was observed for patients dying from MI (RRR 35%; 95% CI, 10%-53%, $p = 0.0097$), yet, no significant difference was observed for those dying from other causes (RRR 4%; $p = 0.075$). Treatment for 1 year with ramipril limits adverse ventricular remodeling after an MI and improves ventricular function. It is likely that recurrent MI during the prolonged follow-up period was better tolerated in patients randomized to ramipril with enhanced left ventricular function. However, if ramipril had been

continued beyond the 13-month treatment period of the AIRE study, it is highly likely that mortality from recurrent MI would have been reduced by 20%, as observed in the HOPE study. The observations from the AIREX extension study, added to the vascular protection benefits proven in the HOPE study, support long-term treatment with ramipril for all patients following MI.

The SOLVD Study recently reported the 12-year follow-up of patients with both symptomatic heart failure and asymptomatic left ventricular dysfunction, who had received either enalapril or placebo for 3 years. In an analysis of the combined treatment and prevention arms of the trial, mortality after 12 years in the group receiving enalapril was 10% less than patients receiving placebo. Enalapril treatment for 3 years prolonged median survival by 9.4 months.[16]

New directions in the inhibition of the RAS system

Multiple mechanisms are involved in the cardioprotective effects of the ACE inhibitor, ramipril (Table 3). Although the blood pressure (BP) lowering effect of ACE inhibition undoubtedly plays a role, the magnitude of reduction in adverse outcomes is almost twice that predicted from the modest 3.3 mm Hg reduction in systolic BP observed in the HOPE trial.[17] Recent analyses of the HOPE study have identified new directions that not only help to explain the added benefits of ACE inhibition, but also suggest that these benefits extend beyond the duration and indications for treatment used in the clinical trial.

Diuretic-induced adverse events

With the publication of the results of the ALLHAT trial, there will be increased use of diuretics for treating hypertension. In ALLHAT, hypokalemia was observed more frequently in the patient group randomized to chlorthalidone. An analysis of the HOPE study has shown that hypokalemia was associated with an almost 50% increase in the risk of death/MI or stroke (Primary endpoint: K^+ <3.5 mmol/L in 22%; K^+ normal in 15.5%; and K^+ >5 mmol/L in 15.7%; hazard ratio of hypokalemia 1.44, $p = 0.023$). Treatment with ramipril in the HOPE study reduced the risk of an adverse outcome by 22% for patients not taking diuretics (primary outcomes: placebo 16.8%, ramipril 13.4%) and 25% for the patients receiving diuretics (placebo 23.2%, ramipril 17.7%).

The recently reported EPHESUS trial[18] demonstrated that the aldosterone inhibitor, eplerenone, significantly reduced the risk of sudden death, especially in patients with a low left ventricular ejection fraction. It is possible that medications which reduce the effects of the renin-angiotensin-aldosterone axis exert part of their benefit by limiting the adverse impact of hypokalemia, especially in patients simultaneously receiving diuretics.

Table 3: Mechanisms of the cardiovascular benefits of ACE inhibition

- Blood pressure lowering
- Vasodilatation
- Antiproliferative
  - Vessel wall
  - Myocardium: reduces LVH
- Enhances glucose metabolism
  - Prevents diabetes
- Nephroprotection
  - Reduces microalbuminuria
  - Prevents onset of overt nephropathy
- Arrhythmias
  - Reduces sudden death / ventricular fibrillation
  - Prevents atrial fibrillation
- Enhances fibrinolysis

LVH = left ventricular hypertrophy

Prolonged treatment with ACE inhibition for patients at risk

The vascular protective benefit of ACE inhibition has been observed in trials that extended observation to 42-48 months. Prevention of MI with an ACE inhibitor in the SOLVD combined trials, SAVE, and HOPE, is enhanced over time, with a widening difference between treatment and placebo outcomes, thus suggesting a persistent treatment benefit. The HOPE-TOO study (also presented at the ESC meeting) examined whether the treatment benefit of ramipril during the 4.5 years of the trial was maintained during an additional 2.6 years of follow-up. After a total of 7.1 years, there was a sustained reduction in the primary endpoint (CV death, MI, stroke, RR 0.83; 95% CI, 0.75-0.91). During the 2.6-year extended follow-up, there was a trend towards an incremental reduction in the occurrence of MI in patients in the original ramipril group (ramipril 5.1%, placebo 6.1%; RR 0.81, 95% CI, 0.65-1.10), despite a high proportion of patients in both groups taking open-label ramipril during the extended follow-up period. New diabetes was also diagnosed less often in the original

Table 4: Cumulative benefits of cardiovascular protective treatment in high-risk patients[20]

	RRR	Cumulative risk
No treatment		8%
+ Aspirin	25%	6%
+ Beta-blockers	25%	4.5%
+ Lipid lowering	30%	3%
+ ACE Inhibition	25%	2.3%

ramipril group than in the placebo group during the extended follow-up (ramipril 2.7%, placebo 4.0%; RR 0.66, 95% CI, 0.57-0.86).

The extended follow-ups of the HOPE and AIRE studies demonstrate a sustained treatment benefit with ramipril during the period of the clinical trial and suggest benefit from more prolonged treatment.

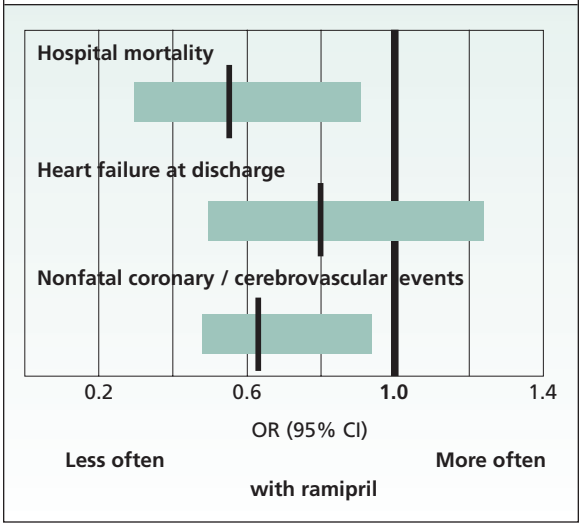
Benefit of ACE inhibition in addition to standard preventative treatment

HOPE study patients were given optimal cardiovascular preventive medications as indicated during the period of the study. The benefits of ramipril were observed on top of preventative treatment with aspirin, beta-adrenergic blockade, and lipid-lowering treatment. A similar reduction in the primary endpoint (mortality, MI, or stroke) was observed with ramipril whether or not patients were treated with all or none of the 3 preventative medications. A similar benefit of ACE inhibition was observed with perindopril for patients with coronary artery disease in the EUROPA study,[19] where a higher proportion of patients were receiving aspirin, beta-adrenergic blocking agents, and lipid-lowering medication. Thus, the cardiovascular protective benefits of ACE inhibition were observed on top of current preventative management. Furthermore, it is estimated that with the additive effects of preventative medical treatment, the cumulative benefits are likely to be a >75% reduction in adverse cardiovascular events (Table 4).[20]

ACE inhibition and vascular protection: A class effect?

Both the HOPE study and the EUROPA trial have shown that the ACE inhibitors, ramipril and perindropril, respectively, reduce adverse cardiovascular outcomes in patients at high risk. The SAVE and SOLVD trials also indicated an associated reduction in MI when captopril and enalapril, respectively, were used to treat patients with heart failure. Hence, it might be suggested that similar

Figure 2: Event rates for patients taking ramipril or other ACE inhibitors in the MITRA-PLUS registry[23]



vascular protective benefits could be observed with all ACE inhibitors. However, the ACE inhibitors differ in their chemical structure, lipophilicity, tissue-binding, and safety profile.[21] Furthermore, the angiotensin-converting enzyme has 2 active binding sites[22] and it is possible that the available ACE inhibitors have different relative activities at each site. Clinical trials of individual ACE inhibitors in vascular protection and in heart failure have shown benefit at the doses used; however, for the prevention of vascular events, it is difficult to guess the effective dose of agents not yet tested in this setting. It is possible that the QUIET study (quinapril 20 mg daily) failed to show any cardiovascular benefit over a 3-year period in patients with coronary artery disease because of inadequate dosing, despite the fact that quinapril at 20 mg daily is an effective antihypertensive dose. An alternative explanation, other than dosage, sample size, and duration of observation, is that quinapril lacks the vascular protective benefits observed with ramipril and perindopril.

The MITRA-PLUS registry examined the impact of ACE inhibition on cardiovascular outcomes following discharge in 53,853 patients with acute MI.[23] In the overall population, use of ACE inhibitors was associated with a 32% reduction in mortality when high-risk features (e.g. diabetes, reduced LV ejection fraction <40%, dyspnea with more severe NYHA II class symptoms, or left bundle branch block) were present. The registry observed a 46% lower in-hospital mortality (95% CI, 32%-90%) for patients treated with ramipril compared to

other ACE inhibitors and a 35% lower rate of non-fatal adverse coronary and cerebrovascular events (95% CI, 46%-93%; Figure 2). However, the incidence of heart failure at discharge was similar whether ramipril or another ACE inhibitor was used. Although not conclusive, this registry data suggest that there may be different clinical benefits from one ACE inhibitor to another, yet, it is unclear why this differential benefit was only observed for very early events and not over an 18-month period of follow-up.

Conclusions

The role of blockers of the RAS has broadened. In addition to the proven benefits of ACE inhibitors in the management of hypertension, heart failure, and following MI, the HOPE and EUROPA studies have confirmed that there are also vascular-protective effects with ramipril and perindopril. Clinical trials do not suggest that the ARBs are as effective in most clinical applications; however, there may be a role for combined ACE inhibition/ARB in the treatment of heart failure. Cumulative data suggest that ACE inhibitors and perhaps ARBs prevent diabetes; the DREAM and NAVIGATOR studies will further evaluate this hypothesis. In addition, recent evidence indicates that blockade of the RAS prevents recurrence of atrial fibrillation and this role is being further investigated in the ACTIVE trial.

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