SMH ST. MICHAEL'S HOSPITAL Cardiology
UNIVERSITY OF TORONTO
A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO

Scientific Update™

The Role of Angiotensin-converting Enzyme (ACE) Inhibitors in the Prevention and Treatment of Atherosclerosis: A Clinical Approach

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Satellite symposium at the XIXth Congress of the European Society of Cardiology

Stockholm, Sweden, August 24, 1997

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Almost half of the 50 million deaths that occur annually worldwide are due to chronic diseases, such as ischemic heart disease, stroke, and other vascular diseases. Angiotensin-converting enzyme (ACE) inhibitors clearly reduce morbidity and mortality in patients with left ventricular (LV) dysfunction, particularly after myocardial infarction (MI), and are a key therapy in preventing death post-MI. Recent long-term follow-up data from the Acute Infarction Ramipril Efficacy (AIRE) study extension (AIREX) underlines the long-term effectiveness of ACE-inhibitor therapy in post-MI patients with transient or persistent clinical evidence of heart failure.[1,2] The emerging role of ACE inhibitors in cardiac and vascular protection is addressed.

The global problem of atherosclerosis

The majority of the 50 million deaths that occur annually worldwide are secondary to chronic diseases, such as ischemic heart disease, stroke, other vascular diseases, cancer, and diabetes. While the rate of morbidity and mortality due to chronic diseases is decreasing markedly in developed countries, ischemic heart disease and stroke are increasing substantially in developing countries. By 2015, up to 75% of cardiovascular disease will exist in developing countries.

One can apply current clinical strategies drawn from epidemiologic studies and interventional trials in Western countries to the global management of major cardiovascular (CV) problems, such as atherosclerosis. For example, today, 500 million people worldwide will eventually be killed by smoking-related CV diseases – 250 million in middle age (35-69 years), resulting in an average of 20 years of lost life per person. As developing countries are increasingly Westernized, this number promises to increase.

Morbidity and mortality due to coronary artery disease (CAD) will increase substantially as developing countries become more urbanized and greater numbers of people become sedentary, switch from primarily vegetarian to high-energy and high-fat diets, and are exposed to greater psychosocial stress. These changes will eventually lead to obesity, hyperlipidemia, hypertension, and greater insulin resistance – factors that increase the risk of cardiovascular events in patients with CAD.

Emerging approaches in the prevention of atherosclerosis

The importance of cardiovascular risk factors beyond smoking, hyperlipidemia, and hypertension is increasingly recognized. These risk factors include activation of the renin-angiotensin system (increased renin), fibrinogen, plasminogen activator inhibitors (PAI-1), low-density lipoprotein (LDL), oxidation, and hyperhomocystinemia.

Several studies have established an increased risk of cardiovascular disease (CVD) among individuals with high renin levels, independent of other CAD risk factors, such as hypertension, hyperlipidemia, and smoking.

ACE inhibitors have been shown to improve or restore endothelial function in both animal models and patients with CVD. This effect appears to be mediated primarily by bradykinin accumulation. Bradykinin has a direct vasodila-

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tory effect and acts by the release of a potent arteriolar dilator, nitric oxide (NO). In turn, NO beneficially affects endothelial integrity and function: it inhibits platelet adhesion and aggregation, smooth muscle cell mitogenesis, and proliferation. Therefore, ACE-inhibitor therapy may theoretically prevent the development of proliferative atherosclerotic lesions in response to a vascular injury, such as plaque rupture.

Do ACE inhibitors have a role in treating atherosclerosis?

Experimental animal models of atherosclerosis have demonstrated the effectiveness of ACE inhibition in reducing intimal-medial proliferation and atherosclerosis. In addition to improving endothelial function, ACE inhibitors may contribute to plaque stabilization. These beneficial effects may be responsible for the significant 15% reduction in the incidence of myocardial infarction (MI) in large-scale, placebo-controlled clinical trials of ACE inhibitors.

Potential clinical effects of ACE inhibition in atherosclerosis are currently being assessed in several large-scale trials with both surrogate and clinical outcome measures in high-risk patients with clinically manifest atherosclerosis, principally CAD (Table 1). The results of these trials should further elucidate the beneficial mechanisms of ACE inhibition and further define their role in therapy of patients at high risk for or with established CAD.

The impact of ACE inhibitors on the fibrinolytic system

ACE inhibitors may have anti-ischemic properties. A potential mechanism for this beneficial effect is the prevention of vascular toxicity, which is induced by activation of the renin-angiotensin system (RAS) and derived from the deleterious effects of angiotensin on fibrinolytic balance.

The plasminogen activator system is a major endogenous defense mechanism against intravascular thrombosis and plays an important role in vascular and tissue remodeling. Vascular fibrinolytic balance is largely determined by the competing effects of plasminogen activators and plasminogen activator inhibitor-1 (PAI-1), both of which are locally synthesized in the vascular endothelium.

PAI-1 is the most important physiological inhibitor of tissue-type plasminogen activator (tPA) in plasma. High levels have been linked to an increased risk of CAD and recurrent infarction. Angiotensin II stimulates the release of PAI-1, a prothrombotic factor, and inhibits the release of tPA, an antithrombotic factor, from human vascular endothelium–facilitating intracoronary clot formation. Low levels of bradykinin decrease the release of tPA, increasing the risk of thrombosis (Figure 1).

A recently published substudy of 120 patients from the Healing and Early Afterload Reducing Therapy (HEART) study has examined the effects of an ACE inhibitor (ramipril) on plasma fibrinolytic variables.[3]

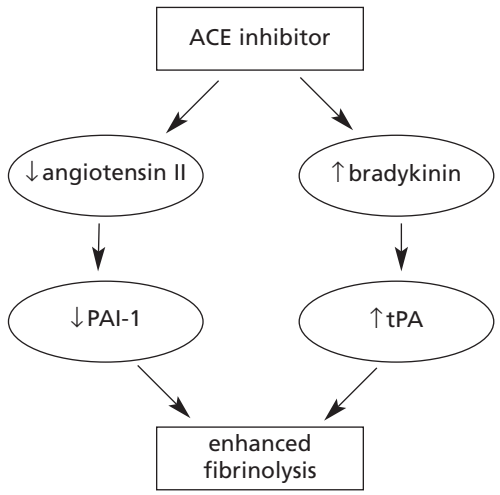
Table 1: Ongoing, long-term clinical trials of ACE inhibitors in patients with CAD progression, ischemic events without heart failure, and low ejection fraction

Trial	ACE inhibitor	Primary outcome	No. of patients	Duration (years)
HOPE	ramipril	Composite endpt.: CV death, MI, stroke	9,000	4
SECURE	ramipril	B-mode ultrasound measures of carotid atherosclerosis	700	4
SCAT	enalapril	Quantitative coronary angiographic measures of CAD progression	470	5
PART-II	ramipril	B-mode ultrasound measures of carotid atherosclerosis	600	4

ACE=angiotensin-converting enzyme
CAD=coronary artery disease
HOPE=Heart Outcomes Prevention Evaluation
SECURE=Study to Evaluate Carotid Ultrasound Changes with Ramipril and Vitamin E
SCAT=Simvastatin and Enalapril Coronary Atherosclerosis Trial
PART=Prevention of Atherosclerosis with Ramipril Therapy

Adapted from Lonn et al, *Circulation* 1994;90:2056-69

Figure 1: The impact of ACE inhibitors on the fibrinolytic system



ACE=angiotensin-converting enzyme
PAI-1=plasminogen activator inhibitor
tPA=tissue plasminogen activator

Adapted from McMurray

HEART was a double-blind, placebo-controlled trial of acute anterior-MI patients, who were randomly assigned within 24 hours of the onset of symptoms to receive low-dose ramipril (0.625 mg daily), full-dose ramipril (1.25 mg titrated to 10 mg daily), or placebo for 14 days, followed by full-dose ramipril.

Compared with the placebo group, PAI-1 antigen levels were 44% lower (p=0.004) and PAI-1 activity levels were 22% lower (p=0.002) at day 14 in ramipril-treated patients. It appears that ACE-inhibitor therapy has a significant impact on plasma fibrinolytic variables during recovery after acute MI.

Long-term ACE inhibition in post-myocardial infarction

The results of the Acute Infarction Ramipril Efficacy (AIRE) Extension (AIREX) study have recently been published.[2] The original AIRE study was an international, randomized, placebo-controlled trial of 2006 post-MI patients complicated by clinical evidence of congestive heart failure.[1] Patients received either placebo or ramipril (up to 10 mg daily) on day 3 to 10 post-MI with a minimum 6-month and average 15-month follow-up. Ramipril was associated with a 27% reduction in all-cause mortality (95% CI: 11-40%; p=0.002) (Figure 2).

In AIREX, the mortality status of all 603 patients recruited from 30 U.K. centers in the AIRE study was ascertained exactly 3 months after the close of the AIRE study. Patients were followed for a minimum of 42 months and a mean of 59 months.

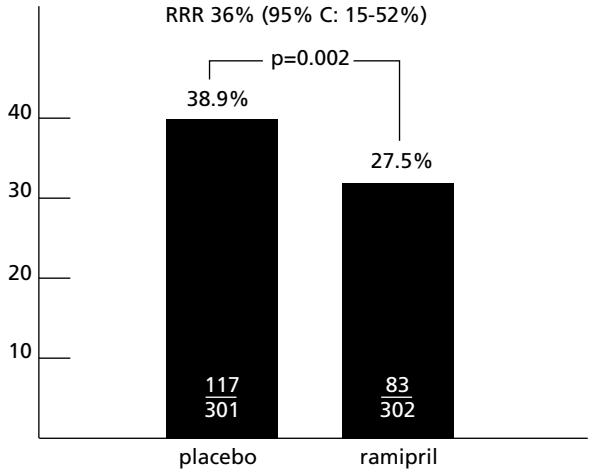
The average duration of treatment with blinded trial medication was 13.4 months for placebo and 12.4 months for ramipril. After this time, ongoing therapy was determined by the patient's physician, who continued to be blinded to the original randomization.

A striking 36% reduction in the relative risk of total mortality occurred among the 302 ramipril-treated patients, compared to the placebo group. In other words, if 1,000 patients with post-MI heart failure were treated with ramipril for an average of one year, after 5 years, 114 more patients would have survived, compared to placebo. Remarkably, this means that only 9 patients with post-MI congestive heart failure need to be treated with ramipril to save 1 additional life.

Economic analysis

In the context of other post-MI treatments known to produce a favourable impact on long-term survival, the number of lives saved with ramipril (57 per 1,000 in AIRE; 114 per 1,000 in AIREX) compares well with those saved by Aspirin® (20-30 per 1,000), thrombolytic agents (20-30 per 1,000), and beta-blockers (15-20 per 1,000).

Figure 2: AIREX trial – 5-year all cause mortality.



Within each bar, the numerator indicates the total number of deaths and the denominator the number of patients assigned to study therapy.

RRR=relative-risk CI=confidence interval

Cost-effectiveness with ramipril in heart failure

At a subsequent briefing, Dr. Ball and Frederik Andersson (Health Economist, Sweden) presented a recently published Swedish substudy of the AIRE trial.[4] In addition to providing long-term clinical benefit, the use of ramipril in patients with heart failure post-MI is highly cost effective and compares very favourably to other common medical treatments in cardiovascular medicine. The study estimated the cost-effectiveness of ramipril based on resource data from four participating Swedish hospitals that enrolled 162 patients. Treatment with ramipril reduced the risk of hospitalization by 4.7%, 8.6%, and 11.3% in patients followed for 1, 2, and 3.8 years, respectively. These reduced hospital costs compensated to a great extent for drug costs. Since the number of life-years saved for each patient increased with the duration of ramipril therapy, treatment became more cost-effective further into the study. Thus, per life-years saved, the costs at 1 and 3.8 years were about $5,790 and $2,480 CDN, respectively. Extrapolating these data to the Canadian setting, one could estimate that treating 200,000 patients with heart failure with an ACE inhibitor, such as ramipril, would add $68 million to drug costs but save over $140 million CDN/year.

Conclusion

The global problem of atherosclerosis highlights the need for further research into emerging CV risk factors, such as activation of the renin-angiotensin system, and preventive strategies to minimize CV risk.

The undisputed role of ACE-inhibitor therapy in the setting of LV dysfunction, particularly post-MI, is further strengthened by results of the AIREX study, which provides robust evidence that administration of ramipril to patients with clinically defined heart failure after MI results in a survival benefit that is not only large in magnitude but sustained over many years.

Based on the growing body of evidence indicating that ACE inhibition may have antiproliferative, antithrombotic, and plaque-stabilizing properties and restorative effects on endothelial function, this group of agents has the potential to prevent and treat the consequences of atherosclerosis.

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