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Scientific Update™

Is ACE Inhibition the Standard of Care for Management of Coronary Artery Disease?

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In 1991, Dzau and Braunwald published their classical illustration of the cardiovascular continuum, linking the relationship between cardiovascular risk factors, the development of atherosclerosis, subsequent myocardial infarction (MI), cardiac remodelling, and the outcomes of heart failure and sudden death. At that time, the molecular mechanisms connecting the events in the continuum were poorly understood; however, research over the past decade has identified many of the responsible factors. Angiotensin was shown to play a pivotal role in the linkage between risk factors and atherosclerotic complications as well as the deterioration of cardiac function after myocardial injury. Basic science and clinical trials have also demonstrated the importance of angiotensin-converting enzyme (ACE) and its inhibitors (ACEIs) in the pathophysiology and treatment of cardiac and vascular disease.

Beneficial effects of ACE Inhibition

Research during the past decade has shown that ACE inhibitors exert their beneficial properties by multiple mechanisms (Table 1).

The first indication that ACE inhibition had an impact on myocardial ischemic events came unexpectedly from large multi-centre controlled trials in left ventricular dysfunction and heart failure such as SAVE and SOLVD. The HOPE trial – specifically designed to address whether ACE inhibition with ramipril would reduce the risk of cardiovascular events in a group of high risk patients – demonstrated a convincing benefit over a wide range of end-points. With this powerful evidence, the role of ACE inhibition in the preventative management of patients at high risk of MI and stroke must be considered.

Molecular mechanisms for the vasculo-protective properties of ACE: inhibition

Endothelial cell dysfunction is central to the development of vascular disease and its acute complications of MI and stroke. The endothelium, as an important source of nitric oxide, maintains vascular homeostasis by inhibiting vascular smooth muscle growth and the expression of pro-inflammatory cytokines (eg, VCAM-1 and MCP-1). As the production of reactive oxygen species such as super-oxide increases, nitric oxide catabolism is enhanced with consequent impaired relaxation, increased inflammatory cell adhesiveness, and smooth muscle cell proliferation. Angiotensin II is a central part of the molecular mechanisms leading to

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Table 1: Beneficial properties of ACE inhibitors

- Antihypertensive
- Cardio-protective
  - Prevents adverse ventricular remodelling
- Vascular-protective
  - Restores endothelial function
  - Reduces progression of atherosclerosis
  - Reduces acute complications of atherosclerosis
- Metabolic
  - Lipid neutral
  - Improves glucose metabolism

increased oxidative stress and the development of atherosclerosis and its complications (Figure 1).

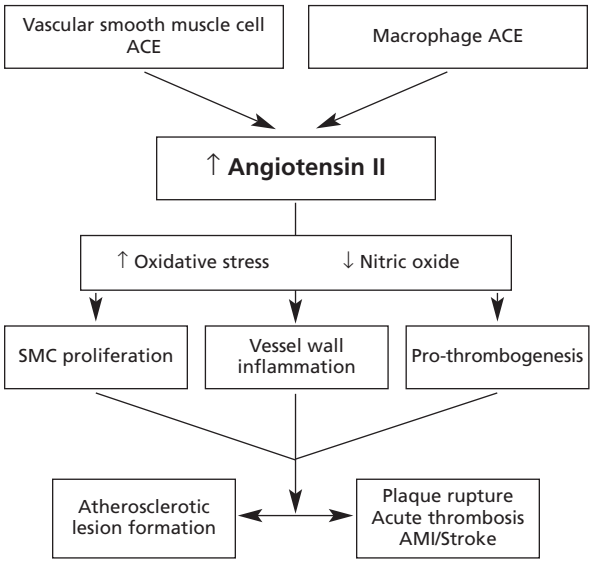
Furthermore, inflammation within the vessel wall promotes a vicious cycle with further activation of tissue ACE, cathepsin G, and chymase, all enzymes that increase the synthesis of angiotensin II, thereby promoting more oxidative stress and inflammation. Experimental evidence has demonstrated the pivotal role of both tissue ACE activity and angiotensin II concentrations in both the development of atherosclerosis and subsequent athero-thrombotic complications. In animal models of atherosclerosis, the relationship between tissue ACE activity and the development of atherosclerosis has been shown to be much greater than that with serum ACE activity.

Tissue ACE activity and angiotensin II synthesis plays an important role in the pathophysiology of acute coronary syndromes. Rupture of the vulnerable atherosclerotic plaque is associated with an inflammatory infiltrate around the thin shoulder region of the thin fibrous cap. The presence of angiotensin II co-localizes with the inflammatory infiltrate, which is an important source of the matrix metallo-proteinases that weakens the fibrous cap, thereby facilitating cap rupture and promoting thrombosis.

Importance of tissue ACE activity

Most ACE is found in the endothelium of arteries and arterioles, a little is found in normal adult cardiac muscle cells, while only 10% is found in a circulating form. Yet elevated wall stress and vascular injury are potent stimuli for the upregulation of tissue ACE. ACE is a single polypeptide

Figure 1: Tissue ACE concept and atherogenesis



chain with two active enzymatic sites and a hydrophobic site which encourages adherence to cell surfaces.

ACE inhibitors with greater tissue binding to the ACE enzyme (eg, ramipril and quinapril) may have advantages over agents with lesser tissue ACE affinity (eg, enalapril). In the Quo Vadis study,[2] quinapril pretreatment reduced angiotensin formation in segments of human internal mammary artery, whereas captopril exerted no appreciable effect. Experimental studies have shown a greater reduction of cardiac hypertrophy with quinapril compared to enalapril, despite similar inhibition of circulating ACE.[3] Endothelial function appears to improve to a greater extent with ACE inhibitors that have greater tissue binding. Hornig et al[4] demonstrated that the acute administration of quinaprilat improved nitric oxide-dependent, flow-mediated vasodilatation, whereas enalaprilat had no effect even when administered at high doses. In the BANFF trial,[5] quinapril administered for 8 weeks improved flow-mediated brachial arterial dilatation, yet neither enalapril, nor losartan had any beneficial effect.

The role of bradykinin in vascular protection is as yet undefined. Both ramipril and enalapril significantly reduced smooth muscle cell hypertrophy in a balloon-injured rat carotid artery.[4] In this model, the benefits observed with the ACE inhibitor were not seen with the angiotensin receptor blocking agent losartan and were markedly reduced when a

Table 2: A summary of trials examining the role of ACE inhibitors in patients with atherosclerotic vascular disease			
	ACE inhibitor	**End-point**	**Result**
1) Reduction of atherosclerotic burden			
QUIET-A[9]	Quinapril	Quantitative coronary angiography (QCA)	Neutral overall Decreased progression in patients with high LDL
SCAT	Enalapril	QCA	Neutral
SECURE	Ramipril	Carotid atherosclerosis B mode ultrasound	Reduced progression with ramipril
PART-2[10]	Ramipril	Localized carotid wall thickness	Neutral
2) Prevention of restenosis after angioplasty			
MERCATOR	Cilazapril	QCA	Neutral
MARCATOR[11]		QCA	Neutral
Yanabe et al[12]	Cilazapril	QCA	Reduced restenosis in patients pre-treated with ACEI
3) Prevention of ischemic events after coronary bypass surgery			
QUO-VADIS	Quinapril	Death, AMI, recurrent angina	Reduced combined ischemic events
APRES[13]	Ramipril	Death, AMI, heart failure	Reduced combined events
IMAGINE	Quinapril	Clinical combined endpoints	On going trial
4) Prevention of cardiovascular events in high risk patients independent of LV function			
HOPE[14]	Ramipril	Clinical events	Important reduction of all clinical events
PEACE	Trandilopril	Cardiac events	Reports 2002
EUROPA	Perindopril	Cardiac events	Ongoing trial

bradykinin B2 receptor antagonist was coadministered with the ACEI.

Is endothelial function a surrogate marker for vascular events and does an improvement in endothelial function relate to improved clinical outcomes? Impaired brachial[6] and coronary artery[7] vasodilator function are related to both long term atherosclerotic disease progression and cardiovascular event rates. Severe endothelial dysfunction in patients with mild coronary artery disease, (as measured by the change in coronary artery diameter during graded doses of acetylcholine), is associated with an increased incidence of cardiac death, MI, heart failure, and a need for revascularization.[8]

ACE inhibitors and coronary artery disease

Clinical trials have examined the role of ACE-inhibitors in the management of patients with atherosclerotic vascular disease. A summary of these trials is shown in Table 2. Reduction of the progression of carotid atherosclerosis was observed in the SECURE study in patients treated with ramipril. However, no overall benefit was shown by angiographic measures of coronary artery disease: an insensitive method to observe changes in the vessel wall.

Although experimental studies suggest that ACEI reduces the progression of balloon-induced endothelial injury, only one study has shown a reduction of restenosis after coronary angioplasty when patients were pre-treated for 7 days prior to angioplasty. For patients after coronary artery bypass surgery, the QUO-VADIS study suggests there may be benefits in administering quinapril to reduce the combined events of death, MI, and angina recurrence. The majority of the events in this study involved the return of exertional angina. However, the benefits of quinapril in reducing all ischemic events appear to be preserved at least for one year. A more definitive study – IMAGINE – will enroll 2200 patients, and is currently in progress investigating the role of quinapril for the prevention of ischemic events in this high risk group after bypass surgery.

Reduction of cardiovascular events independent of left ventricular function

The Heart Outcomes Prevention Evaluation (HOPE) trial[13] examined the benefit of ramipril in 9,297 patients at

Table 3: Summary of the HOPE Trial[10]

Patients: > 55 years old, evidence of vascular disease, or diabetes plus one cardiovascular risk factor, no heart failure or known low LVEF

Medication: Ramipril 10 mg daily or Placebo. Follow-up 5 years

Results

	Ramipril (%)	Placebo (%)	Risk Reduction (%)	P value
Primary End Point				
MI, CVA, CV death	14.0	17.8	22	<0.001
Cardiovascular mortality	6.1	8.1	26	<0.001
Myocardial Infarction	9.9	12.3	20	<0.001
Revascularisation procedures	16.0	18.3	15	<0.002
Stroke	3.4	4.9	32	<0.001

high risk of future vascular events. Details of this trial have been presented in previous *Cardiology Scientific Updates*.

HOPE unequivocally showed that ramipril resulted in an important reduction of all major outcomes in these high risk patients. (Table 3). These benefits were significantly greater than what would have been expected from the modest reduction of blood pressure. At least 70% of the benefit observed from ramipril treatment in the HOPE study resulted from factors other than BP lowering.

Further information will be available from two large randomized clinical trials, PEACE and EUROPA, that are evaluating the benefits of ACE inhibitors in patients with coronary artery disease without left ventricular dysfunction.

Conclusions

- ACE inhibition, especially with agents with high tissue ACE affinity such as quinapril or ramipril, results in an improvement of endothelial function.
- ACE inhibition with ramipril in patients, with or without left ventricular dysfunction, who are at high risk of cardiovascular events, improves survival, reduces morbidity from stroke and MI, and reduces the need for coronary revascularization.
- Although the lipid lowering agents have had an important impact on mortality in patients with elevated cholesterol, between 70-80% of deaths are not prevented by statin treatment. ACE inhibition with an agent with high tissue affinity such as ramipril has been shown to provide additional benefit in high risk patients.
- ACE inhibition will rapidly become a standard of care for patients at high risk of cardiovascular events, independent of the left ventricular function.

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