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Scientific Update™

Markers, Endothelial Function and Clinical Events: Novel Aspects of Tissue ACE Inhibition

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The development of atherosclerosis is closely linked to exposure of the endothelium to stresses that impair its ability to maintain vessel wall integrity. Well recognized risk factors for atherosclerosis, (ie, smoking, hypertension, diabetes, hypercholesterolemia, and hyperhomocysteinemia) are associated with endothelial dysfunction.[1] Such dysfunction results in impaired vasodilatation, increased smooth muscle proliferation, expression of proinflammatory molecules (eg, VCAM-1 and MCP-1), impaired thrombolysis, and impaired neovascularisation or angiogenesis. These abnormalities contribute to the development and progression of atherosclerosis, promotion of the atherothrombotic complications of atherosclerosis, and failure to generate adequate collateral vessels in the event of vascular occlusion.

Oxidative stress is the common factor by which the clinically recognized risk factors cause endothelial dysfunction by reducing the availability of nitric oxide (Figure 1). Angiotensin II, itself a major source of oxidative stress, is synthesized more readily in circumstances of high oxidative stress, thereby creating a positive feedback, further promoting the generation of more highly damaging free oxygen radicals.[2] Furthermore, angiotensin II co-localizes with markers of the inflammatory response (eg, VCAM, IL6) found in the atherosclerotic lesion, especially in the vulnerable shoulder region of the plaque. Enhanced oxidative stress and increased angiotensin II synthesis are therefore associated with both the progression of atherosclerosis and the development of plaque rupture. The central role of angiotensin II in the progression of atherosclerosis and its complications has led to the evaluation of angiotensin-converting enzyme (ACE) inhibitors as agents in the management of patients with coronary artery disease.

ACE inhibition and endothelial function

ACE inhibition not only reduces the synthesis of angiotensin II, it also increases the availability of bradykinin which can interact with endothelial cells to stimulate nitric oxide synthesis. An increase in nitric oxide availability should translate into an improvement in endothelial health as demonstrated by the vasomotor response to an endothelial-dependent vasodilator such as acetylcholine or increased arterial flow. More than 18 studies have examined whether ACE inhibition can improve endothelial dependent vasodilatation. Most examined the forearm brachial artery response, were not placebo-controlled, and enrolled small numbers of subjects. Consequently, the results of these studies are not consistent, with some showing benefit and others showing no effect.

The TREND study[3] was a placebo-controlled study showing the effect of a six-month treatment with quinapril on endothelial-dependent coronary artery vasodilatation. Endothelial function – as measured by the vasodilator response to intracoronary acetylcholine – was significantly improved by quinapril, but there was no change in placebo-treated patients. An improvement in endothelial function was observed in patients with minimal nonobstructive coronary disease who did not have risk factors such as severe

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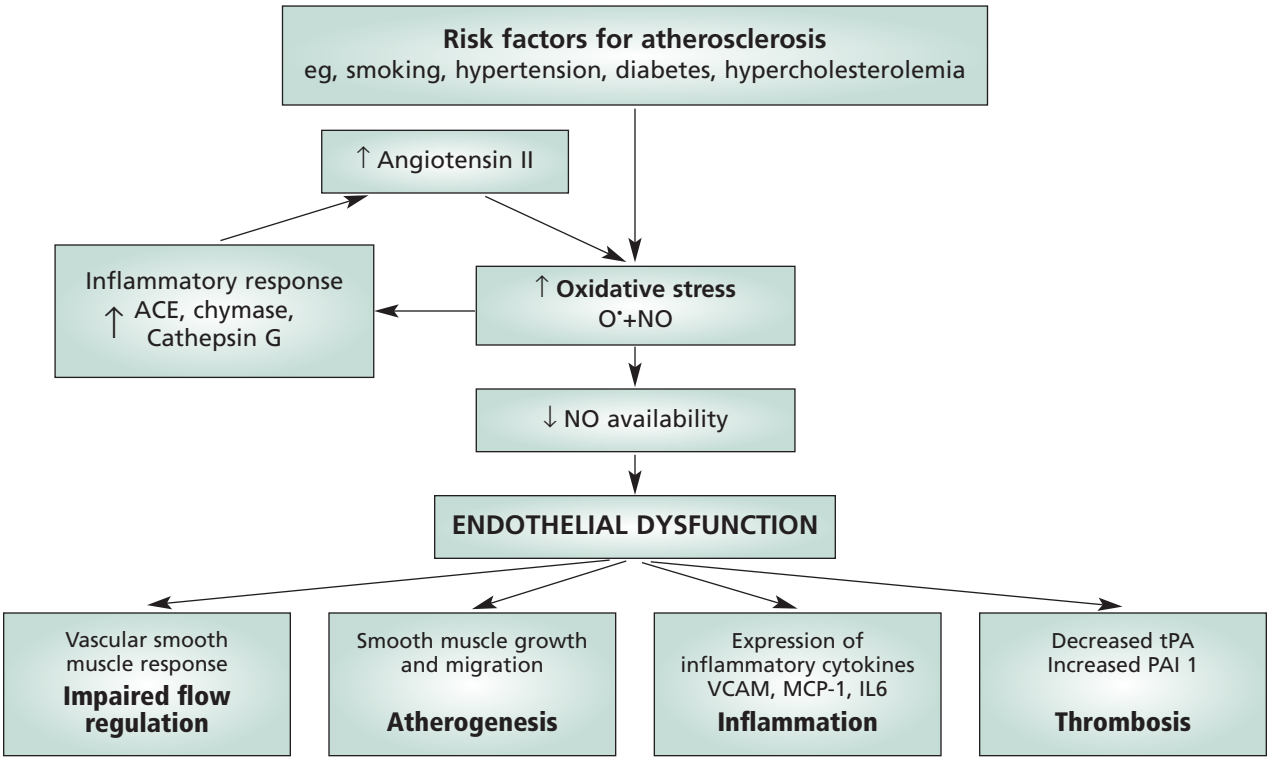
Figure 1: Pathway of endothelial dysfunction



hyperlipidemia or hypertension Yet the greatest improvement in endothelial dysfunction was observed in patients with LDL cholesterol >130 mg/dL.[4]

The Brachial Artery ultrasound Normalization of Forearm Flow (BANFF) study[5] examined the effect of the ACE inhibitors quinapril and enalapril, the angiotensin II receptor blocker losartan, and the calcium channel blocker amlodipine on endothelial flow-dependent dilation of the brachial artery in patients with coronary artery disease. The study found that these patients have significant impairment of flow-mediated vasodilation compared to healthy subjects. Amongst the four agents studied, only quinapril caused a significant improvement in flow-mediated brachial artery dilation. As well, despite the similar antihypertensive properties of the four agents, only quinapril improved endothelial function. It has been suggested that quinapril, in contrast to enalapril, improved endothelial function because of its higher affinity for tissue ACE.

ACE inhibition in the prevention of coronary events

The prevention of coronary events by ACE inhibitors has been observed in several clinical circumstances (Table 1). Prevention of heart failure or its deterioration was the primary goal of the SOLVD treatment trial,[6] the SOLVD prevention trial,[7] and the SAVE trial.[8] An unexpected finding in these studies was the important reduction in the incidence of myocardial infarction (MI) and acute coronary events. When data from SOLVD, SAVE, AIRE, and TRACE are combined, there is a 21% (95% CI, 11-29%, p=0.001) reduction of risk for subsequent MI. In the combined SOLVD trials, a 20% (95% CI, 9-29%, p=0.001) reduction of hospitalization for unstable angina was observed.[9] Furthermore, in the SAVE trial, the need for revascularisation procedures was reduced 24% (95% CI, 6-39%, p=0.014). The findings of reduced ischemic events in SOLVD and SAVE led to the conclusion that ACE inhibitors may result in the same benefits in a broader group of high-risk patients with preserved left ventricular function.

Prevention of ischemic events in coronary artery surgical patients

Following coronary artery bypass surgery, there is an important risk of acute vascular events such as MI, recurrent angina, and stroke. Although a proportion of these events may be technically related to the surgical procedure, an important number of acute ischemic outcomes are due to destabilization of atherosclerotic plaque and new vascular

Table 1: Prevention of coronary events by ACE inhibition: Clinical circumstances			
	Study	**ACE inhibitor**	**Reduction of ischemic events**
Cardiac failure / LV dysfunction	SOLVD Treatment Prevention	Enalapril	 24% 23% reduction of MI
Post-MI	SAVE	Captopril	25% reduction of MI
	AIRE	Ramipril	5% reduction of MI (ns)
Post-coronary artery bypass surgery	QUO-VADIS	Quinapril	78% reduction of ischemic events
High risk for vascular event	HOPE	Ramipril	23% reduction of MI, stroke and cardiovascular death

events. The Quinapril On Vascular Ace and Determinants of Ischemia (QUO-VADIS) study[10] examined the effects of quinapril, compared to placebo, on a wide composite endpoint of clinical ischemic events. Patients were randomized to either placebo or quinapril 40 mg before coronary artery bypass surgery; treatment was continued for one year after the operation. Ischemic events (MI, recurrence of angina, stroke or transient ischemic attack, need for a revascularization procedure, and cardiac death) during the year of treatment were reduced from 18% in the placebo-treated group to 4% in the patients given quinapril ($p<0.03$). As a result of the observations in the QUO-VADIS study, a large prospective trial (IMAGINE) will evaluate the effect of quinapril, initiated at the time of coronary artery bypass surgery, on the occurrence of ischemic events as the primary endpoint.

Experimental support for the benefit of tissue ACE inhibition at the time of acute revascularization comes from studies by Lazar et al.[11] They examined the effect of ACE inhibition administered to a porcine model of acute coronary occlusion for 90 minutes, subsequent 45 minutes cardioplegic arrest, and finally, 180 minutes of reperfusion. The ACE inhibitor (either enalaprilat or quinaprilat) was given during the period of acute coronary occlusion. Both reduced the endpoints for ischemic damage as determined by the number of cardioversions for ventricular arrhythmias, left ventricular wall motion score after reperfusion, and the area of necrosed myocardium. Following completion of the *in vivo* experiment, the response of excised segments of the coronary arteries to endothelium-dependent and independent relaxation was assessed (Table 2). Enalaprilat did not have any beneficial effect on the recovery of endothelial dependent relaxation in arteries excised from the ischemic territory. However, quinaprilat increased vascular relaxation up to four-fold, and as well resulted in a further reduction in infarct size. Thus, it is possible that the presence of an ACE inhibitor such as quinapril, with a high tissue potency, may not only reduce myocardial damage, but also

Table 2: Wall motion, area of necrosis and recovery of endothelial function after revascularization of acutely ischemic myocardium[11]			
	No ACE inhibitor	**Enalaprilat**	**Quinaprilat**
Wall motion score	1.52 ± 0.07	3.20 ± 0.15*	3.08 ± 0.23*
Area of necrosis/area at risk	40.0 ± 1.7	24.3 ± 0.8*	15.6 ± 2.6*+
Maximal arterial relaxation to Ca ionophore %	20.5 ± 10.3	13.1 ± 5.3	83.5 ± 8.9*+
Maximal relaxation to bradykinin %	30.6 ± 10.7	32.1 ± 7.6	65.6 ± 12.6*+

*p<0.05 from no ACE
+p<0.05 from quinaprilat

preserve endothelial function during coronary artery bypass surgery. Maintaining endothelial health should translate into less subsequent vascular events. This hypothesis is currently being tested for clinical relevance in the IMAGINE study.

ACE inhibition in the prevention of vascular events in high-risk patients

Patients at high risk of a vascular event by virtue of a history of significant cardiovascular disease or with diabetes, were enrolled in the Heart Outcomes Prevention Evaluation (HOPE) study[12] to examine the effects of the ACE inhibitor ramipril on major cardiovascular events (cardiovascular death, MI, and stroke). This study was terminated prematurely when it became evident that patients treated with ramipril had an important reduction in vascular events.

9541 patients were randomized to either placebo or ramipril 10 mg daily. Baseline characteristics indicated that these patients were at high-risk of an adverse outcome with 80.6% having known coronary artery disease; of these, 52.8% had had a previous MI. Significant peripheral vascular disease was present in 43.4%, a history of stroke or TIA was present in 10.6%, 38.3% of the patients were diabetic, and 46% were hypertensive. Hypercholesterolemia, or the need for current treatment, was present in 65.8%.

The primary composite endpoint of MI, stroke, or cardiovascular death was reduced by 23% with ramipril 10 mg daily for up to 4 years [ramipril 13.9%, placebo 17.5% (RR 0.77, 95% CI, 0.70-0.86) p<0.000002]. The treatment effect appeared to be present throughout the average 4.6 year study period, with the individual endpoints of cardiovascular death, MI, stroke, and total mortality all significantly reduced by treatment with ramipril. The need for revascularization was reduced from 18.4% to 16.0%.

Benefit was observed in patients whether or not they had normal or reduced left ventricular function. Similar beneficial treatment effects were observed in patients with or without diabetes, a history of cardiovascular disease, age greater than 65 years old, hypertension, and cerebrovascular or peripheral vascular disease. Benefits of ramipril were observed over and above those obtained from treatment with a beta-adrenergic blocker, aspirin, or lipid-lowering agents. Not only did ramipril prevent major vascular events in this population, it also reduced the development of heart failure, new-onset diabetes, and progression of diabetic renal disease.

The benefit of treatment with ramipril in this population is much greater than would be expected from the average 3.3 mm Hg reduction of systolic arterial pressure alone. In a meta-analysis of 14 anti-hypertensive trials, a reduction of diastolic blood pressure of 4-5 mm Hg was associated with a 14% reduction in fatal and non-fatal cardiac events.[13] In the combined SOLVD trials, diastolic blood pressure was reduced an average 4 mm Hg, yet incidence of fatal or non-fatal MI was reduced 23%. Similar observations in the HOPE study support the hypothesis that the benefit of ACE inhibitors is at least partly due to mechanisms unrelated to the blood pressure lowering effect. It appears that the protective effect of ramipril in the HOPE trial may be due to mechanisms such as restoration of endothelial function.

Conclusions

• Endothelial dysfunction consequent to oxidative stress is an important mediator of atherosclerosis and its complications. Angiotensin II plays an important role in the generation of oxidative stress and endothelial dysfunction.

• Inhibition of ACE results in an improvement in endothelial function.

• ACE inhibition in a wide range of patients at high risk of vascular events results in an important reduction in cardiovascular mortality and morbidity over and above that provided by current treatments such as aspirin, beta-adrenergic blocking agents, and lipid-lowering drugs.

• ACE inhibition should be considered as a standard of care in patients at high risk of vascular events.

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