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™

Functional effects of ACE inhibitors in the human vasculature

Originally presented by: VICTOR DZAU, PAUL RIDKER, HELMUT DREXLER, DOUGLAS VAUGHAN, KENNETH BERNSTEIN, WIEK VAN GILST, JEFFREY ISNER, and RONALD CRYSTAL

A Satellite Symposium at the 71st Scientific Sessions of the American Heart Association

Dallas, Texas, November 7, 1998

Reported and discussed by
DAVID FITCHETT, MD

Risk factors for the development of atherosclerotic coronary heart disease include family history, hypertension, diabetes, smoking, hypercholesterolemia, and sedentary lifestyle. Mechanisms that link these risk factors to the generation of atherosclerotic plaque include endothelial dysfunction, oxidative stress, and an inflammatory response. Over the past decade we have recognized an important role played by angiotensin II as a modulator of functional and structural changes in subendothelial space. Of even more immediate relevance is the favorable effect of ACE inhibitors on endothelial dysfunction – an important component of the atherosclerotic process in the coronary arteries. This update reviews the evidence that supports the notion that treatment with ACE inhibitors may be associated with prevention of vascular events in patients with atherosclerosis. This evidence was first brought to light by the observations of reduced rate of myocardial infarction in patients treated with captopril (SAVE study) and is being formally tested in on-going large trials (HOPE and PEACE).

The endothelium is responsible for a multitude of functions that maintain the health of the normal blood vessel. These include control of vascular tone and blood flow, balance of thrombosis and thrombolysis, vessel wall permeability to macromolecules, and adhesion of inflammatory leukocytes. Patients with greater numbers of risk factors are more likely to have endothelial dysfunction resulting in vasoconstriction and a pro-thrombotic environment.

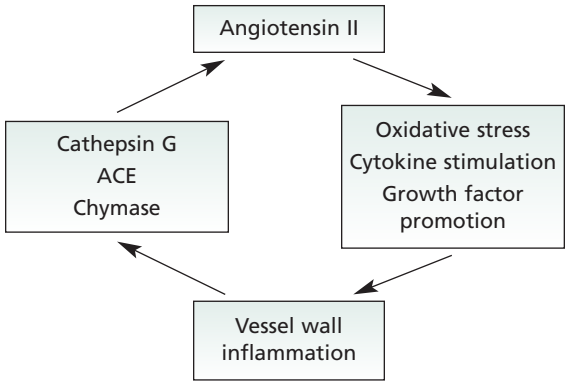
Atherogenic risk factors provoke oxidative stress, which not only mediates endothelial dysfunction but also activates transcription factors (NFkB, AP1). These factors turn on pro-inflammatory genes such as GmSF, VCAM1, and MCP1 that attract and activate leukocytes. Monocytes that attach and migrate through the vessel wall eventually become macrophages, oxidize LDL, and become foam cells responsible for fatty streaks. The pro-inflammatory response might also be an important part of the process that induces leukocyte infiltration into the fibrous cap overlying the atherosclerotic plaque. Inflammation and the secretion of proteinases result in weakening of the fibrous cap, with eventual plaque rupture and clinical presentation as an acute coronary syndrome.

Endothelial dysfunction promotes atherogenesis, but it also limits angiogenesis, that through collateral channels might compensate for vascular occlusion caused by the complications of atherosclerosis. Thus, if endothelial function can be improved, it is possible that both atherosclerosis and its complications will be limited and new blood vessels will be created to restore an adequate blood supply. Because angiotensin II has been shown to be an important mediator of endothelial dysfunction, the experimental and clinical effects of inhibiting angiotensin II synthesis (by ACE inhibition) and receptor activation have been targets of intense research activity. We are now seeing the progress from basic research to successful clinical research, with improved outcomes in patients with atherosclerotic heart disease.

St. Michael's Hospital, 30 Bond St., Suite 9-004, Queen Wing, Toronto, Ontario M5B 1W8 Fax: (416) 864-5330

The topics presented in *Cardiology Scientific Update* are independently determined and the content authored exclusively by physician-members of the Division of Cardiology, St. Michael's Hospital. This publication is made possible by unrestricted funding from the publisher, Snell Medical Communication Inc., which has received educational grants from the pharmaceutical industry in support of this work.

Figure 1: The amplification cascade



Angiotensin II mediates risk factors of atherosclerosis

Excess angiotensin II can promote endothelial dysfunction, oxidative stress, and an inflammatory response: all vital factors in the development of atherosclerosis.

Angiotensin II effect is pro-inflammatory cytokine since it stimulates the development of free oxygen radicals through the regulation of NADH/NADPH oxidase, as well as through AT_1 receptor-dependent promotion of monocyte adhesion. Furthermore, ACE, which will increase local levels of angiotensin II, is found expressed in association with the inflammatory cells in the atherosclerotic arterial wall. Thus, it appears that angiotensin II can be part of an amplification cascade that promotes both inflammation and oxidative stress (Figure 1) and mediates the pathologic mechanisms that result in the clinical outcomes associated with atherosclerosis (Figure 2).

Endothelial function and ACE inhibition

Angiotensin II plays an important role in promoting endothelial dysfunction. Studies in humans have recently demonstrated that reducing the synthesis of angiotensin II by using an ACE inhibitor with high tissue affinity, such as quinapril, will result in important improvements in vascular responses dependent upon endothelial integrity.

The TREND study showed that the coronary artery vasoconstrictor response to acetylcholine (an indication of endothelial malfunction) could be converted into a vasodilator response (indicating normal endothelial function) after six months of treatment with the ACE inhibitor quinapril but not with placebo.[1] The BANFF (Brachial Artery Normalization of Forearm Function) study demonstrated that flow-mediated arterial vasodilatation was enhanced during an eight-week treatment period with quinapril, an ACE inhibitor with high tissue affinity, but not with the less specific ACE inhibitor enalapril, nor with the calcium channel blocker amlodipine or the angiotensin receptor blocker losartan.[2] These recent studies illustrate how ACE inhibition can exert beneficial effects on endothelial function in humans and can explain the vascular protective effects demonstrated in clinical trials.

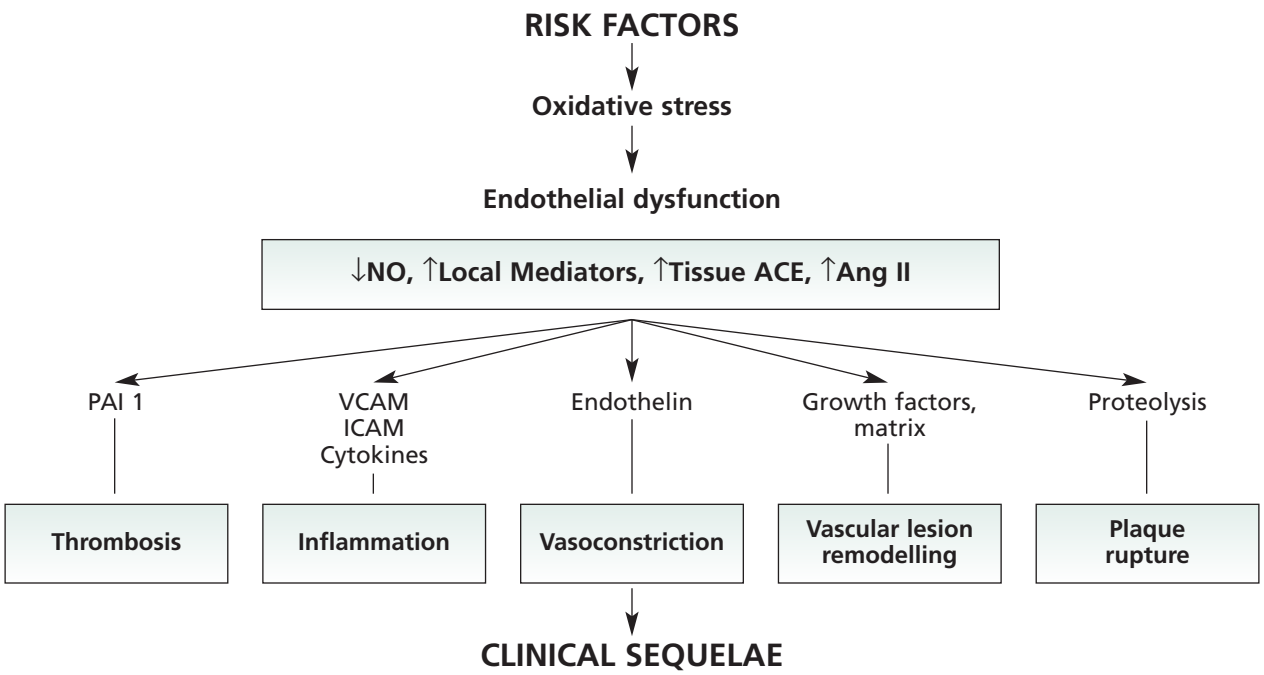
ACE inhibition and angiogenesis

The development of new collateral vessels might compensate for vascular occlusion due to the complications of atherosclerosis. The growth and differentiation of new vessels (angiogenesis) depends upon adequate endothelial function, especially the ability of the endothelial cells to generate nitric oxide (NO). NO is a crucial mediator of the angiogenic response, and it appears to be particularly important in promoting endothelial cell differentiation into vascular tubes.[3] Mice genetically engineered to lack the gene for endothelial NO synthetase which synthesizes NO from L-arginine, have reduced capability to form new blood vessels in an ischemic-limb model; this capability is not restored by the angiogenetic growth factor vascular endothelial growth factor (VEGF).[4]

Isner et al have recently demonstrated that quinapril can induce angiogenesis in a rabbit ischemic hind-limb model to a degree similar to that observed with the specific vascular growth promoter VEGF.[5] However, in these studies, an ACE inhibitor with little tissue ACE inhibition (such as captopril) had no significant effect on angiogenesis. The effectiveness of the new vessels on tissue perfusion was assessed not only by the tissue capillary density, but also by the normalization of blood pressure in the calf. Both VEGF and quinapril, but not captopril, restored endothelial- and non-endothelial-dependent increase in limb flow, indicating an important increase in the size of the vascular bed. Both captopril and quinapril resulted in similar *plasma* ACE inhibition, yet quinapril and captopril reduced *tissue* ACE activity to less than 25% and approximately 70%, respectively, of control levels.

An alternative explanation of the differing effects of captopril and quinapril on angiogenesis might be related to the sulfhydryl group of captopril-inhibiting endothelial-cell metalloproteinases, enzymes vital for the initiation of angiogenesis.[6] Similar experiments must be repeated comparing a

Figure 2: The pathological mechanisms associated with atherosclerosis



tissue-active ACE inhibitor to a less selective inhibitor without sulfhydryl groups.

Why does ACE inhibition behave like the angiogenic promoter VEGF? The answer is probably due to both agents having the capability to upregulate NO production. As ACE inhibitors are known to normalize endothelial function in a wide spectrum of disease states, it is likely, but as yet unproven, that some of the beneficial effect may be related to angiogenesis.

Mechanisms of ACE inhibition: New concepts

ACE inhibitors have resulted in remarkable improvements in outcomes of patients with heart disease. When ACE inhibitors were first introduced, their benefits in patients with heart failure were thought to result from hemodynamic effects. ACE inhibitors were later shown to limit remodeling of the damaged heart and deterioration of cardiac function, not only by their hemodynamic effects, but also by limiting the effect of tissue angiotensin II on the development of pathologic hypertrophy. Studies of the same era (SAVE, SOLVD, AIRE) also demonstrated that ACE inhibitors give a degree of vascular protection that results in a reduction of fatal and non-fatal myocardial infarction.[7-9] More recently, the role of the vascular protective effect of ACE inhibition has been strengthened by results of the ABCD study of moderate hypertension in diabetics; it showed that enalapril was more effective than the calcium channel blocker nisoldipine in reducing fatal and nonfatal myocardial infarctions (relative risk reduction 5.5, 95% confidence interval, 2.1-14.6).[10]

Promotion of angiogenesis can now be added to the benefits of ACE inhibition. What will its role be in improving the outcome of patients with ischemic heart disease and normal ventricular function? If angiogenesis is important in vascular protection, then it would appear that an ACE inhibitor with a high degree of inhibition of vascular ACE activity will confer special benefit; however, we must await the results of several trials (such as HOPE) that are testing the hypothesis that ACE inhibition improves cardiovascular outcome in patients at high risk of vascular events.

QUO-VADIS

QUO-VADIS[11] was a double-blind study of 149 patients with exercise-induced myocardial ischemia who were scheduled for coronary bypass surgery. The patients had not received an ACE inhibitor over the past two years, had a left ventricular ejection fraction in the normal range, no history of heart failure, no evidence for left ventricular hypertrophy, and were not taking a diuretic.

Four weeks prior to surgery, patients were randomized to treatment with either quinapril or placebo. All patients had at least one arterial coronary bypass graft. The patients were observed during one year of follow-up. One year after surgery, all patients had a graduated exercise electrocardiogram and a 48-hour Holter monitor recording.

The primary endpoint of the study was the change in total exercise time; secondary endpoints were the time to onset of myocardial ischemia and ECG evidence of ischemia during either the stress test or the 48 hours of Holter monitoring. Other endpoints included combined ischemic events: cardiac death, myocardial infarction, the need for further revascularization, recurrence of angina, and ischemic stroke or transient cerebral ischemic episodes (Table 1).

Table 1: Ischemic events in QUO-VADIS Study

Event	Quinapril	Placebo
Myocardial infarction	1	3
Recurrent angina	2	7
PTCA/repeat CABG	1	0
CVA/TIA	1	1
Total events	**5**	**11**

On 48-hour Holter monitoring, 20% of placebo patients compared with 13% of quinapril patients had one or more ischemic episodes (Odds ratio: 0.63 (0.21-1.90)). A significant reduction in clinical ischemic events could be demonstrated; 18% of placebo patients compared with 4% of quinapril patients had a clinical ischemic event within one year post-CABG (Odds ratio: 0.2 (0.04-0.96), p=0.03). Total ischemic events were reduced from 11 in the control group to 5 in patients treated with quinapril (Table 1).

Conclusion

The QUO-VADIS raises the hypothesis that the tissue-selective ACE inhibitor quinapril can reduce combined ischemic vascular outcomes in patients at high risk of ischemic cardiac events. Larger studies are needed to provide a more definitive answer in defining the vascular protective benefit of ACE inhibitors. Until then, we should not hesitate to administer ACE inhibitors to patients with hypertension and diabetes or to those with left ventricular dysfunction and coronary disease who are known to benefit, with the knowledge that ACE therapy will provide proven vascular protection. Another benefit (as yet unproven) might include the promotion of collateral coronary vessels through the stimulation of angiogenesis.

References

1. Mancini GBJ, Henry GC, Macaya C, et al. Angiotensin-converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease. The Trial on Reversing Endothelial Dysfunction (TREND) Study. *Circulation* 1996;94:258-265.
2. Anderson TJ, Overhiser RW, Haber H, Charbonneau F. A comparison study of four antihypertensive agents on endothelial function in patients with coronary disease. *J Am Coll Cardiol* 1998;31(2, suppl A):327A.
3. Babaei S, Teichert-Kuliszewska K, Monge JC, et al. Role of nitric oxide in the angiogenic response in vitro to basic fibroblast growth factor. *Circ Res* 1998;82:1007-1015.
4. Muruhara T, et al. Nitric oxide synthetase modulates angiogenesis in response to tissue ischemia. *J Clin Invest* 1998;101:2567-2578.
5. Isner JM, Walsh K, Symes J, et al. Arterial gene therapy for therapeutic angiogenesis in patients with peripheral arterial disease. *Circulation* 1995;91(11):2687-2692.
6. Volpert OV, et al. Captopril inhibits angiogenesis and slows the growth of experimental tumors in rats. *J Clin Invest* 1996;98:671-679.
7. The SOLVD Investigators. Effect of enalapril on patients with reduced left ventricular ejection fraction and congestive heart failure. *N Engl J Med* 1991;325:293-302.
8. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality in patients with left ventricular dysfunction after myocardial infarction: Results of the Survival and Ventricular Enlargement Trial. *N Engl J Med* 1992;327:669-677.
9. The Acute Infarction Ramipril Efficacy (AIRE) study investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;342:821-828.
10. Estacio RO, et al. The effects of nisoldipine as compared to enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes mellitus and hypertension. *N Engl J Med* 1998;338:645-652.
11. Oosterga M, Voors AA, Veeger N, et al. Beneficial effects of quinapril on ischemia in coronary bypass surgery patients: One-year clinical follow-up of the QUO-VADIS study. *Circulation* 1998:98(suppl 1):I-636 (abstract).