CLINICAL TRIALS UPDATE:
Tissue ACE inhibition offers new hope for treating cardiovascular disease

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The concept of endothelial dysfunction, its association with cardiovascular risk factors and with common comorbid diseases, such as hypertension and atherosclerosis, has become known to physicians only in the past few years. A dramatic increase in knowledge has established the central role of the endothelium in cardiovascular health and disease, and the importance of tissue angiotensin-converting enzyme (ACE) in mediating endothelial function and cardiovascular disease processes (Figure 1). A basic advance has been the recent awareness that endothelial dysfunction can be treated, if not prevented, with available cardiovascular therapies. Clinical trials over the past decade have established an increasingly prominent role for ACE inhibition in the treatment and prevention of cardiovascular disease, including a demonstrated ability to improve endothelial function.

The recent guidelines from the Joint National Committee on High Blood Pressure Prevention, Detection, Evaluation and Treatment (JNC VI) specify initial drug choices according to the severity of hypertension as well as the presence of comorbid conditions and complications. The use of ACE inhibitors is recommended for a significant proportion of hypertensive patients. JNC VI cites the presence of heart failure, myocardial infarction (MI), diabetes, and renal insufficiency as compelling indications for their use (Table 1).
Recently, the HOPE (Heart Outcomes Prevention Evaluation) Study powerfully confirmed the benefits of tissue ACE inhibition...now extended to high-risk patients with vascular disease and normal left ventricular function, whether they have hypertension or not.\(^5\) HOPE builds on the foundation of other studies of tissue ACE inhibition conducted in patients with coronary artery disease (CAD) and preserved left ventricular function, including TREND (Trial on Reversing ENdothelial Dysfunction), BANFF (Brachial Artery ultrasound Normalization of Forearm Flow), QUO VADIS (effects of QUinapril On Vascular ACE and Determinants of ISchemia), and QUIET (Quinapril Ischemic Events Trial).

This monograph provides an overview of the following topics:

- The vascular biology of the renin-angiotensin system (RAS) and tissue ACE: effects on endothelial function
- Trials using ACE inhibitors with good tissue potency: TREND, BANFF, QUO VADIS, QUIET, and HOPE
- How variations among ACE inhibitors in tissue ACE avidity may influence endothelial function and effect clinical outcomes

**THE VASCULAR BIOLOGY STORY: THE RAS & TISSUE ACE**

Recognition of the importance of tissue ACE began with the identification of 2 types of RAS functioning in different environments. The circulating RAS has an endocrine effect and regulates acute blood pressure and hemodynamics; the tissue RAS has an autocrine/paracrine effect, influencing long-term changes in vascular structure and function. Over 90% of ACE is expressed locally in the tissue, primarily in the vascular wall, but also in the heart, kidney, and brain; less than 10% occurs in the circulating RAS.\(^6\)

Tissue ACE helps maintain the balance between vasodilation and vasoconstriction, growth promoters and inhibitors, pro- and anti-inflammatory factors, and thrombotic and fibrinolytic pathways in the vascular wall.\(^7\) ACE catalyzes the conversion of angiotensin I to angiotensin II (A II), a potent vasoconstrictor. It is the principal enzyme involved in the breakdown of bradykinin, a vasoactive substance that stimulates production of nitric oxide (NO), prostacyclin, and endothelium-derived hyperpolarizing factor, all potent vasodilators.\(^8\)

Endothelium-derived NO is probably the most important vasodilator involved in local vascular control; NO inhibits platelet aggregation, smooth muscle cell proliferation, monocyte adhesion, and adhesion molecule expression, protecting the vessel wall against the development of atherosclerosis and thrombosis.\(^9\)

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**Table 1. JNC VI treatment algorithm: Compelling indications and treatment choices.** Adapted from JNC VI.\(^4\)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Drug therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>ACE I, calcium antagonists and low-dose diuretics</td>
</tr>
<tr>
<td>Diabetes mellitus with proteinuria</td>
<td>ACE I</td>
</tr>
<tr>
<td>Heart failure</td>
<td>ACE I, diuretics</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td>Diuretics (preferred), calcium antagonists (long-acting DHP)</td>
</tr>
<tr>
<td>(older patients)</td>
<td>ACE I (with systolic dysfunction); β-blockers (non-ISA)</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td></td>
</tr>
</tbody>
</table>
Elevations in A II in hypertension increase oxidative stress by activating membrane NADH/NADPH oxidase, which potentiates vascular superoxide production. Oxidative stress plays a pivotal role in endothelial dysfunction and may be the unifying event linking hypertension with other risk factors that lead to vascular remodeling and ischemic disease (Figure 1).3

**ENDOTHELIAL INJURY, THE INITIATOR OF ATHEROSCLEROSIS**

Endothelial injury with resulting dysfunction is the initiating event in atherosclerosis; it is also important in the ischemic manifestations of the disease process.9 Dysfunction of the endothelium is detected in cases of established atherosclerotic disease and also in asymptomatic individuals with risk factors for atherosclerotic disease.11 Recent studies suggest that impaired endothelial function predicts long-term risk for cardiac events in patients with even mild CAD. In follow-ups ranging from 28 months to nearly 7 years, the rate of cardiac events was significantly greater in patients with the most severe endothelial dysfunction.12-14 Two studies identified impaired endothelial vasoreactivity as an independent risk factor for cardiac events.12, 13

**ANTI-ISCHEMIC EFFECTS OF TISSUE ACE INHIBITION...**

ACE inhibitors reduce cardiovascular risk through cardioprotective and vasculoprotective effects by blocking both the circulating and tissue RAS, inhibiting the formation of A II, as well as preventing the degradation of bradykinin, thereby enhancing the release of NO by the endothelium.15 Among their vasculoprotective effects, ACE inhibitors decrease platelet aggregation and maintain fibrinolytic balance by reducing plasminogen activator inhibitor-1 (PAI-1) and increasing tissue plasminogen activator (t-PA).2 ACE inhibitors exert antiproliferative and antimigratory effects on vascular smooth muscle cells (Figure 2). They also function as antioxidants by blunting the production of superoxide anions associated with increased A II.10

... **A LONG RECORD OF DEMONSTRATED EFFICACY**

A pooled analysis of major clinical trials of ACE inhibitors in patients with documented cardiovascular disease and low left ventricular ejection fraction, including AIRE, TRACE, SAVE, and SOLVD, indicated that long-term ACE inhibition produced a 21% reduction in the risk for MI (Figure 3).16 The anti-ischemic effects of ACE inhibition included significant reductions in worsening angina (11%), hospitalizations for stable angina (10%), and revascularization procedures (24%).17,18

**Figure 2. Vasculoprotective effects of ACE inhibitors.**
Adapted from Dzau VJ, et al.8

**Figure 3: Reduction in MI with ACE inhibitors.**
Adapted from Yusuf S, Lonn E.16
**TRIALS OF TISSUE ACE INHIBITION: IMPROVING ENDOTHELIAL FUNCTION**

More recent trials have demonstrated the beneficial effects of tissue ACE inhibition in patients with CAD and normal left ventricular function, including TREND,¹⁹-²² BANFF,²³ QUO VADIS,²⁴,²⁵ QUIET,²⁶-²⁸ and HOPE⁵ (Table 2). In TREND, 6 months of therapy with quinapril 40 mg in 129 normotensive patients with CAD significantly improved vasodilation in coronary artery segments.¹⁹ In a TREND substudy of smokers versus nonsmokers, there was an accelerated progression of endothelial dysfunction in smokers compared with nonsmokers²⁰; however, endothelial function did not deteriorate in smokers treated with quinapril.²¹ In a second substudy comparing patients with above median versus below median LDL-C levels, quinapril-treated patients with LDL-C ≥ 130 mg/dL had significantly greater improvement in endothelial function than patients with lower LDL-C.²²

The BANFF trial compared the effects of 4 widely used cardiovascular agents (the ACE inhibitors quinapril and enalapril, the angiotensin II inhibitor losartan, and the calcium channel blocker amlodipine) on endothelial function in patients with CAD.²³ In 8-week trials of each drug, only quinapril significantly improved endothelium-mediated dilation. This indicates that ACE inhibitors and other vasodilators differ in their ability to improve endothelial function. Furthermore, the subset with the DD ACE genotype, a characteristic known to increase ACE activity, showed no improvement. This suggests that the response to quinapril is related to ACE genotype.

QUO VADIS compared the effect of a tissue-avid ACE inhibitor versus a nontissue-avid ACE inhibitor on ischemia in patients who had undergone coronary artery bypass grafting. In part one of the study (n = 187), preoperative treatment with quinapril, but not captopril, blocked conversion of angiotensin I to A II in segments of the artery removed at surgery.²⁴ This effect on A II, as well as improved vascular response in patients, suggests that there are functional differences between the 2 drugs. In part two of QUO VADIS (n = 149), treatment with quinapril was associated with an 80% reduction in ischemic events compared with placebo at a 1-year follow-up.²⁵

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Drug</th>
<th>Major result</th>
</tr>
</thead>
<tbody>
<tr>
<td>TREND¹⁹-²²</td>
<td>129</td>
<td>Quinapril</td>
<td>† Coronary dilation † Endothelial function in smokers and those with higher LDL-C</td>
</tr>
<tr>
<td>BANFF²³</td>
<td>56</td>
<td>Quinapril</td>
<td>† Endothelial function</td>
</tr>
<tr>
<td></td>
<td>55</td>
<td>Enalapril</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>Losartan</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>Amlodipine</td>
<td>NS</td>
</tr>
<tr>
<td>QUO VADIS-I²⁴</td>
<td>187</td>
<td>Quinapril</td>
<td>Blocks A I conversion to A II in vascular preparations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Captopril</td>
<td>NS</td>
</tr>
<tr>
<td>QUO VADIS-II²⁵</td>
<td>149</td>
<td>Quinapril</td>
<td>↓ 80% in ischemic events</td>
</tr>
<tr>
<td>QUIET²⁶-²⁸</td>
<td>1750</td>
<td>Quinapril</td>
<td>Trend towards ↓ nonfatal ischemic events ↓ Atherosclerosis progression with ↑ LDL-C</td>
</tr>
<tr>
<td>HOPE⁵</td>
<td>9297</td>
<td>Ramipril</td>
<td>↓ 22% risk for MI, CVD death, stroke</td>
</tr>
</tbody>
</table>

Table 2. Tissue ACE trials in CAD patients with preserved LV function.
QUIET was a randomized 3-year trial to investigate the effects of long-term tissue ACE inhibition on plaque progression in 1750 low-risk patients with CAD and normal left ventricular function.²⁶, ²⁷ Patients were enrolled 12 to 72 hours after revascularization and randomly given quinapril 20 mg or a placebo. While there were no significant differences between the groups in combined ischemic events, the group that received quinapril showed a trend toward reduction in cardiac deaths, nonfatal MI, and resuscitated cardiac arrest. However, the low incidence of events (1.5% MI/year) precluded a definitive conclusion. The angiographic effects of quinapril were neutral, based on follow-up angiography in about 30% of the patients.

Concern has arisen that trial design and several other factors may have confounded the outcome of the study.²⁸ A primary question is whether the quinapril dose was too low. Recent studies show that the ability of ACE inhibition to decrease morbidity and mortality in heart failure patients depends on the use of high doses.²⁹ Further confounding factors include the evaluation of less severe stenoses at baseline and the inclusion of low-risk patients.

A subanalysis of the QUIET data suggests that beneficial effects of quinapril on atherosclerosis may be related to LDL-C levels. In patients with elevated LDL-C (≥ 130 mg/dL), quinapril assignment was associated with no progression of atherosclerosis. In contrast, the progression of atherosclerosis was accelerated in the placebo group with high LDL-C (Figure 4).³⁰

HOPE was a large randomized trial lasting 4.5 years that investigated the preventive use of the tissue ACE inhibitor ramipril 10 mg daily. The study included 9297 high-risk patients aged ≥ 55 years with a history of CAD, peripheral vascular disease, stroke, or diabetes and at least 1 other risk factor.⁵ Patients with low ejection fractions or heart failure were excluded. Treatment with ramipril significantly reduced the combined outcome of death, MI, and stroke by 22%, nonfatal MI by 20%, nonfatal stroke by 31%, revascularizations by 16%, and worsening angina by 11% compared with placebo. The risks of new onset diabetes and diabetic complications were 32% and 16% lower, respectively (Figure 5).

“While there were no significant differences between the groups in combined ischemic events, the group that received quinapril showed a trend toward reduction in cardiac deaths, nonfatal MI, and resuscitated cardiac arrest.”

[Figure 4. QUIET: Effect of quinapril on CAD progression according to LDL-C level. Adapted from Cashin-Hemphill L, et al.³⁰]
The importance of tissue ACE suggests that differences in tissue ACE-binding affinity might influence clinical response. In pharmacologic studies, ACE inhibitors vary in binding affinity for tissue ACE (Table 3). The potent new group of tissue-avid ACE inhibitors range upward in potency from ramipril to benazepril to quinapril. Results of the tissue ACE trials suggest that agents with a high tissue affinity may be especially beneficial in enhancing endothelial function and potentially improving cardiovascular outcomes.

In this and other studies of ACE inhibition, it is unlikely that the observed reduction in ischemic events can be explained by the blood pressure-lowering action of ACE inhibitors alone, since the magnitude of risk reduction was far greater than that expected from the modest reductions in blood pressure that occurred. Indeed, in HOPE, 56% of the entering cohort was normotensive. The findings of the tissue ACE trials suggest that improvement of endothelial function is a likely mechanism for the favorable clinical outcomes.

Future directions for tissue ACE inhibition as anti-ischemic therapy

The results of these studies continue to expand the role for tissue ACE inhibition for the treatment and prevention of ischemic disease in an increasingly broad spectrum of patients. Their benefits have now been documented not only in patients with hypertension, CAD, and impaired left ventricular function, but also in high-risk patients with CAD and normal left ventricular function, whether or not they have hypertension.

**Figure 5. HOPE: Risk reduction with ACE inhibition.** Adapted from the HOPE Study investigators.

![Figure 5. HOPE: Risk reduction with ACE inhibition.](image)


**Plasma**
- Quinaprilat
- Benazeprilat
- Fosinoprilat
- Ramiprilat
- Perindoprilat
- Lisinopril
- Enalaprilat
- Captopril

**Tissue**
- Quinaprilat
- Benazeprilat
- Ramiprilat
- Perindoprilat
- Lisinopril
- Enalaprilat
- Captopril

“The findings of the tissue ACE trials suggest that improvement of endothelial function is a likely mechanism for the favorable clinical outcomes.”
REFERENCES


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