Data Alert #2. . .

Subject: HOPE: New validation for the importance of tissue ACE inhibition

Dear Colleague:

The results of the recently published HOPE (Heart Outcomes Prevention Evaluation) study provide powerful confirmation of the clinical benefits of tissue angiotensin-converting enzyme (ACE) inhibition, now strikingly demonstrated in patients at high risk for cardiovascular events.1 This important trial is the latest in a series of carefully conducted studies supporting the hypothesis that tissue ACE inhibition is a key factor in decreasing morbidity and mortality due to coronary disease.

HOPE: randomized, placebo-controlled trial of patients at high risk for cardiovascular events

- 267 research centers
- 19 countries in North and South America, Europe
- 9 297 patients ≥ 55 years old with CAD, PVD, stroke, or diabetes + 1 other CAD risk factor
- 4.5-year mean follow-up
- Exclusions: Low EF or HF, taking ACE-I or vitamin E, uncontrolled hypertension, stroke or MI within 4 weeks

The HOPE study was conducted in 267 centers in 19 countries in North and South America and Europe. It lasted 4.5 years with follow-ups at 6-month intervals.2 The study enrolled 9 297 patients aged 55 or older and at high risk for cardiovascular events due to a history of ischemic disease, peripheral artery disease, stroke, or diabetes and 1 risk factor. Patients with low ejection fractions or heart failure were excluded. At baseline, 56% of the patients were normotensive and 44% were hypertensive.
Two arms of the study examined the impact of (1) tissue ACE-inhibition and (2) vitamin E on cardiovascular outcomes.

<table>
<thead>
<tr>
<th>Arms</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramipril 10 mg/d (a tissue ACE-I) vs placebo</td>
<td>CV events</td>
</tr>
<tr>
<td>Vitamin E vs placebo</td>
<td>Heart disease, cancer</td>
</tr>
</tbody>
</table>

The two arms of the HOPE study were designed to determine whether the tissue ACE inhibitor ramipril (10 mg daily) reduces the risk of major cardiovascular events in high-risk patients, and whether the use of vitamin E (400 IU daily) reduces heart disease, stroke, and cancer.

Several months before the scheduled end date, the benefits of the tissue ACE inhibitor were so clearly apparent that the ramipril arm of the study was halted.

**HOPE results reflect a consistent and clear benefit of tissue ACE inhibition in both primary and secondary outcomes**

Tissue ACE inhibition resulted in a 22% reduction in relative risk for the combined outcome of cardiovascular death, nonfatal myocardial infarction, and stroke. The risk of cardiovascular death declined by 25%, nonfatal myocardial infarction by 20%, nonfatal stroke by 31% and worsening angina by 11%. The mean blood pressure decline from baseline levels of 139/79 mm Hg was only 2.5 mm Hg in systolic blood pressure and 1 mm Hg in diastolic blood pressure, indicating that blood pressure effects alone explain only a small fraction of the benefits of treatment.

Patients assigned ramipril were 22% less likely to develop new or worsening heart failure, 16% less likely to require emergency revascularization, and 16% less likely to be hospitalized for heart failure than those treated with placebo. There was evidence that tissue ACE inhibition prevents development of diabetes and diabetic complications, including reductions of 32% in new-onset diabetes ($P = 0.002$), and a 16% decline in complications related to diabetes ($P = 0.03$). The benefits extended to a wide cross section of patients, irrespective of age, gender, or the presence or absence of hypertension. Benefits were also observed whether or not patients were also taking aspirin, β-blockers, lipid-lowering drugs or other antihypertensive agents.
More than 90% of ACE is found locally in the tissues; only 10% occurs in the circulation.

The growing awareness of the importance of tissue ACE inhibition began with the identification of two renin angiotensin systems (RAS), the circulatory RAS, which regulates acute blood pressure, and tissue RAS, which influences long-term changes in vascular structure and function. More than 90% of ACE is expressed locally in the tissues, primarily in the vascular wall, as well as the heart and other tissues. Expression of ACE and angiotensin II increases in disease states.

ACE is a key enzyme in maintaining the balance between vasodilation and vasoconstriction in the vascular wall. It mediates the release of angiotensin II, a potent vasoconstrictor and an important initiator of atherosclerosis. Of equal importance, ACE breaks down bradykinin, a potent vasodilator which also stimulates the release of the vasodilators nitric oxide and prostacyclin.

Given the profound effects of tissue ACE on the vasculature and potentially on coronary artery disease and atherosclerosis in other vascular beds, tissue affinity of ACE inhibitors at the vascular wall may be critical to their therapeutic efficacy.

### The relative tissue- and plasma-binding potency of ACE inhibitors based on radioligand inhibitor binding studies

<table>
<thead>
<tr>
<th>Plasma</th>
<th>Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinaprilat</td>
<td>High  Quinaprilat (33)</td>
</tr>
<tr>
<td>Cilazeprilat</td>
<td>Benazeprilat (27)</td>
</tr>
<tr>
<td>Benazeprilat</td>
<td>Perindoprilat (17)</td>
</tr>
<tr>
<td>Fosinoprilat</td>
<td>Ramiprilat (11)</td>
</tr>
<tr>
<td>Ramiprilat</td>
<td>Lisinopril (6)</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Enalaprilat (2.3)</td>
</tr>
<tr>
<td>Enalaprilat</td>
<td>Fosinoprilat (1.7)</td>
</tr>
<tr>
<td>Captpril</td>
<td>Low</td>
</tr>
</tbody>
</table>

Studies show that ACE inhibitors differ in their binding affinity for plasma and tissue ACE. Quinapril, which has the highest degree of tissue penetration, is particularly effective at inhibiting tissue ACE. Its tissue-binding affinity exceeds that of ramipril, the HOPE study agent which is also considered a tissue ACE-specific inhibitor. Other ACE inhibitors have lower tissue-binding capacities.
HOPE study confirms the beneficial endothelial effects of tissue ACE inhibition

The HOPE study confirms and extends the impressive clinical findings of TREND,9 BANFF,10 QUO VADIS,11,12 and Hornig and Drexler.13 Together these studies have demonstrated that tissue ACE inhibition with quinapril or ramipril significantly improves endothelial function and clinical outcomes in patients with coronary artery disease or heart failure. The HOPE data provide the strongest support to date that tissue ACE inhibition is an important factor in reducing coronary morbidity and mortality.

![Graph showing risk reduction in myocardial infarction and angina](image)

Evidence for the anti-ischemic effects of ACE inhibitors from clinical trials

The HOPE study joins the ranks of such ground-breaking long-term trials as SOLVD14,15 and SAVE16,17 that have established the prominent role of ACE inhibitors in the treatment and prevention of cardiovascular disease. The benefits of ACE inhibition extend over a spectrum of high-risk patients, not only with symptomatic heart failure,18 but also with asymptomatic left ventricular dysfunction,14,15 or at risk for developing heart failure following a myocardial infarction.16,17 Now in one of the most compelling sets of data ever recorded, the HOPE study has confirmed the benefits of tissue ACE inhibition in high-risk patients with normal left ventricular function whether or not they have hypertension.

Sincerely,

Carl J. Pepine, MD
REFERENCES


