Angiotensin-converting enzyme (ACE) inhibitors, first introduced almost 20 years ago, have proven effective in the treatment of hypertension and congestive heart failure (CHF) (1,2). Recent evidence suggests these agents may provide protection against adverse cardiovascular events when used in patients with atherosclerotic cardiovascular disease without high blood pressure (BP) or left ventricular (LV) dysfunction (3). The ACE inhibitors also protect against cardiac events in patients with type 2 diabetes and insulin resistance (3). Insulin resistance and hyperinsulinemia sensitize the cardiovascular system to the adverse effects of both angiotensin II and aldosterone (4). This accounts, in part, for the increased prevalence of hypertension in patients with insulin resistance or type 2 diabetes, as well as the common occurrence of left ventricular hypertrophy (LVH) and diffuse intimal thickening in patients with insulin resistance, even if they have normal or high normal BP (5). The ACE inhibitors, by blocking activation of the renin-angiotensin system, interfere with atherogenesis (6), favorably remodel the LV and arteries (6) and may improve the prognosis of patients with atherosclerosis (3). In a large, randomized, controlled trial of >9,000 patients with established atherosclerotic disease, ramipril decreased the occurrences of death, myocardial infarction (MI), stroke and new-onset diabetes (3). The ACE inhibitors are safe, well tolerated and affordable medications. Should all patients with coronary artery disease (CAD), stroke or peripheral arterial disease be started on an ACE inhibitor, even before the development of atherosclerotic cardiovascular disease? How and why do ACE inhibitors improve the prognosis of CAD? Which ACE inhibitors are best for these indications? These are relevant questions with far-reaching implications that clinicians are asking in light of novel and compelling data.

The effect of ACE inhibitors on cardiovascular outcomes. Clues regarding the potential, unique cardioprotective properties of ACE inhibitors have been noted for several years. One meta-analysis (1) of >9,000 patients treated with an ACE inhibitor for depressed LV systolic function and CHF showed a 23% reduction in the risk of MI in the patients receiving active therapy. The reduction in risk appeared to be independent of BP-lowering effects,

References:

1. From the Mid America Heart Institute, St. Luke’s Hospital, Kansas City, Missouri; and Ochsner Heart and Vascular Institute, New Orleans, Louisiana.

2. Manuscript received May 8, 2000; revised manuscript received August 10, 2000, accepted September 14, 2000.
diabetic status, use of other medications, etiology of the heart failure and left ventricular ejection fraction (LVEF). To further investigate this unexpected finding, a large, randomized, controlled trial was performed.

**The HOPE study.** The Heart Outcomes Prevention Evaluation (HOPE) study (3) evaluated the effect of ramipril in 9,297 patients who had either 1) established atherosclerotic disease (80% of patients had known CAD, 43% had peripheral vascular disease, 11% had a previous stroke or transient ischemic attack); or 2) diabetes with at least one other risk factor (hypertension, elevated total cholesterol, depressed high density lipoprotein cholesterol, smoking or microalbuminuria); 38% of the study patients were diabetic. Patients were excluded from the trial if they had a history of CHF or an LVEF <40%. Although hypertension was present in 47% of patients, BP was controlled with medications other than ACE inhibitors before enrollment in the trial. Patients randomly received 10 mg of ramipril or placebo once a day. The study was stopped prematurely at 4½ years when the ramipril group was noted to have a 22% reduction (p < 0.001) in the primary outcome: a composite end point comprised of MI, stroke or death from cardiovascular disease. In addition, a significant risk reduction was noted for most individual end points, such as all-cause mortality (16%), MI (20%), stroke (32%), cardiac arrest (37%) and revascularization procedures (15%). Of interest, the development of new diabetes was reduced by 34% (p < 0.001) in the ramipril-treated group.

The beneficial effects of ramipril in the HOPE study were observed consistently among all subgroups, including patients with and without diabetes, with and without hypertension, older and younger than 65 years of age and with or without documented CAD (the magnitude of benefit appeared to be similar in the group of patients without documented CAD, but the sample size was too small to yield a significant p value), and independent of the effects of concomitant cardiovascular medications (such as aspirin, beta-blockers, lipid-lowering agents or other BP agents). The risk reduction was largely independent of the modest lowering of BP (−3/2 mm Hg) noted with ramipril. The average BP at baseline for the entire group was 139/79 mm Hg. At the end of the study, the mean systolic BP of the ramipril group was 136 mm Hg, compared with 139 mm Hg in the placebo group. The reduction in risk attributable to the ACE inhibitor was apparent by one year into the study, and the survival curves continue to diverge throughout the course of the study (Fig. 1).

The impressive benefits found in the HOPE trial occurred despite the fact that 21% of patients in the ramipril-treated group were not receiving ACE inhibitor therapy by study end, and 12% of placebo-assigned patients were taking an ACE inhibitor. The noncompliance rate may have diluted the results, suggesting that the actual benefit of ramipril may be even greater than that noted by this intention-to-treat analysis.

**ACE inhibitor therapy for MI.** More than 120,000 patients have been studied in randomized, controlled trials evaluating the effects of ACE inhibitors during and after acute MI. A recent meta-analysis of these trials (7) showed a 7% reduction in 30-day mortality among the patients assigned to ACE inhibitor therapy. The absolute benefit was particularly large in high-risk patients, such as those in Killip class II or III (mild to moderate CHF), heart rate >100 beats/min, anterior infarction and diabetes (8,9).

**ACE inhibitors after revascularization.** The QUO VADIS study (effects of QUinapril On Vascular ACE and Determinants of ISchemia) enrolled 149 patients undergoing elective coronary artery bypass graft surgery who were subsequently randomized to receive quinapril 40 mg/day or placebo at least two weeks before surgery (10); treatment was continued for one year. Like the HOPE study, patients in the recently reported QUO VADIS study did not have traditional indications for an ACE inhibitor (BP was controlled and LV function was normal). By one year, an 80% reduction in ischemic events (MI, ischemic stroke, transient ischemic attack or recurrence of angina pectoris) was noted in the quinapril-treated group. During this study, 18% of placebo-assigned patients and 4% of quinapril-treated patients (p = 0.04) experienced ischemic events.
mortality rate, compared with those using other classes of BP medications, including calcium channel blockers, diuretics and beta-blockers (14). Hypertension usually coexists within a cluster of risk factors. The ACE inhibitors not only lower BP but also positively influence many other aspects of the atherogenic milieu.

Not all studies support the concept that ACE inhibitors are superior to other antihypertensive drugs in terms of event reduction. The CAPtopril Prevention Project (CAPPP) studied 10,985 hypertensive patients randomized to receive captopril, 50 mg once or twice daily, versus a beta-blocker and diuretic (15). Cardiovascular outcomes were similar during the six-year study. However, the fact that the combination beta-blocker/diuretic group achieved lower BP levels than the captopril group almost certainly influenced the outcomes and limits the clinical relevance of the findings.

Effects on endothelial function. Endothelial dysfunction plays a fundamental role in the genesis and development of a variety of cardiovascular diseases and is the final common pathway through which most cardiovascular risk factors contribute to atherosclerosis and inflammation (16). Unlike most other antihypertensive agents, ACE inhibitors have been shown to improve endothelium-dependent vasodilation (17). Endothelial health is largely the result of a balance between angiotensin II and nitric oxide. Angiotensin II is a powerful vasoconstrictor, which also stimulates mitogenesis (16), resulting in smooth muscle cell hyperplasia, fibroplastic proliferation and collagen deposition (18), all of which produce increases in arterial wall mass and reductions in compliance in both the LV and the vascular system. Angiotensin II depletes nitric oxide production, generates toxic vascular prooxidants such as peroxynitrite, stimulates the release of norepinephrine and enhances production of endothelin-1 (a potent systemic vasoconstrictor) (16). Aldosterone is also released in response to increased angiotensin II concentrations, which independently increases myocardial fibrosis and intimal hyperplasia, heightens sympathetic activity and stimulates sodium and water retention and potassium excretion (19).

To counter these vasoconstrictive, mitogenic and pressor effects, there is nitric oxide. Healthy endothelium produces nitric oxide, which promotes vasodilation and inhibits vascular hypertrophy. Our modern life-style and diet, especially in a genetically predisposed individual, often results in shifting of this balance to an angiotensin II/aldosterone dominance. This disturbance frequently leads to hypertension, atherosclerosis, MI, stroke, CHF and other adverse cardiovascular events. The ACE inhibitors reduce angiotensin II levels and increase nitric oxide production, both directly and indirectly by blocking degradation of bradykinin (which stimulates the local release of nitric oxide), resulting in restoration of more normal endothelial function (16). Although other antihypertensive medications lower BP as well or better than ACE inhibitors, they are not as
effective as ACE inhibitors for improving endothelial function (17,20,21).

**Effects on LVH and arterial wall mass.** Left ventricular hypertrophy is one of the strongest independent risk factors for adverse cardiac events, especially in the elderly population (22). In the Framingham population, the presence of LVH by echocardiographic criteria increased the risk of sudden death fivefold and the risk of coronary disease threefold (23). Left ventricular hypertrophy is also a powerful predictor for the development of CHF and life-threatening ventricular dysrhythmias (22). Regression of LVH improves these risks. In a recent study using echocardiographic techniques, those patients who experienced significant LVH regression by antihypertensive therapy had a 75% lower risk of subsequent cardiovascular events over an eight-year follow-up, compared with those who did not have regression of LVH (24).

The presence or absence of LVH is only partially explained by BP levels. Insulin resistance, overt type 2 diabetes and obesity all act synergistically with elevated BP (especially systolic pressure or pulse pressure) (25) to result in LVH (4). Hyperinsulinemia sensitizes the cardiovascular system to the trophic effects of angiotensin II and aldosterone (19,26). Because angiotensin II and aldosterone stimulate myocyte hypertrophy and increased formation of extracellular matrix (e.g., collagen) (18), it is not surprising that ACE inhibitors are the most effective of the antihypertensive medications for the prevention and regression of LVH (27). The magnitude of this effect is large; one longitudinal study showed that ACE inhibition reduced LV mass by ~40% over the course of a three-year study, bringing the LV mass into a normal range (28).

Hypertension and insulin resistance also promote smooth muscle hypertrophy, hyperplasia and increased fibrous tissue deposition in the arterial walls (16). This leads to reduced arterial compliance and endothelial dysfunction—the milieu that promotes the genesis and progression of atherosclerotic plaque. Angiotensin-converting enzyme inhibition facilitates the reversal of these processes and the normalization of arterial wall structure and function (17,18,20,21). However, a recent randomized study involving 617 patients with documented atherosclerosis at baseline found no effect of ramipril on the progression of carotid atherosclerosis over a four-year period (29). This study, though underpowered to look at event reduction, showed a 34% decreased risk of nonfatal MI or coronary heart disease death. Similarly, a four-year randomized angiographic trial reported that although enalapril did not affect coronary atherosclerotic progression, it did significantly reduce adverse cardiovascular events (29a). This suggests that the cardioprotection of ACE inhibitors is not related to changes in atherosclerotic progression. Finally, ACE inhibitors appear to augment the development of collateral blood flow in the myocardium (30). This action may account for some of the observed benefit of ACE inhibition in the prevention of MI.

**Other potentially beneficial effects of ACE inhibition.** The metabolic effects of ACE inhibitors probably also play a role in favorably altering cardiovascular outcomes. Insulin resistance is slightly improved by ACE inhibition, although the remarkable 34% reduction in the occurrence of new diabetes during the HOPE study is unlikely to be accounted for by this mild effect alone (3). In CAPPP, similar results were reported, with a 14% risk-adjusted decrease in the incidence of new diabetes in the ACE inhibitor–treated group over a five-year period. In contrast, beta-blockers and high dose diuretics worsen insulin resistance and may increase the risk of developing type 2 diabetes (31). The lipid profile is unaffected or mildly improved by ACE inhibitor therapy, unlike many other classes of antihypertensive medications, such as diuretics and beta-blockers, which modestly worsen most lipid variables.

Fibrinolysis is largely regulated by endothelial expression of tissue plasminogen activator (t-PA) and plasminogen activator inhibitor (PAI-1), which is the major physiologic inhibitor of t-PA. Epidemiologic evidence suggests that elevated PAI-1 and impaired fibrinolysis are risk factors for thrombotic cardiovascular events, such as MI and stroke (32). Levels of PAI-1 are generally elevated in patients with diabetes, obesity and insulin resistance (32).

The angiotensin-converting enzyme is a crucial mediator of the interaction between PAI-1 and t-PA (31). Bradykinin stimulates the production and release of t-PA, whereas angiotensin II is a stimulus for the endothelial production of PAI-1. Accordingly, activation of the RAS increases PAI-1, and ACE inhibition decreases it. In one study, ramipril lowered PAI-1 antigen levels by 44% and PAI-1 activity by 22% (33). Angiotensin II increases platelet aggregation and promotes oxidative stress of the blood vessel, which upregulates expression of the adhesion molecules that initiate the inflammatory response mediating atherosclerosis (16). The clinical relevance of these effects on pathologic vascular thrombotic events is uncertain so far. A recent meta-analysis reported a 20% decrease in sudden death in patients with CHF treated with ACE inhibitors (34). Ramipril has been shown to decrease QT dispersion (35), a possible mechanism by which ACE inhibition might reduce the risk of sudden death.

**Is an ACE an ACE? Practical considerations.** Are the benefits of ACE inhibition a “class effect”? Ten ACE inhibitors are now available on the U.S. market. These drugs vary greatly with respect to half-life, degree of lipid solubility, route of elimination, price and tissue levels (Table 1). Head-to-head, long-term outcome studies have not been performed with the ACE inhibitor class, and thus the issue regarding benefits of specific agents versus a class effect remains speculative.

When using this class of drugs for preventing adverse cardiovascular events, it may be particularly important to achieve effective ACE inhibition in the tissues of the vessel wall and the myocardium. Because lipophilicity enhances tissue penetration, ACE inhibitors with good lipid solubility...
Table 1. Comparative Data on Angiotensin-Converting Enzyme Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing Range (mg)</th>
<th>Target Dose (mg/day)</th>
<th>Half-Life (h)</th>
<th>Target Dose Price per Month</th>
<th>Maximal Dose Price per Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benazepril</td>
<td>5–40</td>
<td>20</td>
<td>10–11</td>
<td>$26.00</td>
<td>$26.00</td>
</tr>
<tr>
<td>Captopril</td>
<td>25–50</td>
<td>150</td>
<td>&lt;2</td>
<td>$89.00</td>
<td>$89.00</td>
</tr>
<tr>
<td>Enalapril</td>
<td>5–40</td>
<td>20</td>
<td>11</td>
<td>$51.00</td>
<td>$101.00</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>10–40</td>
<td>20</td>
<td>11</td>
<td>$28.00</td>
<td>$28.00</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>5–40</td>
<td>20</td>
<td>13</td>
<td>$30.00</td>
<td>$44.00</td>
</tr>
<tr>
<td>Moexepril</td>
<td>7.5–30</td>
<td>15</td>
<td>2–9</td>
<td>$21.00</td>
<td>$42.00</td>
</tr>
<tr>
<td>Perindopril</td>
<td>4–16</td>
<td>8</td>
<td>8–10</td>
<td>$42.00</td>
<td>$84.00</td>
</tr>
<tr>
<td>Quinapril</td>
<td>5–80</td>
<td>20</td>
<td>2</td>
<td>$31.00</td>
<td>$61.00</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25–20</td>
<td>10</td>
<td>13–17</td>
<td>$36.00</td>
<td>$72.00</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>1–8</td>
<td>4</td>
<td>16–24</td>
<td>$23.00</td>
<td>$46.00</td>
</tr>
</tbody>
</table>

(like ramipril, trandolapril, fosinopril and quinapril) may be particularly effective for improving prognosis. Ramipril and trandolapril both have very long half-lives, resulting in excellent ACE inhibition throughout a 24-h cycle after a single daily dose. Without question, ramipril possesses the most impressive clinical data with respect to event reduction (the HOPE study [5] and others [2,11,35]). Trandolapril has been shown to improve life expectancy after anterior infarction by >100% in subgroups of patients with diabetes or hypertension (36). Quinapril has a relatively short half-life (2 h), but it does have an active metabolite that remains in the circulation for an entire 24-h dosing period.

The ACE inhibitor class is not expensive compared with other classes of modern medications such as the statins. In an economic study of the HOPE trial, the cost per year of life saved with ramipril was $3,100, or about half the cost of statins in comparable analyses (37). However, most patients with CAD are on a growing list of medications, and often the cumulative cost is burdensome. Table 1 lists the average wholesale price of the various ACE inhibitors that are available in the U.S. If cost is a limiting factor, ACE inhibitors with a flat pricing schedule (whereby all doses have the same price per unit) offer opportunities for substantial savings, especially if the pills can be split in half.

The side-effect profile of ACE inhibitors is relatively benign, and the major limitation relates to a dry, nonproductive cough (38). All ACE inhibitors seem to exhibit a similar incidence of this common, troublesome, but non-pathologic complaint related to increased bradykinin levels in the lungs. Angioedema occurs in ~0.1% of patients treated with ACE inhibitors. Typically, a patient’s creatinine will rise ~0.1 mg/dl after initiating ACE inhibition. A more substantial rise in creatinine can be anticipated in patients who are dehydrated or in those with significant renal impairment. It is generally safe to start ACE inhibitor therapy in patients with a creatinine <=3.0 mg/dl. In the long term, ACE inhibitor therapy has been shown to be the most effective medication for preventing progressive renal dysfunction, both for diabetic (39) and nondiabetic (40) etiologies of renal failure. Therapy with ACE inhibitors remains “the last best hope” for staving off long-term end-stage renal disease and dialysis for many patients with diabetes, hypertension and chronic azotemia, and thus the increased difficulty of initiating therapy in this setting is usually worth the trouble. In fact, a recent study of 20,000 people aged ≥65 years with depressed LV function found that ACE inhibitor therapy decreased one-year mortality by 37% in those with a creatinine >3.0 mg/dl compared to a 16% reduction in patients with a creatinine of ≤3.0 mg/dl (40a). Patients with azotemia should be well hydrated before starting low-dose ACE inhibitor therapy.

Aspirin and ACE inhibitors. The hypotensive effect of ACE inhibition is partly attributable to increased synthesis of vasodilatory prostaglandins such as prostaglandin E2 (38). Aspirin produces a dose-dependent inhibition of prostaglandins, the basis for its anti-inflammatory effect, that dissipates within 4 to 6 h. Some scientific reports have suggested that aspirin reduces the beneficial effects of ACE inhibitor therapy in patients with CHF and in those who have had an infarction (41,42), whereas other studies showed no such therapeutic antagonism (43). In the HOPE study (5), the ramipril benefits were noted despite the fact that ~75% of patients were receiving aspirin concomitantly. In any case, this potentially problematic interaction can be minimized by strategic dosing of the drugs. The full antiplatelet effects of aspirin can be conferred with 81 to 100 mg/day, a dose too low to interfere substantially with prostaglandin synthesis, especially if the aspirin is given 8 to 12 h before or after the ACE inhibitor.

The benefits of ACE inhibition are, in part, dose-dependent, and thus these drugs should be titrated up to target doses if possible. A four-year study of 3,164 patients with CHF randomized to either low-dose (5 mg/day) or high-dose lisinopril (30 mg) showed that the patients who received the higher dose had an 8% lower incidence of death and 24% fewer hospital admissions for heart failure (44). Although ACE inhibitor therapy does confer significant protection, even at lower doses, full (target) dose therapy (Table 1) is required for maximal benefit.

Indications for an ACE inhibitor. Should an ACE inhibitor be standard therapy for patients with atherosclerotic disease? For most patients the answer is yes. Table 2 lists patients likely to benefit from ACE inhibitor therapy and relative contraindications. Hypertension is very common among patients with CAD or other manifestations of atherosclerotic disease. On the basis of long-term outcome
Table 2. Angiotensin-Converting Enzyme Inhibitor Therapy

<table>
<thead>
<tr>
<th>Indications for ACE Inhibitor Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• CAD without contraindication to ACE inhibitor therapy</td>
</tr>
<tr>
<td>• CAD with systolic blood pressure (\geq 130 \text{ mm Hg})</td>
</tr>
<tr>
<td>• Type 2 diabetes with or without CAD</td>
</tr>
<tr>
<td>• Insulin resistance with systolic blood pressure (\geq 130 \text{ mm Hg})</td>
</tr>
<tr>
<td>• CHF and/or left ventricular dysfunction</td>
</tr>
<tr>
<td>• Angioedema due to ACE inhibition therapy</td>
</tr>
<tr>
<td>• Intolerable cough</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; CAD = coronary artery disease; CHF = congestive heart failure.

data, it is clear that either an ACE inhibitor or beta-blocker should be chosen as the first-line agent for the treatment of hypertension in patients with CAD (38,45). Many patients with CAD without documented hypertension have normal to mildly elevated BP levels. Recent guidelines stress increasingly stringent goals for the target BP (46). Accumulating evidence suggests that the ideal range for systolic BP is \(\leq 130 \text{ mm Hg}\), and for pulse pressure \(\leq 50 \text{ mm Hg}\) (24). With these goals in mind, most patients with CAD will need pharmacologic therapy for optimizing BP. An ACE inhibitor should be either the first or second agent chosen or used liberally as adjunctive therapy (of note, in the HOPE study, ramipril was often added to baseline antihypertensive therapy, including beta-blockers [40%], diuretics [15%] and calcium channel blockers [46%] (3).

Routine use of ACE inhibitor therapy is also indicated for most patients with type 2 diabetes or significant insulin resistance, even if the BP is not elevated. Studies show that patients with type 2 diabetes without documented coronary heart disease have a cardiac risk (for myocardial infarction and cardiac death) as high as patients with established coronary heart disease without diabetes (5). Extensive data support the powerful benefits of ACE inhibitor therapy in patients with diabetes (3). This benefit appears to be present with or without hypertension. The Hypertension Optimal Treatment study recently demonstrated that aggressive BP control (with a target systolic pressure \(<130 \text{ mm Hg}\) and diastolic pressure \(\sim 80 \text{ mm Hg}\)) is especially important for diabetic patients (47).

The syndrome of risk factor clustering with hypertension, depressed high-density lipoprotein levels, elevated triglycerides, abdominal obesity and insulin resistance is very common in patients with coronary heart disease (5). Often, the BP levels in these patients are in the borderline high range or only mildly elevated. The insulin resistance syndrome gives rise to many features that independently worsen the prognosis. Because hyperinsulinemia stimulates exaggerated responses to angiotensin II and aldosterone, it predisposes to LVH, endothelial dysfunction, progressive thickening and hyperplasia of the arterial wall, as well as elevated PAI-1 levels (4,25,26). Therapy with ACE inhibitors has been shown to improve all of the aforementioned abnormalities. In addition, individuals with insulin resistance are at markedly increased risk for the future development of type 2 diabetes as they age (5), and ACE inhibitor therapy reduces this risk (3,15). For all of these reasons, it is logical to use ACE inhibitor therapy liberally in patients who show evidence of insulin resistance (a practical marker for insulin resistance is a high-density lipoprotein level <40 mg/dl and a triglyceride level >150 mg/dl) (5).

Patients with very low baseline BP levels often do not tolerate initiation of an ACE inhibitor. If a patient with CAD is on other BP–lowering agents like diuretics, calcium channel blockers and peripheral alpha_1 blockers that do not have inherent cardioprotective actions, these agents should be discontinued or held to “make room” for an ACE inhibitor. If BP remains depressed (systolic BP \(\leq 90\) to \(110 \text{ mm Hg}\)), the patient may not be a good candidate for ACE inhibitor therapy.

Is an ARB as good as an ACE Inhibitor? Approximately 5% to 10% of patients will not tolerate an ACE inhibitor. The angiotensin receptor blocker (ARB) class is the logical alternative for these patients (48). Long-term outcome data on event reduction comparing ACE inhibitors and ARBs in the setting of secondary prevention or hypertension are not available, although several trials are under way. The Evaluation of Losartan In the Elderly (ELITE II) study (49) compared captopril, 50 mg three times a day, to losartan, 50 mg/d, in 3,152 patients with CHF. The two-year mortality rates were 15.9% for the captopril group and 17.7% for the losartan group \((p = 0.16)\). In a recent study, quinapril (a lipid-soluble ACE inhibitor) was more effective than losartan (an ARB) or enalapril (an ACE inhibitor with relatively poor lipid solubility) at improving flow-mediated vasodilation, a marker of endothelial function (21).

The local release of bradykinin in the tissues stimulates nitric oxide release (improving endothelial function) and shifts the t-PA/PAI-1 balance toward fibrinolysis (16). These actions of ACE inhibitors are not shared by the ARBs. Whether or not these, or other, differences will translate into meaningful differences in clinical event reduction is unknown. What is clear is that the ARBs are remarkably free from side effects, including the bradykinin-stimulated ACE inhibitor cough (33). However, there are compelling data on event reduction for ACE inhibitors but not for ARBs. At the present time, ARBs should not be considered equivalent to ACE inhibitors for this indication, but for patients with an intolerable cough, they are a reasonable alternative.

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