

Cardiovascular and Metabolic Benefits of ACE Inhibition

Moving beyond blood pressure reduction

ACE inhibitors are a class of drugs that inhibit the activity of ACE, an enzyme located on endothelial cells (1–4). In addition to being bound to endothelial cells, ACE also circulates freely in an unbound form. This enzyme has 2 key metabolic effects: 1) it catalyzes the conversion of angiotensin I to angiotensin II, in both circulation and tissue; and 2) it catalyzes the breakdown of bradykinin into inactive products (5). Inhibition of the activity of this enzyme, therefore, may decrease tissue and circulating levels of angiotensin II and may increase levels of bradykinin. Lower levels of angiotensin II result in decreased vasoconstriction, decreased stimulation of vascular smooth muscle growth, decreased sympathetic stimulation, decreased levels of plasminogen activator inhibitor, and decreased platelet aggregation (5). Lower levels of circulating angiotensin II also result in less adrenal production of aldosterone and increased urinary potassium loss; this effect may help maintain optimal β -cell function (6). Increased bradykinin levels lead to direct vasodilation as well as indirect vasodilation through bradykinin-mediated nitric oxide and prostacyclin production. In addition, increased production of nitric oxide helps facilitate insulin-mediated glucose uptake, thereby improving insulin sensitivity (7–10). In addition to all of the above vascular and metabolic effects, inhibition of ACE also reduces blood pressure.

These mechanisms are active in all individuals taking an ACE inhibitor and are all possible explanations for the observed beneficial effect of ACE inhibitors in people at risk for cardiovascular disease. Individuals with diabetes are at a particularly high risk for cardiovascular disease; for example, the presence of diabetes increases the risk of cardiovascular mortality multifold in both men and women (11–14). Therefore, if ACE inhibitors do have particular cardioprotective effects, they may be more easily detectable in this group of high-risk patients than in the general population. Moreover, the benefits of any of the metabolic effects may be more relevant to this population.

This possibility was explored in the Heart Outcome Prevention Evaluation (HOPE) Study, in which 3,577 individuals with diabetes received either placebo or ramipril (up to 10 mg daily) and were followed for 4.5 years (15). Ramipril reduced the risk of the composite outcome of myocardial infarction, stroke, or cardiovascular death by 25% and that of overt nephropathy by 24%. This benefit occurred with a very modest decrease in blood pressure and was shown to be independent of the change in blood pressure. Only 56% of the individuals with diabetes in the study had a diagnosis of hypertension at randomization. Of these patients, 28% were taking β -blockers, 20% were taking diuretics and 44% were taking calcium channel blockers at randomization in addition to either an ACE inhibitor or placebo. Thus, the HOPE Study suggests that ACE inhibitors may have a cardioprotective effect over and above any antihypertensive effect. The study also suggested favorable metabolic effects. Levels of glycated hemoglobin were lower in participants on ramipril than in participants on placebo during the first 2 years of the study. It is important to note that the HOPE Study did not compare ramipril with another active agent and that the study was clearly not designed as a trial to control blood pressure or to be relevant to people with hypertension only.

Other large studies have carefully compared the benefits of an ACE inhibitor with those of other antihypertensive drugs in people with diabetes and hypertension. These studies were carefully sought and analyzed in a systematic overview by Pahor et al. (16) in this issue of *Diabetes Care*. All randomized controlled trials that included hypertensive patients with type 2 diabetes and compared an ACE inhibitor with another active therapy for the treatment of hypertension were included in the overview if they reported a follow-up duration of ≥ 2 years and assessed the development of cardiovascular events. Four clinical trials were identified that studied a combined total of 2,180 individuals for a fol-

low-up of 13,300 person-years. ACE inhibitors were compared with calcium channel blockers, β -blockers, or diuretics in these studies. Comparable blood pressure reduction was achieved in both arms. All of the studies, except for the hypertension component of the U.K. Prospective Diabetes Study (UKPDS), had consistent findings and, when meta-analyzed, demonstrated an overall relative-risk reduction of 51% (95% CI 33–64) for cardiovascular events and 43% (13–62) for all-cause mortality. The UKPDS was not combined because it was statistically heterogeneous in comparison with the other 3 studies. Although the authors provide several explanations for this heterogeneity, the reason remains unclear and is likely to not be resolved until further trials are published.

What conclusions can be drawn, therefore, from this systematic overview and the related trials of ACE inhibitor medication? First, ACE inhibitors are effective antihypertensive agents. Second, they have favorable, or at worst, neutral metabolic effects. Third, clinical trials have uniformly shown that they are safe in the post-myocardial infarction period and, subsequently, with a very low risk of significant side effects. Fourth, there is a growing body of evidence to suggest that they have cardioprotective benefits over and above those related to blood pressure lowering. These data support the recommended use of ACE inhibitors as first-line agents in people with diabetes who are at a particularly high risk for cardiovascular outcomes, including those individuals who previously experienced myocardial infarction, heart failure, and proteinuria (17). Furthermore, they suggest that ACE inhibitors should be used as first-line antihypertensive agents in all people with diabetes. The UKPDS results suggest that further research to clarify the relative benefit of selective β -blockers versus ACE inhibitors is clearly needed. However, in light of the fact that 60% of individuals with diabetes with hypertension require at least 2 agents (18), either a selective β -blocker

or a low-dose diuretic is an appropriate additional agent.

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