ACE Inhibitors for Patients with Vascular Disease without Left Ventricular Dysfunction — May They Rest in PEACE?
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Angiotensin-converting–enzyme (ACE) inhibitors are effective in reducing mortality and morbidity from cardiovascular events among patients who have chronic heart failure due to left ventricular systolic dysfunction and in those who have acute myocardial infarction with or without left ventricular systolic dysfunction. ACE inhibitors are also effective in reducing mortality and morbidity from cardiovascular events in high-risk patients with diabetes mellitus as well as those with renal dysfunction. In addition, ACE inhibitors are effective antihypertensive agents, although current data suggest that they are not more effective in reducing mortality and morbidity from cardiovascular events than other classes of antihypertensive agents with equal blood-pressure–lowering effects.

The Heart Outcomes Prevention Evaluation (HOPE) trial showed the effectiveness of an ACE inhibitor, ramipril, in reducing mortality and morbidity from cardiovascular events among patients with known vascular disease, as well as those with diabetes mellitus and another cardiovascular risk factor who did not have a history of heart failure or left ventricular systolic dysfunction. The findings of that study, recently confirmed by the results of the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA), changed clinical practice and led to increased use of ACE inhibitors in patients with vascular disease but without heart failure or left ventricular systolic dysfunction. The scientific basis for the use of ACE inhibitors in preventing the progression of vascular disease and ischemic events in patients with vascular disease is strong. ACE inhibitors, by inhibiting angiotensin II or by increasing the concentration of bradykinin, are associated with a decrease in vascular NADPH activity and reactive oxygen species. They also lead to reduced activation of important signaling pathways (including pathways involving nuclear factor-κB and activator protein 1); reductions in vascular inflammation, endothelial dysfunction, progression of atherosclerosis, and activation of metalloproteinases 2 and 9; an improvement in plaque stability; a decrease in the tendency toward thrombosis; and an improvement in fibrinolysis.

The results of the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial, reported in this issue of the Journal, are therefore surprising. In this well-designed and well-executed study, patients with known vascular disease but without a history of heart failure or left ventricular systolic dysfunction (after the exclusion of high-risk patients with diabetes mellitus) were randomly assigned either to a placebo or to the ACE inhibitor trandolapril at a dose previously shown to reduce mortality and morbidity from cardiovascular events among patients with left ventricular systolic dysfunction after myocardial infarction. The patients assigned to receive trandolapril did not have any benefit in terms of mortality or morbidity from cardiovascular causes.

One possible explanation for the negative results of ACE inhibition in the PEACE Trial comes from the Trial on Reversing Endothelial Dysfunction (TREND), in which the ACE inhibitor quinapril was shown to be effective in improving endothelial function in patients with coronary artery disease but without left ventricular systolic dysfunction. A retrospective analysis of the data showed that quinapril was significantly effective in improving coronary endothelial function only among patients whose low-density lipoprotein (LDL) cholesterol concentration was above the median in that study (approximately 125 mg per deciliter [3 mmol per liter]). This observation was strengthened by a similar analysis in the Quinapril Ischemic Event Trial (QUIET), which involved patients with coronary disease who did not have left ventricular systolic dysfunction. In that trial, quinapril failed to reduce the rate of cardiovascular events overall but did appear to be effective in reducing the rate of progression of coronary artery disease and cardiovascular events among patients with an increased concentration of LDL cholesterol.

Thus, the failure of ACE inhibition to reduce the rate of cardiovascular events in the PEACE Trial might be explained by the fact that patients in that trial, many of whom were being treated with a statin, had a relatively low concentration of LDL cholesterol. ACE inhibitors and statins have a common mechanism of action: they both reduce activation...
of the lectin-like oxidized LDL receptor and thus reduce oxidation of LDL cholesterol. If the concentration of LDL cholesterol is sufficiently low, ACE inhibitors may no longer be effective in reducing the rate of cardiovascular events.

The possibility that not all ACE inhibitors are equally effective for all indications should also be considered. For example, in a recent prospective, randomized study involving patients who had had a myocardial infarction, the ACE inhibitor quinapril was shown to be significantly more effective than enalapril (at doses previously shown to be effective in reducing the rate of cardiovascular events among patients with left ventricular systolic dysfunction) in reducing the concentration of C-reactive protein, an important marker of vascular inflammation and cardiovascular risk. Thus, the finding that trandolapril at a given dose reduced mortality and morbidity from cardiovascular events among patients with left ventricular systolic dysfunction after a myocardial infarction does not necessarily mean that the same dose will be effective in reducing the rate of cardiovascular events among patients with vascular disease who do not have left ventricular systolic dysfunction. Left ventricular systolic dysfunction is an important stimulus for the activation of various neuropeptides, cytokines, growth factors, and signaling pathways. A higher dose of a given ACE inhibitor may be required in patients who do not have left ventricular systolic dysfunction than in those who do have such dysfunction. Alternatively, efficacy in the former group may depend on lipophilicity or other as-yet unidentified factors.

Regardless of the mechanisms accounting for the failure of trandolapril to reduce the rate of cardiovascular events, the most important finding in the PEACE Trial is that, after the exclusion of high-risk patients with diabetes mellitus, patients with known vascular disease who do not have a history of heart failure or left ventricular systolic dysfunction have a low risk of subsequent cardiovascular events when treated with a statin and other contemporary therapies. In view of the low cardiovascular risk in this group of patients, it is doubtful that the use of an ACE inhibitor or an angiotensin-receptor blocking agent — even if effective in reducing the rate of cardiovascular events — would be cost-effective. The finding that contemporary therapy has reduced cardiovascular risk in these patients to a normal level holds promise for a reduction in cardiovascular risk among high-risk patients with vascular disease, including those with diabetes mellitus. Wider application of strategies known to be effective (such as statin therapy, weight reduction, and glucose and blood-pressure control) as well as strategies currently under investigation could minimize the risk of cardiovascular events and possibly reduce the financial burden associated with vascular disease — a burden that is projected to increase as our population ages.

The results of the PEACE Trial underscore the importance of periodically reviewing previously proven strategies if concomitant therapy has changed over time. For example, percutaneous coronary revascularization has been shown to be effective in reducing the rate of cardiovascular events among patients who have unstable angina pectoris and those who have myocardial infarction without ST-segment elevation. Since such studies were completed, contemporary therapy has changed, and increasing numbers of patients are being treated with effective antiplatelet drugs and high-dose statins. Is coronary revascularization with or without stent placement still effective in reducing the rate of cardiovascular events under these circumstances?

Although trandolapril was not effective in the PEACE Trial, the use of statins, antiplatelet strategies, agents to control blood pressure, and percutaneous coronary revascularization has not yet eliminated the risk of cardiovascular events in all patients with vascular disease who do not have left ventricular systolic dysfunction. Thus, although I will no longer recommend an ACE inhibitor to patients like those included in the PEACE Trial, I will continue to use ACE inhibitors that have been shown to be effective for this indication in several groups of patients: those whose serum lipid concentrations are not adequately controlled or who have other uncontrolled cardiovascular risk factors, those with recurrent symptoms, and those with evidence of ongoing vascular inflammation or plaque instability. Ongoing vascular inflammation, the production of reactive oxygen species, and plaque instability need to be reevaluated in low-risk patients who are receiving contemporary therapy to determine their ability to predict cardiovascular events and thus to allow the selection of those at increased cardiovascular risk for ACE inhibition or other strategies. The results of the PEACE Trial allow me to rest more easily, but it is premature to discard the use of effective ACE inhibitors for all patients who have vascular disease without left ventricular systolic dysfunction.
Dr. Pitt reports having received lecture fees from King Pharmaceuticals and Wyeth; serving as an expert witness on behalf of King Pharmaceuticals and Aventis; having been a consultant to Pfizer, Sankyo, and Novartis; serving on the board of directors of IVAX Pharmaceuticals, a manufacturer of generic drugs; and having stock and stock options in IVAX Pharmaceuticals.

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