All Coronary Artery Bypass Graft Surgery Patients Will Benefit From Angiotensin-Converting Enzyme Inhibitors

Harold L. Lazar, MD

Angiotensin-converting enzyme (ACE) inhibitors have been shown to prolong survival and to decrease infarct size in patients after acute coronary syndromes. Evidence now exists that ACE inhibitors are effective in decreasing myocardial injury during coronary artery bypass graft surgery (CABG) and can reduce the incidence of ischemic events in the years after surgery. It has been suggested that all CABG patients be started on ACE inhibitors, in addition to a statin, aspirin, and β-blocker, as part of a cardioprotective strategy to reduce recurrent ischemic events in these patients. In this issue of Circulation, Rouleau and coworkers’ present data from the Ischemia Management with Accupril post-bypass Graft via Inhibition of the Converting Enzyme (IMAGINE) trial that question this benefit for all CABG patients. They conclude that in low-risk CABG patients, routine early initiation of ACE inhibitor therapy does not appear to improve clinical outcomes up to 3 years after surgery and may actually increase adverse events in the early postoperative period. They feel that ACE inhibitor therapy should be individualized and reassessed over time. Are the results of this study applicable to the vast majority of CABG patients? Can we accurately identify patients who are at low risk of developing future cardiovascular events at the time of CABG surgery? What is the best method of initiating ACE inhibitor therapy in the post-CABG patient, and were these guidelines followed by the IMAGINE investigators? Here, I will attempt to answer these questions as we try to determine the role of ACE inhibitor therapy in the CABG patient.

ACE inhibitors have the potential to benefit CABG patients not only by their antihypertensive effects but also because of their vasculoprotective and antiatherogenic properties. They minimize thrombosis by reducing platelet aggregation and decreasing plasminogen activator-1 and tissue plasminogen activator levels. Endothelial function is preserved by preventing bradykinin breakdown and enhancing nitric oxide production, thus limiting vascular inflammation and oxidative stress, which leads to atherosclerotic plaque formation. Increased levels of ACE have been found in atherosclerotic plaques and saphenous vein grafts in CABG patients. ACE inhibition has been found to reduce restenosis after percutaneous coronary interventions and thus may have a role in decreasing vein graft occlusion after CABG surgery.

Experimental studies have demonstrated the benefits of ACE inhibitors during periods of myocardial ischemia. In a porcine model of coronary occlusion followed by cardioplegic arrest on cardiopulmonary bypass simulating CABG surgery, hearts treated with quinaprilat had significantly reduced infarct size, better recovery of regional wall motion, and better preservation of endothelial function. In another series of experiments using the same porcine model of ischemia-reperfusion on cardiopulmonary bypass, animals were pretreated with quinapril (20 mg) for 7 days before surgery. Quinapril-treated animals required fewer cardiovascular versions for ventricular arrhythmias and had higher wall motion scores, more complete recovery of endothelial function, and smaller infarcts. These results strongly suggested that pretreatment with ACE inhibitors before CABG may minimize ischemic injury.

Several clinical studies have examined the effects of ACE inhibition in the CABG patient. In the Effects of Quinapril on Vascular Angiotensin-Converting Enzyme and Determinants of Ischemia (QUO VADIS) trial, patients were randomized 27 days before CABG to receive either quinapril (40 mg/d) or placebo for 1 year after surgery. Quinapril-treated patients had an 80% reduction in ischemic events (myocardial infarction, stroke, transient ischemic attacks, or recurrence of angina; 18% versus 4%; P=0.04). Quinapril was well tolerated and was not associated with any untoward perioperative hemodynamic events. The Angiotensin-Converting Enzyme Inhibition Post-Revascularization Study (APRES) examined the effects of ramipril in 159 revascularized (130 CABG, 29 percutaneous coronary intervention) normotensive patients with moderately depressed (30% to 50%) ejection fractions. Patients received up to 10 mg of ramipril beginning 5 to 7 days after CABG and 1 to 2 days after percutaneous coronary intervention for 3 years. Ramipril-treated patients had a 58% risk reduction in the composite end point of cardiac death, myocardial infarction, and congestive heart failure (P=0.03). Ramipril also significantly reduced echo-derived end-diastolic and end-systolic volume indexes. Ramipril therapy was well tolerated; no patients had any renal, hemodynamic, or electrolyte complications. These beneficial effects were consistent in all patient groups, regardless of whether CABG or percutaneous transluminal coronary angioplasty was performed. In the Heart Outcomes Prevention Evaluation (HOPE) trial, patients with low to moderate risk for future
cardiovascular events were randomized to ramipril (10 mg) or placebo for 5 years. In this trial, 26% of patients had already received a CABG. Ramipril therapy significantly decreased the combined incidence of MI, stroke, and cardiovascular death by 22%. The beneficial effects of ACE inhibition were evident in multiple subgroups, including men and women, patients of all ages, and those with and without evidence of cardiovascular disease, hypertension, or cerebrovascular disease.

In view of these experimental studies and clinical trials, how can we explain the results reported by Rouleau and coworkers, which failed to show any cardioprotective benefits with ACE inhibitors in this cohort of CABG patients? A major reason is the sole inclusion of a “low-risk” patient cohort. This group is not indicative of the vast majority of patients currently undergoing CABG surgery in whom a high incidence exists of hypertension, diabetes mellitus, reduced ejection fraction, and acute coronary syndromes requiring urgent or emergent surgery. Furthermore, only 5% of all patients screened and only 13% of eligible patients in this trial were actually randomized. Fifty percent of eligible patients were excluded for reasons that are not indicated in the article. The event rates in both groups were extremely low. This reflected the increased use of statins, aspirin, and β-blockers in both groups. All of these agents have been shown to reduce recurrent ischemic events in the post-CABG patient. Hence, the cardioprotective effects of ACE inhibitors in this trial were more likely to be seen after 5 to 10 years rather than 3 to 6 months. The median follow-up for this study was only 2.95 years. Although the incidence of the primary end point was significantly higher in the ACE inhibitor group for the first 3 months (3.2% versus 4.8%; \( P=0.036 \)), no significant difference was observed after 3 months (10.0% versus 10.7%; \( P=0.5 \)). This implies that ACE inhibition actually did confer some degree of cardioprotection after a longer follow-up period.

Patients treated with ACE inhibitors in this trial had a significantly higher incidence of hypotension compared with the placebo group (5.5% versus 12%; \( P<0.001 \)). Although the definition of hypotension is not provided by the authors, this could easily have contributed to the increased incidence of recurrent angina seen within the first 3 months in the ACE inhibitor group. Hypotension was not increased in the HOPE, QUO VADIS, or APRES trial. This difference raises questions as to the methodology used by the authors to institute ACE inhibitors in their study. In our own clinical practice, ACE-inhibitor therapy is initiated only after β-blockers are instituted on the first postoperative day and when systolic blood pressure is \( \geq 100 \) mm Hg. Our preference is to start with either 2.5 mg ramipril or 5 to 10 mg quinapril or lisinopril. Serum creatinine, blood pressure, and signs of increasing cough are carefully monitored. It has been our experience that \( \geq 80\% \) of patients can be discharged on an ACE inhibitor after CABG surgery using this dosing regimen. On discharge, patients are followed up by a visiting nurse and are seen by their primary care physician within 4 weeks. This helps to minimize any episodes of hypotension. Those patients who cannot tolerate an ACE inhibitor in the immediate postoperative period will have the drug started by their primary care physician or the local referring cardiologist over a 3-month period. It is unclear as to how frequently blood pressure was monitored after discharge in this trial. However, the 12% incidence of hypotension reported by the authors in this study has never been observed in our practice.

Although the authors categorized their patients as low risk, all CABG patients have to be recognized as having atherosclerotic disease and endothelial dysfunction; consequently, they are at increased risk for future cardiovascular events. Thus, these patients, similar to the low-risk group in the HOPE trial, will continue to benefit from long-term ACE inhibition. The major issue from this trial is whether ACE inhibition should be instituted in low-risk, elective, normotensive, nondiabetic CABG patients but what the optimal method is to safely initiate and maintain ACE inhibitor therapy in these patients. ACE inhibitors should not be instituted in the immediate postoperative period if systolic blood pressure is \( \leq 100 \) mm Hg or if patients develop hypotension in the hospital after receiving an ACE inhibitor. However, on the basis of data from both experimental and clinical studies, I would urge that all CABG patients receive ACE inhibitors, but with a sensible dosing regimen that minimizes hypotension. Thus, the potential long-term benefits of ACE inhibitors can be achieved in this low-risk but potentially vulnerable group of patients.

Disclosures

None.

References


**Key Words:** Editorials ▪ angiotensin ▪ coronary artery bypass grafting
All Coronary Artery Bypass Graft Surgery Patients Will Benefit From Angiotensin-Converting Enzyme Inhibitors
Harold L. Lazar

Circulation. 2008;117:6-8
doi: 10.1161/CIRCULATIONAHA.107.747337

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/117/1/6

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/