Patterns of Use of Perioperative Angiotensin-Converting Enzyme Inhibitors in Coronary Artery Bypass Graft Surgery With Cardiopulmonary Bypass Effects on In-Hospital Morbidity and Mortality

Benjamin Drenger, MD*; Manuel L. Fontes, MD*; Yinghui Miao, MD, MPH; Joseph P. Mathew, MD; Yaacov Gozal, MD; Solomon Aronson, MD, FCCP; Cynthia Dietzel, MD; Dennis T. Mangano, PhD, MD; for the Investigators of the Ischemia Research and Education Foundation and the Multicenter Study of Perioperative Ischemia Research Group

Background—Despite proven benefit in ambulatory patients with ischemic heart disease, the pattern of use of angiotensin-converting enzyme inhibitors (ACEIs) in coronary artery bypass graft surgery has been erratic and controversial.

Methods and Results—This is a prospective observational study of 4224 patients undergoing coronary artery bypass graft surgery. The cohort included 1838 patients receiving ACEI therapy before surgery and 2386 (56.5%) without ACEI exposure. Postoperatively, the pattern of ACEI use yielded 4 groups: continuation, 915 (21.7%); withdrawal, 923 (21.8%); addition, 343 (8.1%); and no ACEI, 2043 (48.4%). Continuous treatment with ACEI versus no ACEI was associated with substantive reductions of risk of nonfatal events (adjusted odds ratio for the composite outcome, 0.69; 95% confidence interval, 0.52–0.91; \( P = 0.009 \)) and a cardiovascular event (odds ratio, 0.64; 95% confidence interval, 0.46–0.88; \( P = 0.006 \)). Addition of ACEI de novo postoperatively compared with no ACEI therapy was also associated with a significant reduction of risk of composite outcome (odds ratio, 0.56; 95% confidence interval, 0.38–0.84; \( P = 0.004 \)) and a cardiovascular event (odds ratio, 0.63; 95% confidence interval, 0.40–0.97; \( P = 0.04 \)). On the other hand, continuous treatment of ACEI versus withdrawal of ACEI was associated with decreased risk of the composite outcome (odds ratio, 0.50; 95% confidence interval, 0.38–0.66; \( P<0.001 \), and cardiovascular events (\( P<0.001 \) and \( P = 0.005 \), respectively). No differences in in-hospital mortality and cerebral events were noted.

Conclusions—Our study suggests that withdrawal of ACEI treatment after coronary artery bypass graft surgery is associated with nonfatal in-hospital ischemic events. Furthermore, continuation of ACEI or de novo ACEI therapy early after cardiac surgery is associated with improved in-hospital outcomes. (Circulation. 2012;126:261-269.)

Key Words: anesthesia ■ angiotensin-converting enzyme inhibitors ■ cardiopulmonary bypass ■ coronary artery bypass ■ postoperative complications

Mortality from coronary artery bypass (CABG) surgery has become infrequent with an incidence as low as 2%1-2; however, the occurrence of nonfatal cardiovascular events remains unacceptably high.3-5 Over the past decade, several classes of antiischemic agents, including statins, \( \beta \)-blockers, and platelet inhibitors, have emerged as standard therapies for mitigating perioperative cardiovascular complications.6-10

Editorial see p 249
Clinical Perspective on p 269

The renin-angiotensin-aldosterone system (RAAS) becomes hyperactive during and after cardiopulmonary bypass (CPB) and is likely an important mediator of microvascular ischemic injury, as was also demonstrated in ischemia/reperfusion injury and during sepsis.11,12 It is known that
long-term overexposure of tissue angiotensin-converting enzyme (ACE) alters the angiotensin II/bradykinin balance, resulting in endothelial dysfunction. Angiotensin II promotes numerous vascular deleterious effects, including inflammation, thrombosis, apoptosis, atherosclerosis, fibrosis, and plaque rupture. Thus, antagonism of the RAAS with either ACE inhibitors (ACEIs) or angiotensin receptor blockers may afford additive cardioprotection to aspirin and statins. Furthermore, with the intense inflammatory response of the CPB involving platelet activation, the proinflammatory antiinflammatory and antiangiogenic capacity of ACEI may afford protection against cerebrovascular and renal adverse events and reduce other perioperative vascular complications in CABG surgery. Unfortunately, perioperative use of ACEI has been plagued with controversy, primarily because of historical reports linking it to protracted vasoplegia before, during, and after CPB. Consequently, in the setting of surgery, its pattern of practice, both in the United States and internationally, is uncertain, and cessation of ACEI therapy may be as detrimental as statin and renin-angiotensin system blockade withdrawal.

Therefore, the International Multicenter Study on Perioperative Ischemia (McSPI)–Epidemiology II (EPI-II) Research Group sought to prospectively characterize the pattern of perioperative ACEI use in patients having CABG surgery with CPB, to describe related hemodynamic effects, and to determine the association between the timing of ACEI renewal and in-hospital fatal and nonfatal vascular events.

Methods

Study Design

The Ischemia Research and Education Foundation (IREF)/McSPI EPI-II is a prospective and longitudinal study that prospectively enrolled 5436 patients from 72 medical institutions among 17 countries in North America, South America, Europe, the Middle East, and Asia who were admitted for CABG surgery using CPB. After individual Institutional Review Board approval was obtained, each center prospectively enrolled up to 100 patients according to a systematic random sampling scheme and after each patient signed a written informed consent. The methods of this study have been previously described in detail and are briefly summarized here.

Data Collection and Management

For each enrolled patient, independent investigators collected >7500 fields of data; treating physicians were blinded to all research data. Clinical decisions were not controlled by study protocol. Once completed, the case report form was sent to the data coordinating center where the data were examined for completeness and accuracy, with all changes documented before database closure.

Outcomes Measures

All outcomes were prespecified, defined by protocol, and discerned by investigators blinded to treatment group. Preoperative left ventricular dysfunction and staging of congestive heart failure (CHF) were defined in detail by entries in the case report form. Fatal and nonfatal outcomes occurring >48 hours after surgery and during the index hospitalization were classified as cardiac (myocardial infarction [MI], CHF, or death resulting from cardiac causes), cerebral (stroke, encephalopathy, or death resulting from stroke), renal (dysfunction, failure), or other (such as gastrointestinal, infectious, pulmonary, or death resulting from any other cause). The primary outcome of the study was defined as the composite outcome of the cardiac, cerebral, and renal events and in-hospital mortality.

Myocardial ischemia was defined as postoperative angina or ischemia detected by the clinician. The diagnosis of MI required the development of either new Q waves or new persistent ST-segment or T-wave changes associated with an elevation of creatine kinase-MB isoenzyme values or autopsy evidence of acute MI. The diagnosis of heart failure after surgery required signs and symptoms by physical examination and monitoring devices, the use of continuous nonroutine inotropic support for at least 24 hours, the use of a ventricular assist device, or autopsy evidence of heart failure. Cerebral outcomes were classified as clinically diagnosed stroke or encephalopathy or computed tomography, magnetic resonance imaging, or autopsy evidence of a focal or global defect. Stroke was defined by new onset of stroke, stupor, coma, encephalopathy, transient ischemic attack, or seizures in the postoperative period. The National Institute of Health Stroke Scale was used to assess stroke severity. Renal dysfunction was defined as a postoperative serum creatinine level of at least 2.0 mg/dL (177 μmol/L) accompanied by an increase of at least 0.7 mg/dL (62 μmol/L) from baseline. Postoperative creatinine records were collected at 8 different time points, and the maximum value was extracted. Renal failure was defined as dysfunction requiring dialysis or autopsy evidence of renal failure. Death was defined as death before hospital discharge.

Medications of the ACEI and angiotensin receptor blocker groups taken by the patients included benazepril, captopril, enalapril, fosinopril, lisinopril, losartan, moexipril, perindopril, quinapril, ramipril, and spirapril, and others. These were recorded and grouped by class in the case report form. Timing of the last dose before surgery and the timing of initiation of ACEI therapy after surgery were recorded, as well as all the antischemic drugs and other medications. For an outcome to be counted as an event, it must have occurred after the administration or withdrawal of the drug. Blood pressure measurements during surgery included highest and lowest values before, during, and after CPB (systolic and mean blood pressures every 15 minutes for the first 4 hours postoperatively and every hour in the remaining first 24 hours). For patients with pulmonary artery catheter, derived data, including cardiac output, were recorded hourly in the intensive care unit (ICU).

Study Sample

In all, 5436 patients were enrolled in the EPI-II study. We excluded 371 for the following reasons: 32 withdrew from the study before surgery; 2 died before surgery; 97 did not undergo surgery or surgery was rescheduled; 132 did not undergo CPB; 11 were enrolled in another clinical trial; and 97 had incomplete data. Of the remaining 5065 patients to be evaluated, 841 were excluded from the study: 555 had valve surgical procedure, 147 had other cardiac surgical procedures, 119 had other noncardiac surgical procedures, 61 had concurrent emergent surgery, and 43 died in the first 48 postoperative hours (15 had emergent surgery or another surgery besides CABG; of the 28 patients who had only CABG surgery, 17 were not on ACEI and 11 were on ACEI preoperatively). Thus, 4224 patients remained, including 1838 treated preoperatively with ACEI and 2386 not treated (Figure 1). After surgery, 4 groups emerged: a continuation group consisting of patients who were on ACEI preoperatively and postoperatively; a withdrawal group comprising patients who were taking ACEI preoperatively but not postoperatively; an addition group consisting of patients who were not on ACEI preoperatively but had it added postoperatively; and a no ACEI group that included patients who did not have any exposure to ACEI.

Statistical Methods

Baseline characteristics and operative factors were compared between patients receiving and those not receiving ACEI preoperatively. Continuous variables were summarized with medians and the 25th and 75th percentiles, and the Wilcoxon rank-sum test was used for comparisons. Categorical data were summarized by frequencies and percentages, and the χ² test or Fisher exact test was applied to compare patients between study groups.

We used the propensity score adjustment method to control for confounding. Applying nonparsimonious logistic regression models, we developed propensity score as the probability of receiving ACEI.
treatment (versus no treatment) given all the baseline variables, including demographic, medical history, surgical, intraoperative, and early postoperative characteristics, as well as treatment selection covariates (see the online-only Data Supplement). The area under the receiver-operating characteristic curve, referred to as the C index, was used to assess the discriminate power of the propensity score. The propensity score of receiving ACEI treatment was calculated in 3 subgroups: no ACEI and ACEI continuation, ACEI continuation and withdrawal, and no ACEI and ACEI addition, separately. The derived propensity scores were then used for multivariable covariate adjustment, together with the ACEI treatment indicator variables and Acute Physiology and Chronic Health Evaluation II (APACHE II)26 Acute Physiology score (partial), which was used to determine the severity of illness within the first 24 hours after each patient was admitted to the ICU. The C index was 0.80 for the propensity score model of ACEI continuation versus no ACEI, 0.71 for ACEI continuation versus withdrawal; and 0.76 for ACEI addition versus no ACEI.

Kaplan–Meier survival analysis was used to examine the differences in unadjusted 30-day event-free status (in-hospital) among the 4 ACEI treatment groups, with the log-rank test used for comparisons. The multivariable logistic regression analysis of the composite outcome included the following predictor variables: demographic, medical history, surgical/intraoperative/early postoperative factors, risk indexes, and ACEI treatment groups. A stepwise (backward and forward) variable selection procedure was applied to identify variables associated with the composite outcome. Model entry and retention criteria were set at $P < 0.20$ and $P < 0.05$, respectively.

All statistical analyses were performed with SAS statistical software version 8.2 (SAS Institute Inc, Cary, NC). Statistical significance was set at $P < 0.05$ (2 tailed).

Results

The demographic and surgical characteristics of patients presenting on ACEI therapy versus no ACEI therapy are presented in Table 1.27 Patients who were not treated with ACEI compared with patients on ACEI treatment before surgery had fewer preoperative cardiovascular risk factors such as hypertension, CHF, and MI and other diseases such as renal disease, diabetes mellitus, and pulmonary and liver disease. Intraoperative clinical and surgical characteristics were similar between the 2 groups except for the duration of CPB and cross-clamp times, which were prolonged in the ACEI group ($P < 0.001$).

ACEI Therapy and Clinical Outcomes

Table 2 presents adjusted odds ratio for fatal and nonfatal cardiovascular outcomes for group comparisons. Results of the multivariable analysis of composite outcomes including ACEI treatment groups (continuation versus no ACEI, continuation versus withdrawal; addition versus no ACEI) are presented in Table 3.

ACEI Continuation Versus No ACEI

After adjustments for both propensity score and APACHE II, continuous treatment with ACEI was associated with a 31% ($P = 0.009$) lower odds of developing the composite outcome and a 36% ($P = 0.006$) lower odds of a cardiovascular event (38% and 37% lower in CHF and MI; $P = 0.05$ and $P = 0.03$, respectively). Additionally, when we included continuous ACEI versus No ACEI treatment as a variable in our multivariable regression analysis (Table 3), it emerged as an independent correlate of composite outcomes (adjusted OR [95% CI], 0.58 [0.44–0.76]; $P < 0.001$).

No significant differences in surgical characteristics were noted. During the first 24 hours in the ICU, the 2 groups had similar median cardiac outputs and a small difference in median systolic blood pressure of 5 mm Hg (Table 4), lower in the ACEI continuation group ($P < 0.001$), whereas the use of ≥2 nonroutine vasopressors was twice as high compared with the no ACEI group ($P < 0.001$).

ACEI Continuation Versus Withdrawal

Half of the patients (923 of 1838) treated with ACEI preoperatively had it stopped postoperatively. Continuous
Table 1. Baseline Characteristics of 4224 Study Patients by Angiotensin-Converting Enzyme Inhibitor Treatment Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients Not Receiving ACEI on Admission or Preoperatively (n=2386)</th>
<th>Patients Receiving ACEI on Admission or Preoperatively (n=1838)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63.5</td>
<td>64.5</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Interquartile range 56.8–70.1</td>
<td>56.9–71.2</td>
<td></td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>419 (17.6)</td>
<td>377 (20.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>1269 (53.2)</td>
<td>932 (50.7)</td>
<td>0.11</td>
</tr>
<tr>
<td>Congestive heart failure with hospitalization</td>
<td>109 (4.6)</td>
<td>237 (12.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction within 90 d</td>
<td>253 (10.6)</td>
<td>402 (21.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dysrhythmia</td>
<td>336 (14.1)</td>
<td>390 (21.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1395 (58.5)</td>
<td>1456 (79.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Valve disease</td>
<td>143 (6.0)</td>
<td>191 (10.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CABG</td>
<td>130 (5.4)</td>
<td>101 (5.5)</td>
<td>0.95</td>
</tr>
<tr>
<td>Neurologic dysfunction (stroke/TIA)</td>
<td>210 (8.8)</td>
<td>226 (12.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Syncope</td>
<td>130 (5.4)</td>
<td>129 (7.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Creatinine on admission (maximum) &gt;1.3 mg/dL</td>
<td>305 (12.8)</td>
<td>371 (20.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal disease</td>
<td>297 (12.5)</td>
<td>354 (19.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dialysis</td>
<td>12 (0.5)</td>
<td>4 (0.2)</td>
<td>0.14</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>347 (14.5)</td>
<td>364 (19.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>596 (25.0)</td>
<td>692 (37.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia (without treatment)</td>
<td>516 (21.6)</td>
<td>387 (21.1)</td>
<td>0.65</td>
</tr>
<tr>
<td>Surgical, intraoperative, or early postoperative factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bypass pump flow, n (%)</td>
<td></td>
<td></td>
<td>0.91</td>
</tr>
<tr>
<td>Pulsatile</td>
<td>328 (13.7)</td>
<td>255 (13.9)</td>
<td></td>
</tr>
<tr>
<td>Nonpulsatile</td>
<td>2058 (86.3)</td>
<td>1583 (86.1)</td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary bypass time, min</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median</td>
<td>89</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Interquartile range 69–112</td>
<td></td>
<td>74–118</td>
<td></td>
</tr>
<tr>
<td>Cross-clamp time, minute</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median</td>
<td>54</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Interquartile range 40–71</td>
<td></td>
<td>42–74</td>
<td></td>
</tr>
<tr>
<td>Fluid intake intraoperative to RDOS, mL</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median</td>
<td>7170</td>
<td>7499</td>
<td></td>
</tr>
<tr>
<td>Interquartile range 5850–8717</td>
<td></td>
<td>5950–9260</td>
<td></td>
</tr>
<tr>
<td>Medication, nonroutine— inotropes/vasoconstrictors</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>intraoperative or on RDOS</td>
<td>1117 (46.8)</td>
<td>1119 (65.2)</td>
<td></td>
</tr>
<tr>
<td>Intubation and re-intubation ≥24 h (within 48 h)</td>
<td>272 (11.5)</td>
<td>322 (17.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Assist device use for low cardiac output or ischemic or angina intraoperative or on RDOS</td>
<td>40 (1.7)</td>
<td>47 (2.6)</td>
<td>0.05</td>
</tr>
<tr>
<td>Risk index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EuroSCORE</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Interquartile range 1–5</td>
<td></td>
<td>2–6</td>
<td></td>
</tr>
<tr>
<td>APACHE II—Acute Physiology Score (partial)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Interquartile range 3–6</td>
<td></td>
<td>3–7</td>
<td></td>
</tr>
</tbody>
</table>

ACEI indicates angiotensin-converting enzyme inhibitor; CABG, coronary artery bypass grafting; TIA, transient ischemic attack; RDOS, remaining day of surgery; EuroSCORE, European System for Cardiac Operative Risk Evaluation; and APACHE II, Acute Physiology and Chronic Health Evaluation II. The 2-group comparison is between preoperative ACEI treatment and no preoperative ACEI treatment.
Perioperative ACEI use was associated with in-hospital fatal outcome (P=0.004), driven entirely by a 37% lower odds in composite outcome of ACEI was associated with a 44% lower odds in composite outcome. After propensity score and APACHE II adjustments, addition of ACEI therapy postoperatively de novo was related to a lowering of odds in overall composite outcomes by nearly one half; and notably, withdrawal of ACEI treatment after surgery was associated with significant rise in odds of cardiac and renal ischemic events.

In ambulatory patients with coronary artery disease, treatment with ACEI is common and associated with improvement in morbidity and fatal vascular outcomes. Whether perioperative use of ACEI confers acute and clinically relevant vascular protection is an important question that we sought to answer in the present study. Also of interest was the association of immediate ACEI withdrawal after CABG surgery. Forty-three percent of our patients were receiving ACEI preoperatively, which was stopped the day before surgery; however, half of this cohort was subjected to immediate withdrawal of ACEI therapy postoperatively. The use of ACEI was associated mostly with better cardiac outcome, with a nearly 40% reduction in odds of both postoperative CHF and MI. Overall, we observed a 31% reduction of odds in the composite end point of cardiac death, acute MI, or CHF. A follow-up of 2.5 years was associated with a 58% reduction in vascular, and renal ischemic events.

ACEI indicates angiotensin-converting enzyme inhibitor; OR, odds ratio; and CI, confidence interval.

*Models were adjusted for propensity score of ACEI treatment and Acute Physiology and Chronic Health Evaluation II (APACHE II) Acute Physiology Scores (partial). It was possible that >1 outcome occurred in the same patient. Fifty-eight covariates of demographics, medical history, and preoperative, intraoperative, and/or early postoperative factors were included in the propensity score model for ACEI treatment (see the online-only Data Supplement). APACHE II–Acute Physiology score (partial) was calculated by 9 physiological variables: temperature (rectal), mean arterial pressure, heart rate, oxygenation, arterial pH, serum sodium, serum potassium, serum creatinine, and hematocrit.

In a cohort of patients requiring coronary revascularization, Kjoller-Hansen et al also found that the addition of oral ramipril 5 to 7 days after surgery and continued for a medium follow-up of 2.5 years was associated with a 58% reduction in the composite end point of cardiac death, acute MI, or CHF. In a double-blind trial, Oostera et al in the QUINapril On Vascular ACE and Determinants of Ischemia (QUO VADIS) study used oral quinapril (40 mg/d) 1 month before CABG surgery and postoperatively for 1 year and reported a significant reduction in recurrent angina. According to our find-
Table 3. Multivariable Logistic Regression for the Composite Outcome in 4224 Study Patients

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuation vs no ACEI</td>
<td>0.58 (0.44–0.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Addition vs no ACEI</td>
<td>0.58 (0.39–0.85)</td>
<td>0.006</td>
</tr>
<tr>
<td>Withdrawal vs no ACEI</td>
<td>1.70 (1.36–2.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Continuation vs withdrawal</td>
<td>0.58 (0.39–0.85)</td>
<td>0.006</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>1.28 (1.03–1.59)</td>
<td>0.03</td>
</tr>
<tr>
<td>History of carotid disease</td>
<td>1.49 (1.14–1.93)</td>
<td>0.003</td>
</tr>
<tr>
<td>History of renal disease</td>
<td>1.39 (1.08–1.80)</td>
<td>0.01</td>
</tr>
<tr>
<td>Warfarin in the past week of admission</td>
<td>1.74 (1.22–2.47)</td>
<td>0.002</td>
</tr>
<tr>
<td>Congestive heart failure on admission or preoperative</td>
<td>1.79 (1.20–2.66)</td>
<td>0.004</td>
</tr>
<tr>
<td>Creatinine on admission (maximum)</td>
<td>&gt;1.3 mg/dL 1.48 (1.15–1.90)</td>
<td>0.002</td>
</tr>
<tr>
<td>Intubation and reintubation (within 48 h)</td>
<td>2.32 (1.83–2.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Assist device use for low cardiac output, ischemic, or angina intraoperatively or on RDOS</td>
<td>3.19 (1.78–5.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fluid intake intraoperative to RDOS</td>
<td>1.009 (1.005–1.012)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>1.07 (1.03–1.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APACHE II Acute Physiology score (partial)</td>
<td>1.05 (1.01–1.09)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; ACEI, angiotensin-converting enzyme inhibitor; RDOS, remaining day of surgery; EuroSCORE, European System for Cardiac Operative Risk Evaluation; and APACHE II, Acute Physiology and Chronic Health Evaluation II. Excluded were 502 patients with missing values for at least 1 covariate. The Hosmer–Lemeshow goodness-of-fit $\chi^2$ test statistic was 7.97 ($P=0.44$). The C index for the model was 0.72. Direct comparison of ACEI treatment groups by contrast functions on model parameters demonstrated decreased risk with ACEI continuation compared with ACEI withdrawal (odds ratio, 0.58; 95% CI, 0.39–0.85; $P=0.006$). Odds ratio for fluid intake intraoperative to RDOS was calculated per 100-mL increment. Odds ratio of EuroSCORE was calculated per 1-unit increment. Odds ratio of APACHE II Acute Physiology score (partial) was calculated per 1-unit increment.

ings, ACEI therapy in cardiac surgery is most valuable when it is provided perioperatively, and importantly, its immediate withdrawal after surgery can be associated with poor outcomes. In comparing the continuation group with the immediate withdrawal cohort, we observed a 50% reduction of odds in overall complications, including a 61% and 46% reduction in CHF and MI, respectively. Furthermore, ACEI withdrawal was related to increased odds of renal event by 113%.

Studies on perioperative use of ACEI in cardiac surgery have yielded both promising and conflicting messages. Earlier reports suggested marked vasoplosia after the induction of anesthesia and in the setting of CPB necessitating greater vasopressor and fluid resuscitation. As a result, withdrawal of ACEI therapy before cardiac surgery became a common practice. Subsequent studies addressing such hemodynamic and other relevant clinical effects have since challenged this view. Pigott et al found that regular withdrawal of ACEI preoperatively resulted in higher mean arterial pressure and increased need for antihypertensive therapy in the early period after CPB. Licker et al also could not demonstrate clinically significant vasoplosia in patients receiving long-term ACEI. Nevertheless, a recent report from the United Kingdom found that the majority of surgeons there continue to opine that the use of ACEI in cardiac surgery leads to hemodynamic instability and an increased need for fluids and vasoactive drugs. Of interest, our cohort of patients on continuous ACEI therapy did have higher requirement for vasopressor support after CPB; however, there were no appreciable differences in hemodynamic parameter or need for assist devices for a low-output state either intraoperatively or postoperatively between this group and the no ACEI treatment group.

Decisions prompting more frequent therapy with cardiovascular support in the continuous ACEI group may very well have been influenced by notable differences in EuroSCORE and APACHE II ($P<0.001$), both suggestive that this group had a higher operative risk. In part, the decision may be indicative of the inherent bias in selection of inotropes and vasopressors after CPB, which is both center specific and clinician specific. However, we attempted to control for such potential practice bias by excluding the “routine” use of inotropes and vasopressors and by including the need for ≥2 vasoactive and cardioactive agents. As demonstrated in Table 4, no clinically significant differences in blood pressure, cardiac output, and extubation times were noted among the groups.

The RAAS is an important contributor to pathological vascular remodeling. Thus, inhibition of the RAAS with ACEIs alone or in combination with angiotensin receptor blockers should be an effective modality for lowering perioperative cardiovascular risks. More recently, the benefits of ACEIs appear to be systemic and independent of its blood pressure effects, providing cerebrovascular and renovascular protection. Because of these secondary actions of ACEIs (endothelial protective effects), there has been a shift in therapeutic approach from the initial pharmacological-antihypertensive to a therapeutic approach having a biological (nonhemodynamic) underpinning.

CPB, a potent mediator of inflammation, is associated with marked activation of the RAAS. These, together with activation of the sympathoadrenal and hemostatic pathways, may provide the groundwork for microvascular injury and organ dysfunction. Thus, inhibition of ACE can mitigate angiotensin production and, importantly, may improve microcirculatory perfusion via the aforementioned mechanisms. Additionally, ACEI added to cardioplegia solution has been shown to directly reduce ischemia/reperfusion injury, to reduce myocardial ACE activity, and to provide antiarrhythmic effects.

Clinical Implications

In this large multicenter, international study, we provide new and important information on the practice pattern of ACEI use in cardiac surgery. The associated improvement in outcomes with ACEI therapy was not surprising given the well-known benefits of blocking the RAAS; however, it is alarming to learn that clinicians chose to immediately discontinue ACEI therapy in nearly 50% of patients after cardiac surgery.
surgery. This pattern of practice was associated with major vascular complications. Immediate withdrawal of ACEI therapy may be particularly harmful in the context of cardiac surgery because an abrupt rebound in ACE activity may further compromise microcirculatory flow. Westendorp et al. studied the effects of ACEI therapy in the setting of acute MI in rats and found that the endothelium-dependent vasorelaxation dissipates rapidly after ACEI withdrawal. Kennedy et al. and Wallace et al. addressed the consequences of drug withdrawal postoperatively and in a general surgical unit and provided evidence that withdrawal of regular cardiovascular medicines adds to the risk of the surgery and complicates outcomes.

**Limitations**

Our prospective study may be limited by a number of factors, including its observational design and the absence of protocols to guide clinical management. However, with nearly 2000 patients in each group (ACEI and no ACEI), there is sufficient power to investigate both morbid and fatal vascular complications. Importantly, the data are robust, were prospectively gathered, and represent an international cohort from 70 institutions. This international experience makes the data very relevant, because use of ACEI has increased in the last decade although its pattern of withdrawal remains high.

Another relevant criticism is the significant difference in clinical characteristics between the ACEI group and the no ACEI group, which suggests a higher operative risk profile (Euro-SCORE) for the ACEI-treated group. To compensate for the large variability in patient characteristics, the associations between ACEI therapy and outcomes were performed with adjustments for propensity score, Euro-SCORE, and APACHE II (modified) score. The APACHE II score was used to determine the severity of illness within the first 24 hours after each patient was admitted to the ICU. Finally, we cannot account for the clinical rational that led to withdrawal of ACEI therapy in nearly half of the patients. The groups had similar cardiac outputs in the ICU and clinically similar systolic blood pressure, extubation times, and need for nonroutine inotropes (less for the no ACEI group), although there was a striking difference in use of assist devices and in transfusion of red blood cells in the withdrawal group intraoperatively.

**Conclusions**

Our multicenter, multinational study suggests that in patients undergoing CABG surgery with CPB, continuation of ACEI...
therapy early after surgery or adding ACEI de novo postoperatively can be associated with a marked improvement in cardiovascular and renal outcomes. Conversely, a practice of withdrawing of ACEI treatment postoperatively is associated with poor in-hospital fatal and nonfatal outcomes.

**Source of Funding**
Support was provided by a grant from the IREF.

**Disclosures**
None.

**References**


CLINICAL PERSPECTIVE

Despite significant improvement in both surgical and medical management of coronary artery bypass graft patients, many experience significant perioperative morbidity that adversely affects quality of life and length of hospitalization and increases resource use. Angiotensin-converting enzyme inhibitors (ACEIs) have been proven effective in the care of cardiovascular patients with hypertensive heart disease and congestive heart failure; however, effect of ACEI on survival in patients undergoing coronary artery bypass graft surgery is equivocal. Unfortunately, ACEI treatment is usually held up before coronary artery bypass graft, primarily because of historical reports linking it to hemodynamic instability during the perioperative period and a larger need for vasoactive drug use and fluid administration. To address these issues, we designed a prospective, international, multi-institutional study that allowed determination of the impact of the current practice pattern of ACEI use on morbidity and mortality after coronary artery bypass graft surgery. We showed that continuation of ACEI therapy early after surgery or adding ACEI de novo postoperatively can be associated with marked improvement in cardiovascular and renal outcomes. Conversely, a practice of withdrawing ACEI treatment postoperatively is associated with poor in-hospital nonfatal outcomes. The associated improvement in outcomes with ACEI therapy was not surprising, given the well-known benefits of blocking the renin-angiotensin-aldosterone system; however, it is alarming to learn that clinicians chose to acutely discontinue ACEI therapy in nearly 50% of patients after cardiac surgery. The present work confirms that acute withdrawal of ACEI therapy may be particularly harmful in the context of cardiac surgery, and attention to restore ACEI therapy soon after operation should be encouraged.
Patterns of Use of Perioperative Angiotensin-Converting Enzyme Inhibitors in Coronary Artery Bypass Graft Surgery With Cardiopulmonary Bypass: Effects on In-Hospital Morbidity and Mortality

Benjamin Drenger, Manuel L. Fontes, Yinghui Miao, Joseph P. Mathew, Yaacov Gozal, Solomon Aronson, Cynthia Dietzel, Dennis T. Mangano and the Multicenter Study of Perioperative Ischemia Research Group

_Circulation_. 2012;126:261-269; originally published online June 19, 2012;
doi: 10.1161/CIRCULATIONAHA.111.059527

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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/126/3/261

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2012/06/18/CIRCULATIONAHA.111.059527.DC1

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/
The IREF is an independent nonprofit foundation, formed in 1987, that develops clinical investigators via observational studies and clinical trials addressing ischemic injury of the heart, brain, kidney, and gastrointestinal tract. The IREF provided all funding for execution of the study, collection of the data, and analysis and publication of the findings. The Multicenter Study of Perioperative Ischemia Research Group, formed in 1988, is an association of 160 international medical centers located in 23 countries organized through and supported by grants from the IREF.

The following institutions and persons coordinated the Multicenter Study of Perioperative Ischemia Research Group EPI-II study. Study Chairman—D. Mangano; Senior Editors—J. Levin, L. Saidman; Study Design and Analysis Center: Ischemia Research and Education Foundation—P. Barash, C. Dietzel, A. Herskowitz, K. Huang, Y. Miao, I. C. Tudor, S. Wang, Y. Weng; Editorial/Administrative Group—D. Beatty, I. Lei, B. Xavier.

The following institutions and persons participated in the McSPI EPI-II Study. Centers and investigators: United States—University of Chicago, Weiss Memorial Hospital—S. Aronson; Beth Israel Hospital—M. Comunale; Massachusetts General—M. D'Ambra; University of Rochester — M. Eaton; Baystate Medical Center—R. Engelman; Baylor College of Medicine—J. Fitch; Duke Medical Center—K. Grichnik; UTHSCSA-Audie Murphy VA, UTHSCSA-University Hospital—C. B. Hantler; St. Luke's Roosevelt Hospital—Z. Hillel; New York University Medical Center—M. Kanchuger, J. Ostrowski; Stanford University Medical Center—C. M. Mangano; Yale University School of Medicine—J. Mathew, M. Fontes, P. Barash; University of Wisconsin—M. McSweeney, R. Wolman; University of Arkansas for Medical Sciences—C. A. Napolitano; Discovery Alliance, Inc.—L. A. Nesbitt; VA Medical Center, Milwaukee—N. Nijhawan; Texas Heart Institute, Mercy Medical Center—N. Nussmeier; University of Texas Medical School, Houston—E. G. Pivalizza; University of Arizona—S. Polson;
Emory University Hospital—J. Ramsay; Kaiser Foundation Hospital—G. Roach;
Thomas Jefferson University Hospital, MCP Hahnemann University Hospital—
N. Schwann; VAMC Houston—S. Shenaq; Maimonides Medical Center—K. Shevde;
Mt. Sinai Medical Center—L. Shore-Lesserson, D. Bronheim; University of Michigan—
J. Wahr; University of Washington—B. Spiess, I. Wright; VA Medical Center, S. F.—A.
Wallace; Austria—University of Graz—H. Metzler; Canada—University of British
Columbia—D. Ansley, J. P. O’Connor; The Toronto Hospital—D. Cheng; Laval
Hospital, Quebec—D. Côte; Health Sciences Centre-University of Manitoba—P. Duke;
University of Ottawa Heart Institute—J. Y. Dupuis, M. Hynes; University of Alberta
Hospital—B. Finegan; Montreal Heart Institute—R. Martineau, P. Couture; St.
Michael’s Hospital, University of Toronto—D. Mazer; Colombia—Fundacion Clinico
Shaio—J. C. Villalba, M. E. Colmenares; France—CHRU Le Bocage—C. Girard; Hospital
Pasteur—C. Isetta; Germany—Universität Wrzburg—C. A. Greim, N. Roewer;
Universität Bonn—A. Hoeft; University of Halle—R. Loeb, J. Radke; Westfalische
Wilhelms-Universität Munster—T. Mollhoff; Universität Heidelberg—J. Motsch, E.
Martin; Ludwig-Maximillians Universität—E. Ott; Universität Krankenhaus
Eppendorf—J. Scholz, P. Tonner; Georg-August Universität Göttingen—H. Sonntag;
Ludwig-Maximilians Universität (Department of Cardiac Surgery)—P. Ueberfuhr;
Hungary—Orszagos Kardiologiai Intezet—A. Szekely; India—Escorts Heart Institute—
R. Juneja; Apollo Hospital—G. Mani; Israel—Hadassah University Hospital—B.
Drenger, Y. Gozal, E. Elami; Italy—San Raffaele Hospital, Universita de Milano—C.
Tommasino; Mexico—Instituto Nacional de Cardiologia—P. Luna; The Netherlands—
University Hospital Maastricht—P. Roekaerts, S. DeLange; Poland—Institute of
Cardiology—R. Pfitzner; Romania—Institute of Cardiology—D. Filipescu; Thailand—
Siriraj Hospital—U. Prakanrattana; United Kingdom—Glenfield Hospital—D. J. R.
Duthie; St. Thomas’ Hospital—R. O. Feneck; The Cardiothoracic Centre, Liverpool—
M. A. Fox; South Cleveland Hospital—J. D. Park; Southampton General Hospital—D.
Smith; Manchester Royal Infirmary—A. Vohra; Papworth Hospital— A. Vuylsteke, R.
D. Latimer.
Appendix 2.

58 Propensity Score Covariates for Preoperative and/or Postoperative ACEI Therapy:

Demographics (7 Variables)

Age over 60 and per 5yr thereof and over 80
Female gender
Private insurance
Ethnicity–African American or Hispanic or American Indian
Education–Some college (at least)
Known history of IV drug use
Known history of alcohol abuse

Medical History (18 Variables)

Unstable angina
Congestive heart failure
Myocardial infarction
Dysrhythmia
Hypertension
Valve disease
Neurologic dysfunction (stroke or transient ischemic attack)
Carotid disease
Syncope
Pulmonary disease
Renal disease
Diabetes
Peripheral vascular disease
Hematologic disorder
CABG surgery
Other non-cardiac surgery
Noncoronary angioplasty/stent
Warfarin in the past week of admission

**Admission/Preoperative Factor (13 Variables)**
Intra-aortic balloon pump
Congestive heart failure
Pulse pressure
Creatinine (maximum) > 1.3 mg/dL
Medications– Antiarrhythmics
Medications–Anticoagulants
Medications–Bronchodilators
Medications–Calcium Channel Blockers
Medications–Diuretics
Medications–Inotropes/Vasoconstrictors
Medications–Peripheral vasodilators
Medications–Antithrombotics
Medications–Electrolyte Supplements

**Surgical/Intraoperative/Early Postoperative Factor (20 Variables)**
Urgent surgery
Use PA Catheter
Cardioplegia

Pump flow bypass techniques (pulsatile vs. nonpulsatile)

Pump type bypass techniques (roller vs. centrifugal)

Oxygenator type bypass techniques (bubble vs. membrane)

Number of bypass grafts

Cardiopulmonary bypass time

Intraoperative transfusion of red blood cell

Intraoperative transfusion of fresh frozen plasma

Intraoperative transfusion of platelets

Mean arterial pressure (maximum) in the first 24 hours after ICU arrival

Intubation and/or re-intubation ≥ 24 hours (within 48 hours after the beginning of surgery)

Intraoperative–Postoperative prior to the 1st occurrence of the composite outcome: Use assist

device for low cardiac output/angina/ischemia

Intraoperative– Postoperative prior to the 1st occurrence of the composite outcome:
Medications–

Beta Blockers

Intraoperative– Postoperative prior to the 1st occurrence of the composite outcome:
Medications–

Calcium Channel Blockers

Intraoperative– Postoperative prior to the 1st occurrence of the composite outcome:
Medications–

Diuretics

Intraoperative– Postoperative prior to the 1st occurrence of the composite outcome:
Medications–
2 or more simultaneous Inotropes

Postoperative prior to the 1st occurrence of the composite outcome: Medications–Statins

Intraoperative–remaining day of surgery: fluid intake