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Cardiovascular Surgery

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

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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; $P<0.001$), as well as a decrease in cardiac and renal 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, β-blockers, and platelet inhibitors, have emerged as standard therapies for mitigating perioperative cardiovascular complications.[6–10]

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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

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long-term overexposure of tissue angiotensin-converting enzyme (ACE) alters the angiotensin II/bradykinin balance, resulting in endothelial dysfunction.[13,14] Angiotensin II promotes numerous vascular deleterious effects, including inflammation, thrombosis, apoptosis, atherosclerosis, fibrosis, and plaque rupture.[15] Thus, antagonism of the RAAS with either ACE inhibitors (ACEIs) or angiotensin receptor blockers may afford additive cardioprotection to aspirin and statins.[16] Furthermore, with the intense inflammatory response of the CPB involving platelet activation, the prophylactic antiinflammatory and antiaggregate capacity of ACEI may afford protection against cerebrovascular[13,17,18] and renal[19,20] 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.[21–23] 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 β-blocker withdrawal.[24,25] 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.[9]

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).[9] 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.[4,6,9] 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 antiischemic 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 χ^2 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
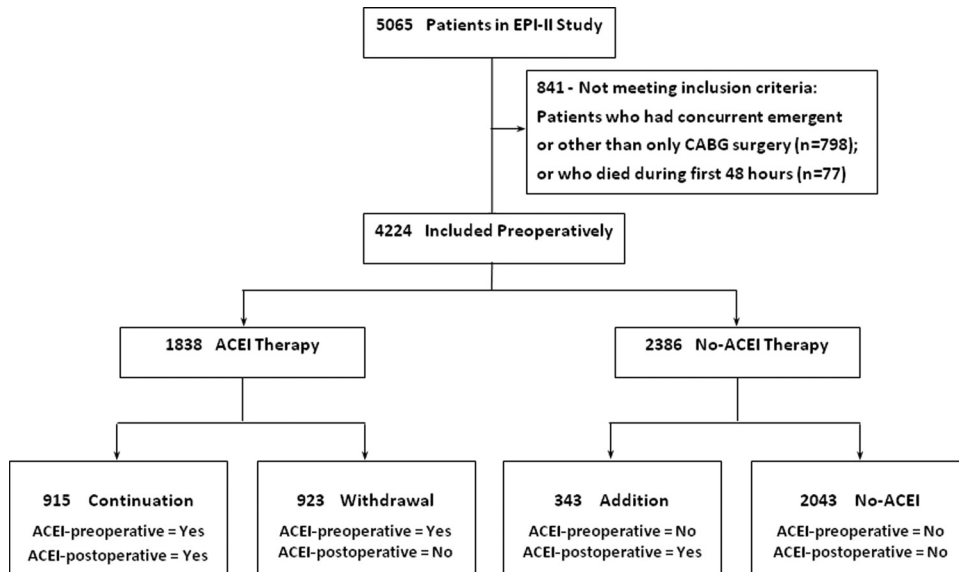
Figure 1. Diagram of patient enrollment through the study. For patients who had postoperative outcome events, postoperative angiotensin-converting enzyme inhibitor (ACEI) therapy was defined as postoperative ACEI medication before or on the same day as the occurrence of the first postoperative composite outcome; for patients who did not have postoperative outcome events, postoperative ACEI therapy was defined as ACEI treatment after coronary artery bypass graft (CABG) surgery. EPI-II indicates International Multicenter Study on Perioperative Ischemia (McSPI)–Epidemiology II.

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 $P \leq 0.20$ 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**

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

ACEI indicates angiotensin-converting enzyme inhibitor; CABG, coronary artery bypass grafting; TIA, transient ischemic attack; RDOS, remaining day of surgery; EuroSCORE[27], 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.

Table 2.   Adjusted Effect of Angiotensin-Converting Enzyme Inhibitor Treatment on Outcome Events

Outcome Event	Effect of ACEI Treatment: Continuation vs No ACEI			Effect of ACEI Treatment: Continuation vs Withdrawal			Effect of ACEI Treatment: Addition vs No ACEI		
	Incidence of Outcome in the No ACEI Group (n=1765), n (%)	Adjusted OR (95% CI)*	Incidence of Outcome in the Continuation Group (n=798), n (%)	P	Adjusted OR 95% CI)*	Incidence of Outcome in the Withdrawal Group (n=764), n (%)	P	Adjusted OR (95% CI)*	Incidence of Outcome in the Addition Group (n=311), n (%)	P
Composite outcome	249 (14.1)	0.69 (0.52–0.91)	102 (12.8)	0.009	0.50 (0.38–0.66)	215 (28.1)	<0.001	0.56 (0.38–0.84)	36 (11.6)	0.004
In-hospital death	15 (0.8)	0.95 (0.41–2.22)	12 (1.5)	0.91	0.63 (0.29–1.35)	23 (3.0)	0.23	1.49 (0.53–4.19)	6 (1.9)	0.45
Cardiovascular event	192 (10.9)	0.64 (0.46–0.88)	69 (8.7)	0.006	0.44 (0.32–0.61)	171 (22.4)	<0.001	0.63 (0.40–0.97)	28 (9.0)	0.04
Congestive heart failure	87 (4.9)	0.62 (0.39–0.99)	32 (4.0)	0.05	0.39 (0.26–0.61)	102 (13.4)	<0.001	0.62 (0.34–1.14)	14 (4.5)	0.13
Myocardial infarction	121 (6.9)	0.63 (0.42–0.95)	40 (5.0)	0.03	0.54 (0.36–0.82)	86 (11.3)	0.004	0.61 (0.35–1.06)	16 (5.1)	0.08
Cerebrovascular event	30 (1.7)	1.26 (0.67–2.38)	23 (2.9)	0.47	0.62 (0.36–1.08)	46 (6.0)	0.09	0.76 (0.33–1.75)	8 (2.6)	0.51
Renal event	43 (2.4)	0.71 (0.40–1.27)	25 (3.1)	0.25	0.47 (0.28–0.79)	59 (7.7)	0.005	0.57 (0.24–1.36)	8 (2.6)	0.20

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.

treatment with ACEI was associated with substantive lower odds of developing a composite outcome and a cardiovascular event (Tables 2 and 3). On the other hand, the withdrawal group showed an adjusted 127% and 113% higher odds in cardiac and renal events (P=0.001 and P=0.005, respectively). Surgical characteristics and ICU events were similar between these 2 groups except for few notable differences as shown in Table 4. Namely, median cardiac outputs, need for ≥2 nonroutine inotropes (first 24 hours postoperatively), and extubation times were comparable, whereas small differences were noted in mean systolic blood pressure (4.9 mm Hg lower in the withdrawal group; P<0.001) and red blood cell transfusion rates (40% versus 48%; P<0.001). In addition to lower blood pressure and higher transfusion rates, the use of an assist device for low cardiac output intraoperatively was 3 times higher for the withdrawal group.

ACEI Addition Versus No ACEI
Addition of ACEI therapy postoperatively de novo was uncommon, prescribed in 14.4% (343 of 2386) of patients. After propensity score and APACHE II adjustments, addition of ACEI was associated with a 44% lower odds in composite outcome (P=0.004), driven entirely by a 37% lower odds in cardiovascular event. No difference in surgical characteristics was noted, but time on mechanical ventilator was less in the addition group (13.2 versus 16.4 hours; P<0.001) and systolic blood pressure was higher by 5.6 mm Hg (Table 4).

Event-Free Survival
The 1-month event-free status after CABG surgery, as estimated by the Kaplan–Meier survival curve, indicated that the withdrawal group had the poorest outcome (P<0.001; Figure 2), with only 71% of the patients being event free. Compared with the other 3 groups, the cumulative composite outcome in the withdrawal group was doubled.

Discussion
In the setting of CABG surgery with CPB, the pattern of perioperative ACEI use was associated with in-hospital fatal and nonfatal vascular outcomes. Treatment with ACEI before and early after surgery was associated with a significantly lower risk of cardiovascular and overall composite events; de novo addition of ACEI therapy postoperatively 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 morbid and fatal vascular outcomes.[28,29] 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 outcome (death, cardiovascular, and renal events) in those patients receiving preoperative and postoperative ACEI compared with no therapy. Similarly, de novo use of ACEI postoperatively was associated with a 44% reduction in odds in composite outcome.

In a cohort of patients requiring coronary revascularization, Kjøller-Hansen et al[30] 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, Oosterga et al[31] 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

Risk Factor	Adjusted Odds Ratio (95% CI)	P
ACEI treatment		
Continuation vs no ACEI	0.58 (0.44–0.76)	<0.001
Addition vs no ACEI	0.58 (0.39–0.85)	0.006
Withdrawal vs no ACEI	1.70 (1.36–2.13)	<0.001
Continuation vs withdrawal	0.58 (0.39–0.85)	0.006
History of hypertension	1.28 (1.03–1.59)	0.03
History of carotid disease	1.49 (1.14–1.93)	0.003
History of renal disease	1.39 (1.08–1.80)	0.01
Warfarin in the past week of admission	1.74 (1.22–2.47)	0.002
Congestive heart failure on admission or preoperative	1.79 (1.20–2.66)	0.004
Creatinine on admission (maximum) >1.3 mg/dL	1.48 (1.15–1.90)	0.002
Intubation and reintubation ≥24 h (within 48 h)	2.32 (1.83–2.95)	<0.001
Assist device use for low cardiac output, ischemic, or angina intraoperatively or on RDOS	3.19 (1.78–5.70)	<0.001
Fluid intake intraoperative to RDOS	1.009 (1.005–1.012)	<0.001
EuroSCORE	1.07 (1.03–1.10)	<0.001
APACHE II Acute Physiology score (partial)	1.05 (1.01–1.09)	0.006

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 χ^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 intraoperatively 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 vasoplegia after the induction of anesthesia and in the setting of CPB necessitating greater vasopressor and fluid resuscitation.[32,33] 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[21] 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[34] and Ryckwaert et al[22] also could not demonstrate clinically significant vasoplegia 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.[35] 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 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.[36,37] 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.[17–20] 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.[30]

CPB, a potent mediator of inflammation, is associated with marked activation of the RAAS.[38] These, together with activation of the sympathoadrenal and hemostatic pathways, may provide the groundwork for microvascular injury and organ dysfunction.[12,39] Thus, inhibition of ACE can mitigate angiotensin production and, importantly, may improve microcirculatory perfusion via the aforementioned mechanisms.[40,41] 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.[40]

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

Table 4. Characteristics in the 24 Hours After Intensive Care Unit Arrival by Angiotensin-Converting Enzyme Inhibitor Treatment Groups

Characteristics	No ACEI (n=2043)	Addition (n=343)	Continuation (n=915)	Withdrawal (n=923)	P*	P†	P‡
Mean cardiac output in the 24 h after ICU arrival, L/min					0.54	0.84	0.93
Median	5.57	5.51	5.61	5.56			
Quartiles 1–3	4.75–6.48	4.62–6.48	4.75–6.60	4.76–6.47			
Mean SBP in the 24 h after ICU arrival, mm Hg					<0.001	<0.001	<0.001
Median	116.2	121.8	120.6	115.7			
Quartiles 1–3	109.3–123.9	113.4–130.0	112.9–128.4	108.7–123.7			
Intubation time, h					<0.001	<0.001	0.36
Median	13.2	16.4	15.6	15.4			
Quartiles 1–3	9.7–18.4	12.0–22.7	11.5–22.2	11.2–21.3			
≥2 Simultaneous nonroutine inotropes on RDOS, n (%)	282 (13.8)	92 (26.8)	257 (28.1)	256 (27.7)	<0.001	<0.001	0.18
Assist device use for low cardiac output or ischemic or angina, n (%)	35 (1.7)	5 (1.5)	12 (1.3)	35 (3.8)	0.31	0.92	<0.001
Intraoperative or on RDOS, n (%)							
Red blood cell transfusion in 24 h after ICU arrival, n (%)	762 (37.3)	149 (43.3)	368 (40.2)	446 (48.3)	0.09	0.004	<0.001

ACEI indicates angiotensin-converting enzyme inhibitor; ICU, intensive care unit; SBP, systolic blood pressure; and RDOS, remaining day of surgery. Bonferroni correction for multiple testing requires $P<0.017$ for significance.

*P was calculated from the Wilcoxon rank-sum test for continuous variables or the χ^2 test for categorical variables for the comparison of the no ACEI group vs the ACEI continuation group.

†P was calculated for the comparison of the no ACEI group vs the ACEI addition group.

‡P was calculated for the comparison of the ACEI continuation group vs the ACEI withdrawal group.

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[41] 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[42] and Wallace et al[25] 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.

Cumulative Composite Outcome							
Continuation (n=915)	0	80	104	111	112	113	113
Withdrawal (n=923)	0	245	262	265	266	267	268
Addition (n=343)	0	33	37	41	41	41	42
No-ACEI (n=2043)	0	269	289	289	293	293	293

Figure 2. Kaplan–Meier survival analysis of event-free status by angiotensin-converting enzyme inhibitor (ACEI) therapy. The curves show data of 30-day in-hospital composite event-free status. The P value shown is for the comparison of Kaplan–Meier survival function among the 4 groups. The P value was calculated from the log-rank test.
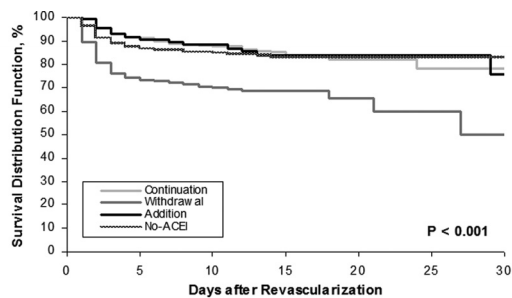
Limitations

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[43] although its pattern of withdrawal remains high.[35]

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.

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Disclosures

None.

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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.

Appendix 1.

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.

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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