ORIGINAL RESEARCH

Comparison of Angiotensin-Converting Enzyme Inhibitor and Angiotensin Receptor Blocker Management Strategies Before Cardiac Surgery: A Pilot Randomized Controlled Registry Trial

Sean van Diepen, MD, MSc; Colleen M. Norris, RN, PhD; Yinggan Zheng, MA, MEd; Jayan Nagendran, MD, PhD; Michelle M. Graham, MD; Damaris Gaete Ortega, RN; Derek R. Townsend, MD; Justin A. Ezekowitz, MBBCh, MSc; Sean M. Bagshaw, MD, MSc

Background—Postoperative clinical outcomes associated with the preoperative continuation or discontinuation of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) before cardiac surgery remain unclear.

Methods and Results—In a single-center, open-label, randomized, registry-based clinical trial, patients undergoing nonemergent cardiac surgery were assigned to ACEI/ARB continuation or discontinuation 2 days before surgery. Among the 584 patients screened, 261 met study criteria and 126 (48.3%) patients were enrolled. In total,121 patients (96% adherence; 60 to continuation and 61 to ACEI/ARB discontinuation) underwent surgery and completed the study protocol, and follow-up was 100% complete. Postoperative intravenous vasopressor use (78.3% versus 75.4%, *P*=0.703), vasodilator use (71.7% versus 80.3%, *P*=0.265), vasoplegic shock (31.7% versus 27.9%, *P*=0.648), median duration of vasopressor (10 versus 5 hours, *P*=0.494), and vasodilator requirements (10 versus 9 hours, *P*=0.469) were not significantly different between the continuation and discontinuation arms. No differences were observed in the incidence of acute kidney injury (1.7% versus 1.6%, *P*=0.991), stroke (no events, mortality (1.7% versus 1.6%, *P*=0.991), median duration of mechanical ventilation (6 versus 6 hours, *P*=0.680), and median intensive care unit length of stay (43 versus 27 hours, *P*=0.420) between the treatment arms.

Conclusions—A randomized study evaluating the routine continuation or discontinuation of ACEIs or ARBs before cardiac surgery was feasible, and treatment assignment was not associated with differences in postoperative physiological or clinical outcomes. These preliminary findings suggest that preoperative ACEI/ARB management strategies did not affect the postoperative course of patients undergoing cardiac surgery.

Clinical Trial Registration—URL: https://www.clinicaltrials.gov. Unique identifier: NCT02096406. **(*J Am Heart Assoc*. 2018;7:009917. DOI: 10.1161/JAHA.118.009917.)**

Key Words: angiotensin-converting enzyme inhibitor • angiotensin receptor blocker • cardiac surgery • vasoplegia

Coronary revascularization with coronary artery bypass grafting (CABG) surgery improves long-term survival in patients with diabetes mellitus or complex multivessel disease.[1–3] Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) reduce mortality and subsequent cardiac events in patients with coronary artery disease undergoing CABG when initiated at least 4 weeks preoperatively.[4]

High-quality studies from which to guide practice regarding perioperative ACEI or ARB management strategies in patients undergoing CABG are lacking. Observational studies, without standardized perioperative medication management, have reported that preoperative ACEI or ARB use is associated with an increased risk of postoperative vasoplegic shock, acute kidney injury (AKI), and mortality; however, other studies have reported that

From the Department of Critical Care Medicine, Faculty of Medicine and Dentistry (S.v.D., C.M.N., D.G.O., D.R.T., S.M.B.), Division of Cardiology, Department of Medicine (S.v.D., M.M.G., J.A.E.), Canadian VIGOUR Center (S.v.D., Y.Z., J.A.E.), Faculty of Nursing (C.M.N.), University of Alberta, Edmonton Alberta, Canada; Division of Cardiac Surgery, University of Alberta Hospital, Edmonton, Alberta, Canada (C.M.N., J.N.).

Accompanying Tables S1 through S3 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.009917

Correspondence to: Sean van Diepen, MD, MSc, 2C2 Cardiology Walter MacKenzie Center; University of Alberta Hospital; 8440-112 St. Edmonton, Alberta, Canada T6G 2B7. E-mail: sv9@ualberta.ca

Received May 26, 2018; accepted September 6, 2018.

Clinical Perspective

What Is New?

- High-quality studies examining the optimal perioperative management of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers before cardiac surgery are lacking.
- In a single-center, open, randomized, registry-based clinical trial, 121 patients undergoing nonemergent cardiac surgery were randomized to angiotensin-converting enzyme inhibitor or angiotensin receptor blocker continuation or discontinuation 2 days before surgery.

What Are the Clinical Implications?

- No differences between study arms were observed in the incidence of vasoplegic shock, postoperative intravenous vasopressor or vasodilator requirements, acute kidney injury, duration of mechanical ventilation, or cardiac surgical intensive care unit length of stay.
- These findings suggest that preoperative angiotensin-converting enzyme inhibitor or angiotensin receptor blocker management is not associated with postcardiac surgery hemodynamic outcomes.
- These findings from a pilot study may inform the design and event rates of a larger future randomized trial.

preoperative ACEIs or ARBs are associated with a reduced risk of perioperative myocardial infarction with no increased risk of AKI or death.[4–15] The only randomized controlled trial (RCT) to date enrolled 40 patients undergoing CABG and randomized participants to preoperative ACEI continuation or discontinuation the day before surgery. It has been reported that ACEI-withdrawal patients required fewer vasopressors during cardiopulmonary bypass but more intravenous vasodilators to control postoperative hypertension.[16] High-quality studies examining the postoperative clinical and hemodynamic outcomes associated with preoperative ACEI or ARB management strategies are currently lacking.

Evaluating the best perioperative ACEI and ARB management practices for postoperative outcomes has important implications for clinical care and resource utilization. Vasoplegic shock and AKI, which have been associated with preoperative ACEI or ARB continuation, are potential risk factors for prolonged cardiac surgical intensive care unit (CSICU) length of stay (LOS) and mortality.[17–20] Conversely, withdrawal is a known precipitant of acute heart failure and increases the risk of postoperative hypertension.[16,21] The conflicting available low-quality data reflect equipoise in contemporary clinical practice reported in a survey of practicing cardiovascular surgeons.[22] Accordingly, in a pragmatic registry-based pilot RCT, we evaluated feasibility, hemodynamic, clinical, and health resource utilization end points in patients undergoing on-pump cardiac surgery randomized to preoperative continuation or discontinuation of an ACEI or ARB.

Methods

Study Design and Patient Population

This prospective, open-label, registry-based RCT was conducted at a single tertiary academic center in Edmonton, Alberta, Canada between May 2014 and June 2017 (NCT02096406). The study was approved by the University of Alberta Health Research Ethics Board (Pro00042749).

Participants were eligible for randomization if they were aged ≥18 years and scheduled for elective or urgent CABG (within 14 days of referral) and/or valve surgery and had been treated with an ACEI or ARB for a minimum of 7 days. Exclusion criteria were as follows: emergency surgery, preoperative shock (defined as systolic blood pressure <90 mm Hg, the need for any vasopressor or inotropic support, or a mechanical cardiac support device), severe uncontrolled preoperative hypertension (defined as blood pressure ≥200 mm Hg systolic or ≥120 mm Hg diastolic or the preoperative need for intravenous antihypertensive agents), or any mineralocorticoid receptor antagonist therapy.

Study Protocol and Randomization

Eligible patients who provided informed consent were randomized 1:1 using a web-based randomization sequence, without stratification or blocking, to presurgical preoperative continuation or discontinuation of their ACEI or ARB. Patients randomized to the continuation arm continued their ACEI or ARB up to and including the morning of surgery, with a sip of water. Patients in the discontinuation arm discontinued the medication 2 days before their scheduled surgery; in the event of any surgical postponement, patients were instructed to continue to hold the ACEI or ARB until the time of surgery. In the immediate postoperative period, local CSICU practice sets systolic blood pressure targets of 90 to 110 mm Hg for the first 4 hours and then 90 to 140 mm Hg thereafter. Patients arrive in the CSICU from the operating room sedated with propofol, and sedation is typically discontinued within 2 to 3 hours in stable patients. The CSICU is a closed unit staffed by in-house board-certified intensivists who admit and direct the postoperative care of all admitted patients in collaboration with the surgical team. The preoperative management of all other medications and the postoperative reintroduction of an ACEI or ARB were at the discretion of the most responsible physician. During the study period, the hospital performed an average of 1490 open heart surgeries including an average of 533 nonemergent CABGs.

Registry Information, Data Collection, and Follow-up

All preoperative demographic, clinical, cardiac catheterization, and intraoperative surgical variables were collected prospectively in the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) data set.[23] This registry captures medical procedural information on all patients undergoing cardiac catheterization and/or cardiac surgery in the province of Alberta. Information is entered into APPROACH by experienced staff members at the time of the procedure, and trained chart abstracters subsequently review all previously entered variables.[24,25] All postoperative study outcomes were abstracted from the participants' chart by study research personnel and entered into a separate case report form. At the completion of enrollment and study follow-up, data from the APPROACH registry were electronically linked to the case report from using unique patient identifiers. All patients were followed through to hospital discharge or 30 days (whichever was longer). The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

End Points

This pilot study captured physiological, clinical, and heath resource utilization outcomes. The physiological outcomes of interest included the incidence and duration of *postoperative shock*, defined as the need for intravenous vasopressors or inopressors (norepinephrine, epinephrine, vasopressin, dopamine, and/or methylene blue) and/or mechanical support devices that were either initiated in the operating room or in the CSICU. *Shock resolution time* was defined as the time when all intravenous vasopressors or inopressors were discontinued for ≥1 hour. The use and duration of postoperative intravenous vasodilators (including nitroglycerine or nitroprusside) to control hypertension was also captured. Clinical outcomes of interest included (1) the incidence of vasoplegic shock, defined as a mean arterial pressure <60 mm Hg requiring vasopressor administration for at least 4 hours and a central venous pressure ≥8 mm Hg; (2) preoperative heart failure deterioration, defined as an increase in diuretic dose in the 48 hours before surgery; (3) postoperative AKI, defined as a doubling of serum creatinine or a >50% decline in glomerular filtration rate[26]; (4) absolute change in serum creatinine; (5) 30-day all-cause mortality; (6) 30-day stroke, defined using Society of Thoracic Surgeons criteria[27]; and (7) ACEI or ARB use at the time of hospital discharge. Health resource outcomes of interest included duration of mechanical ventilation (hours), CSICU (hours) and index hospital LOS (days), initiation of renal replacement therapy, and CSICU all-cause readmission during the index hospitalization. Feasibility outcomes included adherence to the study protocol, the enrollment rate of eligible patients, and the completeness of study outcomes.

Statistical Analysis

Continuous variables were summarized as medians and interquartile ranges, and between-group differences were compared using the Mann–Whitney *U* test. Categorical variables were summarized as numbers and percentages and compared using the χ^2 test or Fisher exact test, as appropriate. The modified intention-to-treat (which included all randomized patients who underwent surgery) assumption was applied to the analysis of study treatment and outcomes (ie, random assignment to ACEI or ARB continuation versus discontinuation). Logistic regression was used to estimate the relative association between study treatment (ACEI or ARB continuation versus discontinuation) and binary outcomes, whereas quantile regression was used for continuous outcomes. To account for possible imbalance between the 2 study arms, the relative associations were adjusted for all baseline characteristics with a $P<0.20$. Variables in the regression included body mass index, history of hypertension, dyslipidemia, prior percutaneous coronary intervention, cerebrovascular disease, chronic lung disease, left ventricular ejection fraction, and preoperation medication of adenosine diphosphate inhibitor or $P2Y_{12}$ inhibitor. Unadjusted and adjusted associations, expressed as odds ratios or quantile regression coefficients, were reported with the corresponding 95% confident interval. Two sensitivity analyses were performed; the outcomes were (1) examined by study treatment received (ie, per-protocol analysis) and (2) stratified by short (≤12 hours) or long (>12 hours) ACEI or ARB half-life.

All analyses were performed using SAS (v9.4; SAS Institute), and all statistical tests were 2-sided and had a 5% level of significance.

Results

A total of 584 patients were screened for inclusion criteria, 261 patients met study inclusion criteria, and 126 (48.3%) were randomized as shown in Figure 1. Three patients did not undergo cardiac surgery (2 patients in the continuation arm and 1 patient in the discontinuation arm), and 1 patient in each arm withdrew consent after randomization. The final modified intention-to-treat study population included 121 patients (96%; 60 in the continuation and 61 in the discontinuation arm). Adherence to the study protocol was 96%. A total of 4 patients in the continuation arm had their ACEI or ARB discontinued before the morning of surgery. Patient follow-up was 100% complete.

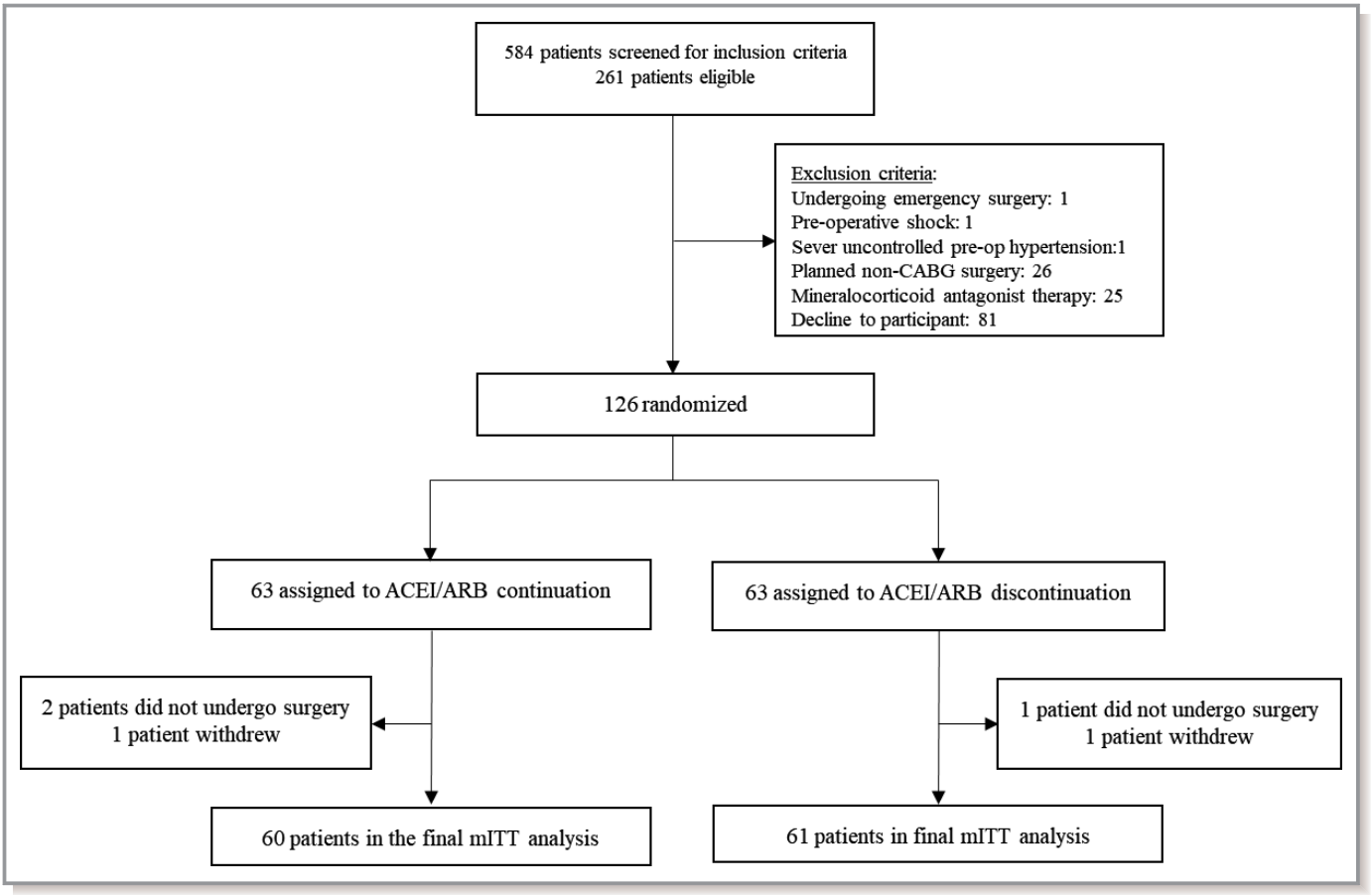

Figure 1. Study cohort diagram. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; mITT, modified intention to treat.

Baseline demographics, preoperative investigations, and medications were similar between treatment arms (Table 1). A median body mass index and a history of cerebrovascular disease and atrial fibrillation/flutter were higher in the discontinuation arm, whereas preoperative adenosine diphosphate or $P2Y_{12}$ inhibitor use was higher in the continuation arm. Surgical and intraoperative variables (Table 2) were similar between the ACEI/ARB continuation and discontinuation arms. A total of 50 patients (41.3%) were admitted to the CSICU with vasopressors or inotropes initiated in the operating room, and 43 (35.5%) were initiated in the CSICU. Intravenous vasodilators were initiated in 18 patients (14.9%) in the operating room and in 74 (61.2%) in the CSICU. No differences were observed between treatment arms.

Outcomes

Postoperative shock (78.3% versus 75.4%; adjusted odds ratio: 0.95; 95% confidence interval, 0.36–2.50; adjusted *P*=0.913), vasodilator use (71.7% versus 80.3%: adjusted odds ratio: 1.78; 95% confidence interval, 0.65–4.88; adjusted *P*=0.261), vasoplegic shock (31.7% versus 27.9%; adjusted odds ratio: 0.87; 95% confidence interval, 0.35–2.15; adjusted *P*=0.767), median duration of vasopressor or inopressor use, and intravenous vasodilator requirements were not significantly different between the continuation and discontinuation arms (Table 3, Figure 2). No differences were observed in the incidence of AKI, stroke, mortality, median duration of mechanical ventilation, or median CSICU LOS between the treatment arms. In sensitivity analyses that examined outcomes according to actual preoperative ACEI or ARB treatment received (Table S1) and stratified by ACEI or ARB short (≤12 hours) or long (>12 hours) half-life (Table S2), no differences in postoperative outcomes were observed. In a post hoc analysis, the initiation of an intravenous vasoactive agent in the operating room (on CSICU admission) versus after CSICU admission were similar between treatment arms (Table S3).

Discussion

In this registry-based RCT of preoperative ACEI or ARB continuation or discontinuation in patients undergoing cardiac surgery, we found that the study protocol was feasible and

Table 1. Baseline Characteristics by Randomized Treatment Assignment

	Continuation (n=60)	Discontinuation (n=61)	*P* Value
Demographics			
Age, y	67 (60–73)	64 (58–71)	0.223
Male, n (%)	56 (93.3)	56 (91.8)	0.748
BMI, kg/m^2	32 (28–36)	29 (27–32)	0.001
Past medical history, n (%)			
Hypertension	47 (78.3)	40 (65.6)	0.119
Dyslipidemia	47 (78.3)	41 (67.2)	0.170
Diabetes mellitus	27 (45.0)	21 (34.4)	0.235
Current/former smoking	34 (56.7)	30 (49.2)	0.410
Prior MI	10 (16.7)	11 (18.0)	0.843
Prior PCI	7 (11.7)	3 (4.9)	0.178
CCS class III/IV	25 (41.7)	28 (45.9)	0.639
Heart failure	4 (6.7)	3 (4.9)	0.680
Atrial fibrillation or flutter	5 (8.3)	0 (0.0)	0.021
Cerebrovascular disease	7 (11.7)	1 (1.6)	0.027
Peripheral arterial disease	4 (6.7)	2 (3.3)	0.391
Chronic lung disease	9 (15.0)	3 (4.9)	0.064
Preoperative investigations			
Extent of coronary stenosis >70%, n (%)	59 (98.3)	60 (98.4)	0.991
Left main or 3-vessel CAD	48 (80.0)	52 (85.2)	0.446
1–2 vessel	11 (18.3)	8 (13.1)	0.430
LVEF, %	50 (45–50)	50 (35–50)	0.087
Hemoglobin, g/L	140 (131–148)	141 (130–150)	0.830
Serum creatinine, μmol/L	88 (77–106)	83 (75–96)	0.132
GFR, n/1.73 m^2	75 (61–89)	80 (68–90)	0.172
Preoperative medications, n (%)			
ADP or P2Y$_{12}$ inhibitor	4 (6.7)	14 (23.0)	0.012
β-Blocker	47 (78.3)	53 (86.9)	0.214
Calcium channel blocker	8 (13.3)	10 (16.4)	0.636
ACEI	42 (70.0)	51 (83.6)	0.076
ARB	14 (23.3)	10 (16.4)	0.339
Diuretic	13 (21.7)	14 (23.0)	0.865
Oral anticoagulant	0 (0.0)	0 (0.0)	…

Continuous variables presented as median (interquartile range). ACEI indicates angiotensin-converting enzyme inhibitor; ADP, adenosine diphosphate inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

that medication discontinuation 48 hours before surgery was not associated with a difference in vasoplegic shock or the incidence or duration of postoperative intravenous vasopressors or vasodilators. Similarly, no differences in preoperative acute heart failure, postoperative clinical outcomes, or CSICU LOS were observed between treatment strategies. Although cardiac surgical procedures are performed globally, there is little standardization of preoperative ACEI/ARB management practices despite the potential impact on patient, CSICU, and health system utilization outcomes. In this RCT, which is >3 times the size of previous trials, no clinically important difference in postoperative outcomes were observed.

Some clinical practice guidelines recommend withholding ACEI or ARB 24 hours before surgery in patients undergoing

Table 2. Operative Characteristics According to Randomized Treatment Assignment

	Continuation (n=60)	Discontinuation (n=61)	*P* Value
Surgical priority, n (%)			
Emergency	1 (1.7)	1 (1.6)	0.221
Outpatient	16 (26.7)	8 (13.1)	
Urgent in-hospital/transfer	11 (18.3)	18 (29.5)	
Urgent out-of-hospital	32 (53.3)	34 (55.7)	
Surgical incidence, n (%)			
First operation	59 (98.3)	61 (100.0)	0.311
Second or more	1 (1.7)	0 (0.0)	
Surgery performed, n (%)			
CABG	53 (88.3)	56 (91.8)	0.558
CABG and valve replacement or repair	6 (10.0)	5 (8.2)	
Isolated valve	1 (1.7)	0 (0.0)	
CABG characteristics			
Number of grafts, median (IQR)	3 (3–4)	3 (3–4)	0.513
Left internal mammary, n (%)	51 (85.0)	52 (85.2)	0.970
Off-pump bypass, n (%)	0 (0.0)	1 (1.6)	0.323
Intraoperative events			
CPB time, min, median (IQR)	90 (75–117)	87 (72–119)	0.559
Aortic cross clamp time, min, median (IQR)	69 (51–96)	68 (53–96)	0.966
Intraoperative RBC transfusion, n (%)	1 (1.7)	6 (9.8)	0.054
Intraoperative FFP transfusion, n (%)	2 (3.3)	1 (1.6)	0.549

CABG indicates coronary artery bypass grafting; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; IQR, interquartile range; RBC, red blood cell.

noncardiac surgery, but this recommendation is based on low-quality evidence.[28,29] Three small randomized trials in the noncardiac surgical population reported an increased risk of intraoperative hypotension associated with ACEI or ARB continuation, but they were too small to evaluate postoperative complications.[30–32] The prospective VISION study cohort reported that ACEI or ARB administration within 24 hours of noncardiac surgery was associated with an increased risk of intraoperative hypotension and the 30-day composite of mortality, stroke, or myocardial infarction but not postoperative hypotension.[33] The significant baseline differences in the perioperative management of other cardiac and antihypertensive medications in this cohort are an important potential confounder that may limit the applicability of the findings. In the cardiac surgical population, the preoperative administration of an ACEI or ARB has also been associated with intraoperative hypotension, but the postoperative hemodynamic effects are less clear.[10,11,34] A single randomized trial of 40 patients reported significantly higher postoperative intravenous vasodilator requirement in the ACEI discontinuation arm.[16] In this analysis, no differences were observed in the incidence or duration of intravenous vasopressor or vasodilator therapy by treatment assignment, although the numerically nonsignificant increase in vasopressor use in the continuation arm and the vasodilator use in the discontinuation arm mirrored the finding in the aforementioned trial of 40 patients.[16] In addition, no differences were observed in a per-protocol analysis or when ACEI or ARB doses were stratified by drug half-life. These findings suggest that preoperative ACEI/ARB management strategies are not significantly associated with postoperative hemodynamic changes among patients primarily undergoing isolated CABG.

Vasoplegic shock, which manifests as a low systemic vascular resistance, is common in the postoperative cardiac surgical population.[17] The association between preoperative ACEI or ARB use and postoperative vasoplegia, mediated in part through reduced vasopressor responsiveness, has been consistently described in observational studies, but prospective controlled trials are lacking.[5,17,18,35] In this study, we observed a 30% overall incidence of vasoplegic shock, with no differences between the continuation and discontinuation arms. The incidence in this study is higher than that in previous reports, and we hypothesize that result this may be related to differences in study populations and hemodynamic definitions. Currently, there is no consensus definition of vasoplegic shock; previous observational studies have varying definitions that include vasopressor doses, mean arterial pressure, calculated hemodynamics, time, and/or cardiac filling pressures.[5,17,18,20,36] In this registry trial, we used a pragmatic vasoplegic shock definition based on duration of vasopressor requirements in a patient population at low risk of low cardiac output syndrome and in which the routine use invasive hemodynamic monitoring could not be clinically justified. Our study suggests that in patients predominantly undergoing isolated CABG surgery, the preoperative continuation of an ACEI or ARB is not associated with vasoplegic shock. Future controlled studies could potentially build on this study by incorporating routine hemodynamic monitoring in a patient population at potentially higher risk for vasoplegic shock such as valve, combined valve/CABG, mechanical circulatory support, and transplant surgeries.

The continuation of ACEI or ARB dosing is known to increase the risk of postinduction and intraoperative hypotension, but the association between ACEI or ARB preoperative management and postoperative clinical outcomes has remained less clear.[33,37] In this pilot study, clinical event

Table 3. Physiological, Clinical, and Health Resource Utilization Outcomes According by Randomized Treatment Assignment

	Unadjusted				Adjusted	
	Continuation (n=60)	Discontinuation (n=61)	Relative Association*	*P* Value	Relative Association*	*P* Value
Physiological outcomes						
Postoperative shock, n (%)	47 (78.3)	46 (75.4)	0.85 (0.36–1.98)	0.703	0.95 (0.36–2.50)	0.913
Duration of postoperative shock,† h	10 (3–25)	5 (1–25)	−5.27 (−15.71, 5.18)	0.497	−6.80 (−12.8, 1.4)	0.125
Postoperative vasodilators, n (%)	43 (71.7)	49 (80.3)	1.61 (0.70–3.83)	0.267	1.78 (0.65–4.88)	0.261
Duration of postoperative vasodilators,‡ h	10 (4–19)	9 (4–17)	−1.45 (−8.77, 5.87)	0.467	−1.50 (−8.1, 5.7)	0.594
Clinical outcomes, n (%)						
Vasoplegic shock	19 (31.7)	17 (27.9)	0.83 (0.38–1.82)	0.648	0.87 (0.35–2.15)	0.767
Preoperative heart failure	0 (0.0)	0 (0.0)	…	…	…	…
Postoperative AKI	1 (1.7)	1 (1.6)	…	…	…	…
Absolute change in serum creatinine, μmol/L	10 (2–19)	10 (5–22)	0.75 (−4.96, 6.46)	0.278	3.79 (0.69–9.64)	0.044
30-d stroke§	0 (0.0)	0 (0.0)	…	…	…	…
30-d all-cause mortality	1 (1.7)	1 (1.6)	…	…	…	…
ACEI/ARB use at hospital discharge	36 (60.0)	32 (52.5)	0.74 (0.36–1.51)	0.404	0.77 (0.35–1.70)	0.521
Health resource outcomes						
Duration of mechanical ventilation, h	6 (5–9)	6 (5–9)	0.18 (−0.85, 1.22)	0.677	1.0 (−0.6, 2.1)	0.227
CSICU LOS, h	43 (23–69)	27 (23–73)	−16.62 (−33.15, −0.09)	0.049	0.38 (−17.7, 4.44)	0.724
Renal replacement therapy, n (%)	0 (0.0)	1 (1.6)	…	…	…	…
Hospital LOS, d	7 (5–12)	7 (6–15)	0.00 (−2.71, 2.71)	0.454	0.36 (−1.5, 1.99)	0.461
CSICU readmission	3 (5.0)	1 (1.6)	0.32 (0.02–2.55)	0.326	. . .	. . .

Continuous variables presented as median (IQR). ACEI indicates angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; CSICU, cardiac surgical intensive care unit; IQR, interquartile range; LOS, length of stay.

*Odds ratios were reported for binary outcomes and relative risk were reported for continuous outcomes. Unadjusted and adjusted relative association for continuous variable expressed as change of median by each unit if patient in discontinuation arm.

†Valid n=93 patient who were treated with intravenous vasopressors or inopressors.

‡Valid n=92 patients treated with intravenous vasodilators.

§Valid n=119 stroke status thorough 30 d missing in 1 patient in each arm.

rates were low (likely reflecting enrollment of patients undergoing isolated CABG with preserved left ventricular function and kidney function), and no differences in clinical or health resource utilization outcomes were observed between treatment arms. Although underpowered to detect major differences in clinical events and physiological end points, the present data are the first from a controlled clinical trial. The inconsistent associations between ACEI or ARB continuation and clinical events (eg, an increased risk of AKI and mortality and a lower risk of myocardial infarction) in observational studies may, in part, reflect differences in the surgical risk between study populations and the lack of clarity around the exact timing of perioperative ACEI or ARB dosing in some of these studies.[6,8,9,11,13,15] A meta-analysis of nonrandomized studies by Bandeali et al reported that a preoperative ACEI administered up to the morning of cardiac surgery was associated with a higher risk of AKI and atrial fibrillation.[7] The present findings are insufficient to change clinical practice; a larger clinical trial, adequately powered for major clinical events such as AKI, stroke, or cardiovascular mortality, is required to rigorously evaluate the efficacy and safety of preoperative ACEI/ARB management strategies. Our results can serve to inform future study design insofar as the inclusion of patients across a wider spectrum of surgical risk for postoperative AKI and mortality will be required to achieve a sufficient number of clinical end points.

Limitations

First, in this registry-based RCT, intraoperative hemodynamic variables were not recorded. Multiple previous studies have documented the postinduction risk of hypotension associated with ACEI or ARB continuation, and the purpose of this study was to evaluate postoperative hemodynamic and clinical outcomes.[33,37] Second, the study was not blinded and perioperative administration of other cardiac medications was left to the discretion of the most responsible physician. Third, given the lack of a consensus definition of

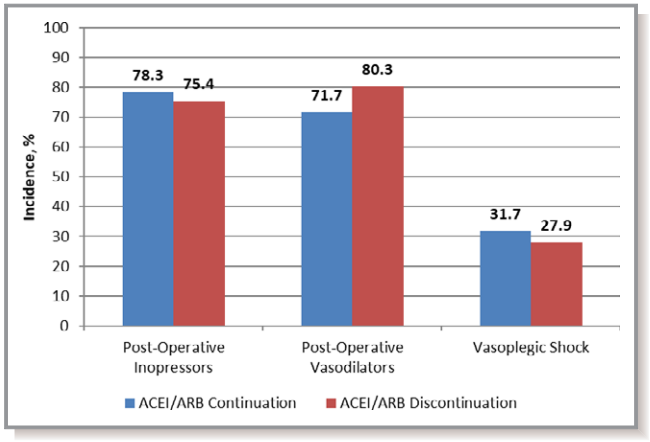

Figure 2. Incidence of postoperative inopressor requirement, intravenous vasodilatory use, and vasoplegic shock by randomized treatment assignment. Error bars are 95% confidence intervals of point estimates. ACE indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

vasoplegic shock, we developed a pragmatic definition that requires validation in future studies. Fourth, the study did not collect information on bleeding or hypertensive urgencies, although the incidence and duration of intravenous vasodilators were similar in both treatment arms. Finally, the study primarily enrolled patients undergoing isolated CABG with preserved left ventricular function and kidney function. Recognizing the association among ventricular function, length of cardiopulmonary bypass, and risk of vasoplegia, the study results may not apply to other surgical populations.[17]

Conclusions

A pragmatic randomized clinical study of preoperative ACEI or ARB continuation or discontinuation in patients undergoing cardiac surgery was feasible, and no differences were observed in the incidence of vasoplegic shock, postoperative intravenous vasopressors or vasodilators requirements, AKI, duration of mechanical ventilation, or CSICU LOS between study arms. These findings suggest that preoperative ACEI/ARB management is not associated with postcardiac surgery hemodynamic outcomes. These findings may serve to inform the design and event rates of a larger future randomized trial.

Acknowledgments

We would like to posthumously acknowledge Dr Masaru Yukawa's contributions toward the study design and patient recruitment.

Sources of Funding

The study was funded by research grants from the University Hospital Foundation and the Cardiovascular Intensive Care Research Fund. Bagshaw was supported by a Canada Research Chair in Critical Care Nephrology.

Disclosures

None.

References

1. Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, Yang M, Cohen DJ, Rosenberg Y, Solomon SD, Desai AS, Gersh BJ, Magnuson EA, Lansky A, Boineau R, Weinberger J, Ramanathan K, Sousa JE, Rankin J, Bhargava B, Buse J, Hueb W, Smith CR, Muratov V, Bansilal S, King S, Bertrand M, Fuster V. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med*. 2012;367:2375–2384.
2. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Ståhle E, Colombo A, Mack MJ, Holmes DR, Morel MA, Dyck NV, Houle VM, Dawkins KD, Serruys PW. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet*. 2013;381:629–638.
3. Serruys PW, Morice M-C, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Ståhle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961–972.
4. Oosterga M, Voors AA, Pinto YM, Buikema H, Grandjean JG, Kingma JH, Crijns HJ, van Gilst WH. Effects of quinapril on clinical outcome after coronary artery bypass grafting. QUinapril on Vascular Ace and Determinants of Ischemia (The QUO VADIS Study). *Am J Cardiol*. 2001;87:542–546.
5. Argenziano M, Chen JM, Choudhri AF, Cullinane S, Garfein E, Weinberg AD, Smith CR, Rose EA, Landry DW, Oz MC. Management of vasodilatory shock after cardiac surgery: identification of predisposing factors and use of a novel pressor agent. *J Thorac Cardiovasc Surg*. 1998;116:973–980.
6. Arora P, Rajagopalam S, Ranjan R, Kolli H, Singh M, Venuto R, Lohr J. Preoperative use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers is associated with increased risk for acute kidney injury after cardiovascular surgery. *Clin J Am Soc Nephrol*. 2008;3:1266–1273.
7. Bandeali SJ, Kayani WT, Lee VV, Pan W, Elayda MAA, Nambi V, Jneid HM, Alam M, Wilson JM, Birnbaum Y, Ballantyne CM, Virani SS. Outcomes of preoperative angiotensin-converting enzyme inhibitor therapy in patients undergoing isolated coronary artery bypass grafting. *Am J Cardiol*. 2012;110:919–923.
8. Benedetto U, Melina G, Capuano F, Comito C, Bianchini R, Simon C, Refice S, Angeloni E, Sinatra R. Preoperative angiotensin-converting enzyme inhibitors protect myocardium from ischemia during coronary artery bypass graft surgery. *J Cardiovasc Med*. 2008;9:1098–1103.
9. Benedetto U, Sciarretta S, Roscitano A, Fiorani B, Refice S, Angeloni E, Sinatra R. Preoperative Angiotensin-converting enzyme inhibitors and acute kidney injury after coronary artery bypass grafting. *Ann Thorac Surg*. 2008;86:1160–1165.
10. Licker M, Schweizer A, Höhn L, Farinelli C, Morel D. Cardiovascular responses to anesthetic induction in patients chronically treated with angiotensin-converting enzyme inhibitors. *Can J Anaesth*. 2000;47:433–440.
11. Miceli A, Capoun R, Fino C, Narayan P, Bryan AJ, Angelini GD, Caputo M. Effects of angiotensin-converting enzyme inhibitor therapy on clinical outcome in patients undergoing coronary artery bypass grafting. *J Am Coll Cardiol*. 2009;54:1778–1784.
12. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso JE, Tracy CM, Woo YJ, Zhao DX. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. *Circulation*. 2013;127:529–555.
13. Rady MY, Ryan T. The effects of preoperative therapy with angiotensin-converting enzyme inhibitors on clinical outcome after cardiovascular surgery. *Chest*. 1998;114:487–494.
14. Rosenman DJ, McDonald FS, Ebbert JO, Erwin PJ, LaBella M, Montori VM. Clinical consequences of withholding versus administering renin-angiotensin-aldosterone system antagonists in the preoperative period. *J Hosp Med*. 2008;3:319–325.
15. Weightman WM, Gibbs NM, Sheminant MR, Whitford EG, Mahon BD, Newman MA. Drug therapy before coronary artery surgery: nitrates are independent

predictors of mortality and beta-adrenergic blockers predict survival. *Anesth Analg*. 1999;88:286–291.

16. Pigott DW, Nagle C, Allman K, Westaby S, Evans RD. Effect of omitting regular ACE inhibitor medication before cardiac surgery on haemodynamic variables and vasoactive drug requirements. *Br J Anaesth*. 1999;83:715–720.
17. Carrel T, Englberger L, Mohacsi P, Neidhart P, Schmidli J. Low systemic vascular resistance after cardiopulmonary bypass: incidence, etiology, and clinical importance. *J Card Surg*. 2000;15:347–353.
18. Mekontso-Dessap A, Houël R, Soustelle C, Kirsch M, Thébert D, Loisance DY. Risk factors for post-cardiopulmonary bypass vasoplegia in patients with preserved left ventricular function. *Ann Thorac Surg*. 2001;71:1428–1432.
19. Antunes PE, Prieto D, Ferrao de Oliveira J, Antunes MJ. Renal dysfunction after myocardial revascularization. *Eur J Cardiothorac Surg*. 2004;25:597–604.
20. Levin RL, Degrange MA, Bruno GF, Del Mazo CD, Taborda DJ, Griotti JJ, Boullon FJ. Methylene blue reduces mortality and morbidity in vasoplegic patients after cardiac surgery. *Ann Thorac Surg*. 2004;77:496–499.
21. Tsuyuki RT, McKelvie RS, Arnold JO, Avezum A, Barretto AC, Carvalho AC, Isaac DL, Kitching AD, Piegas LS, Teo KK, Yusuf S. Acute precipitants of congestive heart failure exacerbations. *Arch Intern Med*. 2001;161:2337–2342.
22. Devbhandari MP, Balasubramanian SK, Codispoti M, Nzewi OC, Prasad SU. Preoperative angiotensin-converting enzyme inhibition can cause severe post CPB vasodilation—current UK opinion. *Asian Cardiovasc Thorac Ann*. 2004;12:346–349.
23. Ghali WA, Knudtson ML. Overview of the Alberta provincial project for outcome assessment in coronary heart disease. *Can J Cardiol*. 2000;16:1225–1230.
24. van Diepen S, Graham MM, Nagendran J, Norris CM. Predicting cardiovascular intensive care unit readmission after cardiac surgery: derivation and validation of the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) cardiovascular intensive care unit clinical prediction model from a registry cohort of 10,799 surgical cases. *Crit Care*. 2014;18:651.
25. Benoit MA, Bagshaw SM, Norris CM, Zibdawi M, Chin WD, Ross DB, van Diepen S. Postoperative complications and outcomes associated with a transition to 24/7 intensivist management of cardiac surgery patients. *Crit Care Med*. 2017;45:993–1000.
26. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004;8:R204–R212.
27. The Society of Thoacic Surgeons: DataCollection. Available at: https://www.sts.org/registries-research-center/sts-national-database/adult-cardiac-surgery-database/data-collection. Accessed January 30, 2018.
28. Duceppe E, Parlow J, MacDonald P, Lyons K, McMullen M, Srinathan S, Graham M, Tandon V, Styles K, Bessissow A, Sessler DI, Bryson G, Devereaux PJ. Canadian cardiovascular society guidelines on perioperative cardiac risk assessment and management for patients who undergo noncardiac surgery. *Can J Cardiol*. 2017;33:17–32.
29. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, Davila-Roman VG, Gerhard-Herman MD, Holly TA, Kane GC, Marine JE, Nelson MT, Spencer CC, Thompson A, Ting HH, Uretsky BF, Wijeysundera DN. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *Circulation*. 2014;130:e278–e333.
30. Bertrand M, Godet G, Meersschaert K, Brun L, Salcedo E, Coriat P. Should the angiotensin II antagonists be discontinued before surgery? *Anesth Analg*. 2001;92:26–30.
31. Coriat P, Richer C, Douraki T, Gomez C, Hendricks K, Giudicelli J-F, Viars P. Influence of chronic angiotensin-converting enzyme inhibition on anesthetic induction. *Anesthesiology*. 1994;81:299–307.
32. Schirmer U, Schurmann W. Preoperative administration of angiotensin-converting enzyme inhibitors. *Anaesthesist*. 2007;56:557–561.
33. Roshanov PS, Rochwerg B, Patel A, Salehian O, Duceppe E, Belley-Cote EP, Guyatt GH, Sessler DI, Le Manach Y, Borges FK, Tandon V, Worster A, Thompson A, Koshy M, Devereaux B, Spencer FA, Sanders RD, Sloan EN, Morley EE, Paul J, Raymer KE, Punthakee Z, Devereaux PJ. Withholding versus continuing angiotensin-converting enzyme Inhibitors or angiotensin II receptor blockers before noncardiac surgery: an analysis of the vascular events In noncardiac surgery patIents cohort evaluation prospective cohort. *Anesthesiology*. 2017;126:16–27.
34. Oh YJ, Lee JH, Nam SB, Shim JK, Song JH, Kwak YL. Effects of chronic angiotensin II receptor antagonist and angiotensin-converting enzyme inhibitor treatments on neurohormonal levels and haemodynamics during cardiopulmonary bypass. *Br J Anaesth*. 2006;97:792–798.
35. Licker M, Neidhart P, Lustenberger S, Valloton MB, Kalonji T, Fathi M, Morel DR. Long-term angiotensin-converting Eezyme inhibitor treatment attenuates adrenergic responsiveness without altering hemodynamic control in patients undergoing cardiac surgery. *Anesthesiology*. 1996;84:789–800.
36. Almeida J, Galas F, Fukushima J, Almeida E, Gerent A, Osawa E, Park C, Nakamura R, Leme A, Sundin M, Filho RK, Jatene F, Hajjar L. Risk factors for severe vasodilatory shock after cardiac surgery. *Crit Care*. 2015;19:P149.
37. Comfere T, Sprung J, Kumar MM, Draper M, Wilson DP, Williams BA, Danielson DR, Liedl L, Warner DO. Angiotensin system Inhibitors in a general surgical population. *Anesth Analg*. 2005;100:636–644.

Supplemental Material

Table S1. **Physiologic, clinical, and health resource utilization outcomes according by study treatment received.**

	Continuation (n=56)	Discontinuation (n=65)	p value
Physiologic Outcomes			
Post-operative shock, n (%)	44 (78.6)	49 (75.4)	0.679
Duration of post-operative shock*, hours	12 (3, 24)	5 (1, 25)	0.439
Post-operative vasodilators, n (%)	39 (69.6)	53 (81.5)	0.126
Duration of post-operative vasodilators†, hours	12 (4, 20)	7 (4, 17)	0.284
Clinical Outcomes, n (%)			
Vasoplegic shock	17 (30.4)	19 (29.2)	0.893
Pre-operative heart failure	0 (0.0)	0 (0.0)	n/a
Post-operative acute kidney injury	1 (1.8)	1 (1.5)	0.915
Absolute change in serum creatinine, umol/L	9 (0, 16)	14 (6, 22)	0.061
30-day stroke‡	0 (0.0)	0 (0.0)	n/a
30-day all-cause mortality	1 (1.8)	1 (1.5)	0.915
ACE/ARB use at hospital discharge	35 (62.5)	33 (50.8)	0.195
Health Resource Outcomes			
Duration of mechanical ventilation, hours	6 (5, 8)	6 (5, 9)	0.431
CSICU LOS, hours	43 (23, 69)	27 (22, 73)	0.440
Renal replacement therapy, n (%)	0 (0.0)	1 (1.5)	0.351
Hospital LOS, days	7 (6, 13)	6 (5, 13)	0.592
CSICU readmission	2 (3.6)	2 (3.1)	0.879

Continuous variables presented as median (Q1, Q3)

† valid n=93 patient who were treated with intravenous vasopressors or inopressors ; ‡ valid n=92 patients treated with intravenous vasodilators

ACE, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; CSICU, cardiac surgical intensive care unit; LOS, length of stay

Table S2. **Physiologic, clinical and health resource utilization outcomes by treatment received stratified by the half-life (i.e., short (≤12 hours) or long (>12 hours) of ACE/ARB.**

† valid n=93 patient who were treated with intravenous vasopressors or inopressors ; ‡ valid n=92 patients treated with intravenous vasodilators.

	Long Half-life			Short Half-life		
	Continuation (n=444)	**Discontinuation (n=56)**	**p value**	**Continuation (n=12)**	**Discontinuation (n=9)**	**p value**
Physiologic Outcomes						
Post-operative shock, n (%)	34 (77.3)	41 (73.2)	0.642	10 (83.3)	8 (88.9)	0.719
Duration of post-operative shock*, median (Q1, Q3), hours	7 (3, 18)	4 (1, 23)	0.450	24 (14, 41)	11 (4, 36)	0.790
Post-operative vasodilators, n (%)	30 (68.2)	45 (80.4)	0.163	9 (75.0)	8 (88.9)	0.423
Duration of post-operative vasodilators†, median (Q1, Q3), hours	12 (4, 18)	9 (5, 18)	0.658	10 (3, 24)	3 (1, 11)	0.149
Clinical Outcomes, n (%)						
Vasoplegic shock	12 (27.3)	14 (25.0)	0.797	5 (41.7)	5 (55.6)	0.528
Pre-operative heart failure	0 (0.0)	0 (0.0)	n/a	0 (0.0)	0 (0.0)	n/a
Post-operative acute kidney injury	1 (2.3)	1 (1.8)	0.863	0 (0.0)	0 (0.0)	n/a
Absolute change in serum creatinine, median (Q1, Q3), umol/L,	9 (-1, 16)	10 (4, 20)	0.096	9 (2, 39)	16 (13, 28)	0.356
30-day stroke	0 (0.0)	0 (0.0)	n/a	0 (0.0)	0 (0.0)	n/a
30-day all-cause mortality	1 (2.3)	1 (1.8)	0.863	0 (0.0)	0 (0.0)	n/a
ACE/ARB use at hospital discharge	29 (65.9)	32 (57.1)	0.372	6 (50.0)	1 (11.1)	0.061
Health Resource Outcomes						
Duration of mechanical ventilation, median (Q1, Q3), hours	6 (5, 8)	6 (5, 8)	0.525	6 (5, 7)	9 (5, 11)	0.619
CSICU LOS, median (Q1, Q3), days	34 (24, 68)	27 (22, 75)	0.503	52 (22, 86)	27 (24, 70)	0.619
Renal replacement therapy, n (%)	0 (0.0)	1 (1.8)	0.373	0 (0.0)	0 (0.0)	n/a
Hospital LOS, median (Q1, Q3), days	7 (6, 12)	7 (5, 15)	0.964	9 (6, 18)	6 (6, 7)	0.119
CSICU readmission	1 (2.3)	2 (3.6)	0.706	1 (8.3)	0 (0.0)	0.375

ACE, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; CSICU, cardiac surgical intensive care unit; LOS, length of stay

Table S3. Use of intravenous vasoactive agent use by admission initiation in operating room versus CSICU in all patients and stratified by treatment arm.

	Overall		Discontinuation Arm		Continuation Arm	
	Pre-Admission	Post-admission	Pre-Admission	Post-admission	Pre-Admission	Post-admission
Vasopressors/inotropes	50	43	25	21	25	22
Vasopressors	46	45	22	22	24	23
Inotropes	5	11	4	7	1	4
Vasodilators	18	74	8	41	10	33