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Angiotensin –Converting Enzyme Inhibition or Mineralocorticoid Receptor Blockade Do Not Affect Incidence of Atrial Fibrillation in Patients Undergoing Cardiac Surgery

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Abstract

Objective—This study tested the hypothesis that interruption of the renin-angiotensin system with either an angiotensin-converting enzyme inhibitor or a mineralocorticoid receptor antagonist will decrease the incidence of atrial fibrillation after cardiac surgery.

Design—Randomized double-blind placebo-controlled study.

Setting—University affiliated hospitals.

Patients—Four-hundred and forty-five adult patients in normal sinus rhythm undergoing elective cardiac surgery.

Interventions—One week to four days prior to surgery, patients were randomized to treatment with placebo, ramipril (2.5 mg the first three days followed by 5mg/day, with the dose reduced to 2.5mg/d on the first postoperative day only), or spironolactone (25 mg/day).

Measurements—The primary endpoint was the occurrence of electrocardiographically confirmed postoperative atrial fibrillation. Secondary endpoints included acute renal failure, hyperkalemia, the incidence of hypotension, length of hospital stay, stroke, and death.

Main Results—The incidence of atrial fibrillation was 27.2% in the placebo group, 27.8% in the ramipril group, and 25.9% in the spironolactone group ($P=0.95$). Patients in the ramipril (0.7%) or spironolactone (0.7%) group were less likely to develop acute renal failure than those randomized to placebo (5.4%, $P=0.006$). Patients in the placebo group tended to be hospitalized longer than those in the ramipril or spironolactone group (6.8 ± 8.2 days versus 5.7 ± 3.2 and 5.8 ± 3.4 days, respectively, $P=0.08$ for the comparison of placebo versus the active treatment groups using log-rank test). Compared to patients in the placebo group, patients in the spironolactone group were extubated sooner after surgery (576.4 ± 761.5 minutes versus 1091.3 ± 3067.3 minutes, $P=0.04$).

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Conclusions—Neither angiotensin-converting enzyme inhibition nor mineralocorticoid receptor blockade decreased the primary outcome of postoperative atrial fibrillation. Treatment with an angiotensin-converting enzyme inhibitor or mineralocorticoid receptor antagonist was associated with decreased acute renal failure. Spironolactone use was also associated with a shorter duration of mechanical ventilation after surgery.

Keywords

angiotensin-converting enzyme inhibitors; aldosterone; atrial fibrillation; renal insufficiency; cardiac surgery

Postoperative atrial fibrillation (AF) complicates cardiac surgery in 20 to 40% of patients, and leads to significant morbidity, increased mortality, prolonged hospitalization, and higher hospital costs.(1–4) The pathophysiology of postoperative AF is complex and involves an interaction between surgical trauma, activation of the inflammatory response, preexisting atrial pathology and increased adrenergic tone.(5) Risk factors for postoperative AF include advanced age, prior history of AF, male gender, decreased left ventricular ejection fraction, left atrial enlargement, mitral valve surgery, chronic obstructive pulmonary disease, chronic renal failure, diabetes mellitus, postoperative withdrawal of β -blockers or angiotensin converting enzyme (ACE) inhibitors, and obesity.(1–4, 6, 7) Postoperative treatment with β -blockers or amiodarone, potassium supplementation, and preoperative treatment with statins have all been reported to reduce the risk of developing postoperative AF.(1, 8) With more than 500,000 patients undergoing cardiac surgical procedures in the United States each year, effective strategies to prevent postoperative AF could reduce morbidity and result in substantial cost savings.

Chronic ACE inhibitor use decreases incident AF in patients with congestive heart failure, and decreases recurrent lone AF in normotensive patients.(9–11) Preoperative ACE inhibitor use is common among patients undergoing cardiac surgery, but the effect of ACE inhibitor use on postoperative AF has not been studied prospectively in a randomized clinical trial. ACE inhibitors attenuate the inflammatory response to cardiac surgery and specifically reduce plasma concentrations of inflammatory biomarkers associated with the development of postoperative AF.(12, 13) Conversely, ACE inhibitor withdrawal is associated with postoperative AF.(3) Nevertheless, many physicians withhold ACE inhibitors in the perioperative period due to concerns about perioperative hypotension and impaired kidney function.(14–16)

Mineralocorticoid receptor (MR) blockers also reduce circulating concentrations of inflammatory biomarkers associated with postoperative AF,(12, 17) and may be expected to have less effect on perioperative blood pressure. We therefore conducted a prospective, randomized placebo-controlled clinical trial to investigate the risks and benefits of an ACE inhibitor or MR antagonist in patients undergoing cardiac surgery.

Methods

The Atrial Fibrillation and Renin Angiotensin Aldosterone System (RAAS) study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00141778) Identifier: NCT00141778) was approved by the Vanderbilt University Institutional Review Board for Research on Human Subjects and conducted according to the Declaration of Helsinki. All patients provided written informed consent. Patients were eligible for the study if they were undergoing elective cardiac surgery including coronary artery bypass graft or valvular surgery. Key exclusion criteria were chronic AF or paroxysmal AF within 6 months, an ejection fraction less than 30 per cent, evidence of coagulopathy, emergency surgery, serum creatinine greater than 1.6 mg/dL, and

hyperkalemia with potassium greater than 5.0 mEq/L. Patients undergoing off-pump surgery were initially excluded but, after consultation with the Data and Safety Monitoring Board (DSMB), the protocol was amended to include all patients undergoing cardiac surgery so as to increase enrollment.

One week to four days prior to surgery, patients were randomized to treatment with placebo, ramipril (2.5 mg the first three days followed by 5mg/day, with the dose reduced to 2.5mg/d on the first postoperative day only), or spironolactone (25 mg/day). Randomization was stratified by age, prior statin use, and prior ACE inhibitor, angiotensin receptor blocker, or MR antagonist use. Preexisting ACE inhibitor, angiotensin receptor blocker, or MR antagonist use was stopped at randomization.

Primary Outcome

The primary endpoint of the study was the occurrence of electrocardiographically confirmed AF of at least 10 seconds duration at any time following the end of surgery until hospital discharge. Patients were monitored continuously on telemetry throughout the postoperative period until discharge. Electrocardiograms were obtained for any rhythm changes detected on telemetry monitoring, and in addition, electrocardiograms were performed preoperatively, at admission to the intensive care unit, and daily starting on postoperative day one. All electrocardiograms and rhythm strips were reviewed in a blinded fashion by a single cardiac electrophysiologist. The duration and any type of intervention for postoperative AF were recorded. AF interventions included cardioversion, administration of a beta blocker or an increase in the dose of beta blocker, administration of amiodarone and/or calcium channel blocker.

Secondary Outcomes

Secondary endpoints were intraoperative mean arterial pressure, intraoperative and postoperative requirements for vasopressors, serum potassium and creatinine concentrations, central venous pressure measurements, postoperative fluid intake and output, weights, length of hospital stay, and death. Predefined criteria for stopping study medication were hypotension (defined as SBP less than 90 mmHg or prolonged need for vasopressors), serum potassium greater than 5.5 mEq/L if confirmed by a repeated measurement, and acute renal failure, defined as a serum creatinine greater than or equal to 2.5 mg/dL.

Predefined biomarkers included ACE activity and aldosterone concentrations, brain-natriuretic peptide, markers of oxidative stress (F₂-isoprostanes) inflammatory biomarkers (including interleukins, plasminogen activator inhibitor-1, C-reactive protein). ACE activity was not ascertained until the end of the study so as to avoid unblinding.

Standardized Patient Treatment

Anesthetic and surgical management were conducted according to institutional protocols as described in the supplemental digital content and previously published.(18)

Safety and Efficacy Analyses

The study was monitored by a 4-person DSMB. The DSMB completed a safety assessment after the first 100 subjects were enrolled and two interim analyses, after the 332 and 550 patients were consented. Mock unblinded data were presented to the DSMB. After the first interim analysis, the DSMB recommended expanding the study to an additional site to increase enrollment. A second site, the Brigham and Women's Hospital, Boston, MA, was added and consented 16 of the patients. At each interim analysis, the study could be stopped either due to efficacy or futility of the primary endpoint. For efficacy, the O'Brien and Fleming boundary was used for a total of 3 planned analyses. For futility, conditional

probability was computed given the observed data to estimate likelihood of finding a statistically significant difference in the incidence of AF. If there was a less than 20% chance (conditional probability given the observed data) of finding a statistically significant difference in the incidence of AF among the three treatment arms, the DSMB would recommend termination. After the second interim analysis the DSMB recommended study termination based on futility on the primary endpoint.

Statistical Considerations

The study originally planned to enroll 777 subjects, equally randomized into the three treatment arms. Sample size calculations were based on a 19.5% incidence of post-operative AF in patients without a prior history of AF enrolled in the Vanderbilt Cardiac Surgery Registry. Using a trend test and assuming rates of AF in the placebo, spironolactone, and ramipril arms, of 19.5%, 14.6% (25% reduction) and 9.75% (50% reduction), respectively, a total sample size of 777 subjects (259 in each arm) provided 88% power to detect a significant linear trend in the three proportions with a 2-sided significance level of 5%. The sample size provided a 72% power to detect a 25% reduction in the risk of AF in either arm.

Data are presented as means plus-minus standard deviations, unless otherwise stated. Discrete variables were compared among treatment groups using chi-square test or Fisher exact test depending on the number of events for three-group or pair-wise comparisons. Continuous variables were compared using one-way analysis of variance (ANOVA) for three group comparison or Kruskal-Wallis one-way ANOVA depending on whether data was normally distributed. For analysis of biomarkers, when appropriate based on biologic mechanism (such as interruption of the renin-angiotensin system versus not, diuresis versus not) one group was compared to the other two using a 2-sample t-test or Wilcoxon rank sum test. Log rank test was used to compare time to event data between groups. General linear models were used to adjust for covariates. All tests are two-tailed. Statistical analyses are performed using the statistical package SAS for Windows (Version 9, Cary, NC) and SPSS Statistics version 19.0 (SPSS Inc., Chicago Illinois).

Results

Six hundred ten patients were consented to participate in the study (Figure 1). Four hundred fifty-eight patients were randomized and were included in the intention-to-treat analysis. Additional details of enrollment appear in the supplement.

Table 1 provides baseline characteristics for the three treatment groups. The groups differed significantly in body mass index and the proportion of smokers, but were similar in all other characteristics prior to treatment.

Primary Outcome

The incidence of postoperative AF was similar among the three treatment groups (Table 2). This was true in the per-protocol analysis as well as the intention-to-treat analysis. The incidence AF lasting more than 12 hours as well as the frequency of intervention for AF was similar among the treatment groups. The incidence of AF was similar among the placebo, ramipril and spironolactone treatment groups even after stratification for prior ACE inhibitor or angiotensin receptor blocker use. In patients undergoing valvular surgery, the incidence of AF was 32.3% in the placebo group, 28.9% in the ramipril group, and 31.7% in the spironolactone group, $P=0.86$. In subjects not undergoing valvular surgery the incidence of AF was 16.7% in the placebo group, 25.5% in the ramipril group, and 13.0% in the spironolactone group, $P=0.30$. In patients with an ejection fraction less than 50%, the incidence of AF was 34.5% in the placebo group, 41.5% in the ramipril group, and 24.1% in

the spironolactone group, $P=0.21$. In patients with an ejection fraction greater than 50%, the incidence of AF was 34.0% in the placebo, 34.0% in the ramipril group, and 32.0% in the spironolactone group, $P=0.89$.

Secondary Outcomes

Pre-operative and intra-operative systolic (not shown), diastolic (not shown) and mean arterial (Figure 2A) pressures were similar among the three treatment groups. Patients in the ramipril treatment group were more likely to receive epinephrine during surgery, however (Figure 2B). Mean arterial and diastolic pressures were similar among the three study groups throughout the postoperative period. Systolic blood pressure was significantly higher in the placebo group compared to the ramipril and spironolactone treatment groups on postoperative day 4 (118.7 ± 17.5 mmHg versus 112.4 ± 17.1 mmHg in ramipril and 112.4 ± 15.2 mmHg in spironolactone group, $p < 0.001$) and 7 (121.4 ± 19.6 mmHg versus 114.8 ± 17.9 mmHg in ramipril and 108.7 ± 12.1 mmHg in spironolactone group, $p = 0.009$). The use of vasopressor agents in the postoperative period was similar among the treatment groups (not shown). Study medication was interrupted or discontinued due to low blood pressure in 8 patients randomized to placebo, 16 patients randomized to ramipril and 15 patients randomized to spironolactone.

Preoperative serum potassium concentrations were similar among the three treatment groups prior to cardiac surgery. During surgery, serum potassium concentrations were significantly increased in the spironolactone group compared to the other two groups (Figure 3). Study drug was discontinued due to hyperkalemia in only one patient in each treatment group, however.

Ten patients were discontinued from the study because the postoperative creatinine was 2.5mg/dL or greater (Table 3). Eight of these were in the placebo group ($P=0.006$). In addition, the rise in creatinine following surgery was significantly higher in placebo-treated patients compared to ramipril- or spironolactone-treated patients, after controlling for baseline estimated glomerular filtration rate and diuretic use from the day of surgery through postoperative day three (Figure 4).

Patients in the placebo group tended to stay in the hospital longer compared to patients in the ramipril and spironolactone groups combined ($P=0.08$). The incidences of myocardial infarction, stroke, pneumonia, adverse event, serious adverse event, and death were similar among the three treatment groups. None of the four deaths was judged to be study related.

Intraoperative central venous pressure was significantly decreased in the spironolactone group compared to in the placebo group. Brain natriuretic peptide concentrations was significantly lower in the spironolactone group compared to the other two groups combined on postoperative day 1 (1.14 ± 1.19 pg/mL versus 1.48 ± 2.42 pg/mL in the placebo group and 1.57 ± 2.66 pg/mL in the ramipril group, $P=0.049$), but not at other time points. There was no difference in daily fluid balance among the three treatment groups (Table 3).

The time-to-tracheal extubation was shorter in the spironolactone group than in the placebo and ramipril groups combined ($P=0.03$ by t-test). Because the data were not normally distributed and transformations did not correct this, and because this is time to event data, we also performed a log-rank test ($P=0.04$ for spironolactone versus placebo). The type of surgical procedure, frequency of off-pump procedures, CPB and aorta cross-clamp times, and chest tube output were similar among the three treatment groups (Supplemental digital content Table 1).

Endocrine Measures

ACE activity was significantly lower at initiation of surgery in patients randomized to ramipril compared to in patient randomized to placebo or spironolactone (Figure 3). This was true among subjects who had been treated with an ACE inhibitor prior to randomization (ACE activity in placebo, ramipril and spironolactone groups 28.1 ± 16.3 U/L, 7.2 ± 5.7 U/L, and 31.6 ± 15.6 U/L, respectively, $P < 0.001$), as well as in those who had not (ACE activity in placebo, ramipril, and spironolactone groups 34.8 ± 12.5 U/L, 7.5 ± 8.1 U/L, and 34.0 ± 13.9 U/L, respectively, $P < 0.001$).

Preoperative serum aldosterone concentration was significantly lower in the ramipril group compared to either the placebo group or the spironolactone treatment group (Figure 3), and trended higher in the spironolactone group compared to placebo ($P = 0.096$). Intraoperative (60 minute) glucose concentrations were also significantly higher in the spironolactone group compared to the other two groups (195.3 ± 53.9 mg/dL in the spironolactone group versus 148.2 ± 55.2 mg/dL in the placebo group and 155.2 ± 44.4 mg/dL in the ramipril group, $P < 0.05$ for the ANOVA and for the individual comparisons).

Inflammatory Biomarkers

Postoperative interleukin (IL)-6 and plasminogen activator inhibitor-1 (PAI-1) concentrations were significantly higher in patients who developed postoperative AF than in those who did not (Supplemental digital content Table 2). Postoperative F₂-isoprostane concentrations did not differ significantly between patients with and without postoperative AF.

There were no differences in pre-operative or postoperative F₂-isoprostanes or PAI-1 among the treatment groups (Supplemental digital content Table 3). IL-6 was increased in the ramipril group compared to the placebo group in the immediate postoperative period, but did not reach statistical significance (202.1 ± 668.7 vs 130.0 ± 213.7 pg/ml, $P = 0.79$). CRP was significantly lower in the spironolactone treatment group on postoperative day 2 ($P = 0.04$ for effect of treatment). Intra-operative tissue-type plasminogen activator concentrations were higher in the ramipril group compared to the other two groups ($P = 0.004$).

Discussion

ACE inhibition or MR antagonism did not alter the risk of postoperative AF in this randomized, placebo-controlled study. Ramipril and spironolactone treatment decreased the incidence of acute renal failure, however, and tended to shorten the length of hospitalization. Spironolactone treatment also shortened the time to tracheal extubation following surgery.

ACE inhibitor use has been reported to reduce the incidence of new onset AF in randomized clinical trials in patients with left ventricular dysfunction,(10, 11) but not in patients without known left ventricular dysfunction.(19) Mathew et al reported that withdrawal of ACE inhibitor use during the perioperative period was associated with an increased risk of postoperative AF whereas continuation of ACE inhibitor use was associated with a decreased risk of AF in patients undergoing cardiac surgery.(3) Dabrowski et al also reported a protective effect of preoperative ACE inhibitor use in a retrospective study of 217 patients undergoing cardiac surgery.(20) In contrast, two recent retrospective studies reported no protective effect of preoperative ACE inhibitor use on the risk of postoperative AF.(21, 22) Our study also showed no effect of ACE inhibition on AF, and was stopped early due to futility. Unlike prior studies, the present study was a double-blind, placebo-controlled prospective trial.

Observational studies have also provided conflicting data regarding the effect of ACE inhibition on kidney function following cardiac surgery. Confounding by indication may influence the findings of nonrandomized studies. Patients prescribed ACE inhibitors may be more likely to have risk factors for kidney injury such as diabetes or preexisting renal disease. (23, 24) At least one study reporting an increased incidence of postoperative renal dysfunction in ACE inhibitor users did not differentiate between patients taking an ACE inhibitor and those taking an angiotensin receptor blocker. (15) Our findings agree with the propensity-adjusted analysis of Benedetto et al, who reported that the incidence of acute kidney injury, defined as a 50 per cent decline in glomerular filtration rate, in patients undergoing coronary artery bypass grafting was decreased in preoperative users of ACE inhibitors.(25)

Ramipril and spironolactone treatment were associated with a decrease in postoperative acute renal failure. Differences in concurrent medication use may have confounded prior studies regarding the relationship of ACE inhibition on the risk of acute renal failure.(26, 27) In particular, use of the antifibrinolytic agent aprotinin has been associated with acute renal injury and death. At least two studies have suggested an interactive effect of aprotinin and ACE inhibition on the risk of acute renal injury.(28, 29) Few patients received aprotinin in the present study. Discontinuation of study drug in patients with low blood pressure could have preserved renal perfusion in patients taking ramipril or spironolactone; however, the incidence of acute renal failure was increased in the placebo group even when patients in whom study drug was held were excluded.

Inflammatory cytokines and acute phase reactants such as PAI-1 are increased during the perioperative period in patients who develop AF,(12, 30) suggesting the hypothesis that therapies that reduce the inflammatory response to surgery will reduce postoperative AF. (31) In two small randomized trials in chronic ACE inhibitor users, postoperative PAI-1 concentrations were lower in patients continued on ACE inhibitor therapy compared to in patients whose ACE inhibitor was stopped prior to cardiac surgery.(13, 32) MR antagonists also reduce inflammatory cytokines and PAI-1 in normotensive or hypertensive subjects.(33, 34) In the present clinical trial, we observed the previously reported association between the inflammatory response to cardiac surgery and postoperative AF. In contrast, short-term preoperative ramipril or spironolactone use did not significantly decrease PAI-1 concentrations in this study.

Unexpectedly, concentrations of the inflammatory cytokine IL-6 were increased at the end of surgery and during the first postoperative day in patients randomized to ramipril compared to in those taking placebo. Fleming and co-workers also recently reported that concentrations of the inflammatory cytokines IL-6 and IL-8 were increased in the first postoperative day in children undergoing cardiac surgery randomized to an ACE inhibitor. (32) Activation of the kallikrein-kinin system contributes to both enhanced fibrinolysis and inflammation following cardiac surgery and, thus, potentiation of the kallikrein-kinin system could account for the increased intraoperative tissue-type plasminogen activator concentrations and increased postoperative inflammation observed in the ramipril group.

Prior observational studies have suggested that ACE inhibitor use is associated with either vasodilatory vasoplegic syndrome or with hypotension in the postoperative period.(16, 35) Compared to patients randomized to placebo or spironolactone, patients randomized to ramipril were more likely to receive epinephrine during surgery in the present study. Intraoperative blood pressure and the use of other vasoconstrictors were similar among treatment groups, however. Patients randomized to either ramipril or spironolactone was more likely to have study medication held or discontinued due to predefined criteria for hypotension. Nevertheless, there were no adverse events attributable to hypotension,

supporting that ACE inhibitors and spironolactone may be used safely if hypotension is avoided.

Consistent with data in animal models and in patients with acute lung injury indicating that diuretic use or fluid restriction improve lung function and decrease dependence on mechanical ventilation,(36, 37) we found that patients randomized to spironolactone required a shorter duration of mechanical ventilation following surgery. The finding that central venous pressure was decreased in this group, suggests that lower intravascular pressures may have led to improved postoperative lung function in patients receiving spironolactone. Spironolactone could also have affected the pulmonary and systemic vasculature by improving endothelial function and decreasing vasoconstriction.(38)

A few limitations warrant mention. This study was conducted primarily in one medical center and the outcomes reflect the surgical population and practices of this population. A large proportion of patients underwent valve surgery. We excluded patients with an ejection fraction less than 30% or a creatinine above 1.6 and therefore the results are not applicable to patients with left ventricular dysfunction or more severe chronic kidney disease. Approximately one third of patients took an ACE inhibitor prior to study enrollment. The results of the study may have been different had we studied only chronic ACE inhibitor users. It is possible that the results would have been different had we studied a higher dose of ACE inhibitor or spironolactone or a longer duration of therapy could have had an effect; however, the biochemical data- such as ACE activity, aldosterone, potassium concentrations, and brain natriuretic peptide concentrations-indicate that washout was sufficient and that therapeutic dosing was achieved.

This randomized clinical trial does not support the use of ACE inhibition or MR antagonism to prevent postoperative AF in patients undergoing cardiac surgery. In contrast, this study provides evidence that interrupting the renin-angiotensin-aldosterone system may reduce the incidence of acute renal failure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Enrollment and study progress.

Figure 2. (A) Mean arterial pressure (MAP) during surgery and on each postoperative day (POD). (B) Proportion of patients treated with specific vasopressors and inotropes during surgery. Data are presented as means $\pm$ SEM.

Figure 3.

(A) Angiotensin-converting enzyme (ACE) and (B) aldosterone concentrations at the initiation of surgery in patients randomized to placebo, ramipril or spironolactone. (C) Serum potassium concentrations during surgery and on each postoperative day (POD). Data are presented as means $\pm$ SEM. * $P < 0.05$ versus the other two study groups, † $P < 0.05$ versus spironolactone group.

Figure 4.

Change in creatinine after controlling for baseline glomerular filtration rate and diuretic use on the day of surgery through the third postoperative day. Data are presented as estimated marginal mean $\pm$ SEM. The estimated marginal means were calculated after controlling for baseline glomerular filtration rate and diuretic use. $P<0.01$ for placebo versus either ramipril or spironolactone.

Table 1

Characteristics of the Patients at Baseline

Variable	Placebo (N=147)	Ramipril (N=151)	Spironolactone (N=147)	P value
Age (yr)	60.0±12.0	58.7±12.3	59.2±12.3	0.64
Male sex (%)	64.0	70.2	65.3	0.48
Race (% white)	93.9	93.4	92.5	0.92
Body-mass index (kg/M ²)	30.1±6.3	29.2±5.4	28.3±5.8	0.03
Current Smoker (%)	16.3	10.6	23.1	0.02
History of hypertension (%)	66.0	58.9	63.3	0.45
History of diabetes (%)	20.4	23.8	20.4	0.73
Blood Pressure (mmHg)				
Systolic	128.6±14.6	129.2±16.5	131.9±17.3	0.16
Diastolic	74.0±11.5	74.3±11.6	75.0±10.7	0.71
Ejection fraction (%)	57.5±8.4	57.3±9.4	56.6±9.8	0.69
Serum creatinine (mg/dL)	1.00±0.23	0.99±0.22	1.00±0.21	0.93
Estimated glomerular filtration rate (mL/min/1.73 m ²)	79.4±22.3	80.8±19.0	78.4±19.0	0.59
Serum potassium (mEq/L)	4.19±0.42	4.21±0.42	4.21±0.39	0.91
Medications (%)				
ACE inhibitor	36.7	38.4	31.3	0.41
Ang receptor blocker	17.0	13.3	19.7	0.32
MR antagonist	1.4	0	1.4	0.40
Thiazide diuretic	19.0	15.2	21.1	0.50
Loop diuretic	18.4	13.9	17.7	0.51
Beta-blocker	49.0	50.3	50.3	0.97
Calcium channel blocker	18.4	19.2	16.3	0.82
Statin	57.1	53.6	52.4	0.69

To convert the values for creatinine to micromoles per liter, multiply by 88.4. Race and ethnicity were self-reported.

Table 2

Primary outcome among treatment groups

Event	Placebo (N=147)	Ramipril (N=151)	Spironolactone (N=147)	P value
Atrial Fibrillation (AF), n (%)	40 (27.2)	42 (27.8)	38 (25.9)	0.95
AF duration > 12 hours, n (%)	18/40 (45.0)	20/42 (47.6)	16/38 (42.1)	0.80
AF intervention, n (%) [*]	35/40 (87.5)	37/42 (88.1)	32/38 (84.2)	0.86

^{*} AF intervention was defined as cardioversion, beta blocker, amiodarone and/or calcium channel blocker administration.

Table 3

Secondary outcomes among treatment groups

Event	Placebo (N=147)	Ramipril (N=151)	Spironolactone (N=147)	P value
Creatinine>2.5mg/dL, n (%)	8 (5.4)	1 (0.7)	1 (0.7)	0.006
Hypotension, n (%) [*]	8 (5.4)	16 (10.6)	15 (10.2)	0.15
Central venous pressure (mmHg)	12.7±5.4	12.2±5.0	11.1±4.9 [†]	0.03
Net Fluid Balance (mL)				
Day of Surgery	679.7±1079.6	593.2±1073.8	610.1±995.9	0.93
Postoperative Day 1	-526.5±1314.2	-493.8±1315.8	-662.6±1243.1	0.64
Postoperative Day 2	-1014.8±1393.2	-813.1±1485.2	-1017.6±1189.5	0.36
Postoperative Day 3	-1035.9±1212.2	-908.9±1182.3	-810.2±1175.0	0.36
Potassium>5.5mEq/L, n (%)	1 (0.7)	1 (0.7)	1 (0.7)	1.00
Potassium <3.5mEq/L	17 (11.6)	21 (13.8)	10 (6.8)	0.14
postoperative day 1–4, n (%)				
Time-to-tracheal extubation (min)	1091.3±3067.3	970.1±3548.1	576.4±761.5 [‡]	0.56
Length of Hospital Stay (days)	6.8±8.2 [§]	5.7±3.2	5.8±3.4	0.15
Death, n (%)	2 (1.4)	3 (2.0)	0 (0)	0.38
Myocardial Infarction, n (%)	3 (2.0)	1 (0.7)	4 (2.7)	0.37
Stroke, n (%)	4 (2.7)	2 (1.3)	3 (2.0)	0.65
Pneumonia, n (%)	6 (4.1)	4 (2.6)	2 (1.4)	0.34
Serious adverse event, n (%)	8 (5.4)	6 (4.0)	5 (3.4)	0.70
Adverse event, n (%)	15 (10.2)	14 (9.3)	11 (7.5)	0.73

^{*} Hypotension was defined as a systolic blood pressure <90 mmHg and/or prolonged requirement for pressor use. For hypotension, the placebo vs ramipril comparison P=0.10; the placebo vs spironolactone comparison P=0.13; the placebo vs ramipril and spironolactone combined comparison P=0.08 using chi-square test. Intraoperative central venous pressure was calculated as the means made at the initiation of surgery and at 30 minutes and 1 hour of surgery.

[†] P<0.05 versus placebo.

[‡] P=0.04 versus placebo, by log-rank test.

[§] P=0.08 versus the other two treatment groups by log-rank test.