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Continuation vs Discontinuation of Renin-Angiotensin System Inhibitors Before Major Noncardiac Surgery

The Stop-or-Not Randomized Clinical Trial

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IMPORTANCE Before surgery, the best strategy for managing patients who are taking renin-angiotensin system inhibitors (RASIs) (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) is unknown. The lack of evidence leads to conflicting guidelines.

OBJECTIVE To evaluate whether a continuation strategy vs a discontinuation strategy of RASIs before major noncardiac surgery results in decreased complications at 28 days after surgery.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial that included patients who were being treated with a RASI for at least 3 months and were scheduled to undergo a major noncardiac surgery between January 2018 and April 2023 at 40 hospitals in France.

INTERVENTION Patients were randomized to continue use of RASIs (n = 1107) until the day of surgery or to discontinue use of RASIs 48 hours prior to surgery (ie, they would take the last dose 3 days before surgery) (n = 1115).

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of all-cause mortality and major postoperative complications within 28 days after surgery. The key secondary outcomes were episodes of hypotension during surgery, acute kidney injury, postoperative organ failure, and length of stay in the hospital and intensive care unit during the 28 days after surgery.

RESULTS Of the 2222 patients (mean age, 67 years [SD, 10 years]; 65% were male), 46% were being treated with angiotensin-converting enzyme inhibitors at baseline and 54% were being treated with angiotensin receptor blockers. The rate of all-cause mortality and major postoperative complications was 22% (245 of 1115 patients) in the RASI discontinuation group and 22% (247 of 1107 patients) in the RASI continuation group (risk ratio, 1.02 [95% CI, 0.87-1.19]; *P* = .85). Episodes of hypotension during surgery occurred in 41% of the patients in the RASI discontinuation group and in 54% of the patients in the RASI continuation group (risk ratio, 1.31 [95% CI, 1.19-1.44]). There were no other differences in the trial outcomes.

CONCLUSIONS AND RELEVANCE Among patients who underwent major noncardiac surgery, a continuation strategy of RASIs before surgery was not associated with a higher rate of postoperative complications than a discontinuation strategy.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03374449

Visual Abstract

Supplemental content

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Group Information: A list of the Stop-or-Not Trial Group appears in Supplement 4.

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Many patients who undergo major surgery have a history of hypertension, diabetes, and heart failure, and are often being treated long-term with a renin-angiotensin system inhibitor (RASI; angiotensin-converting enzyme inhibitors [ACEIs] or angiotensin receptor blockers [ARBs]).[1] The best strategy for managing these medications before major surgery is unknown, and there is little evidence from randomized clinical trials to inform guidelines. The continuation of RASIs might lead to intraoperative hypotension, which has been associated with postoperative complications, including cardiovascular events and acute kidney injury.[2] However, the discontinuation of RASIs also might lead to complications, including postoperative hypertension, heart failure, and arrhythmia.[3]

The 2014 guidelines from the European Society of Cardiology and the European Society of Anesthesiology[4] stated that withholding RASI therapy preoperatively should be considered in patients with hypertension (weak recommendation). During the same year, the American College of Cardiology/American Heart Association[5] issued guidelines that stated the perioperative continuation of RASIs is reasonable (weak recommendation). The most recent guidelines from the European Society of Cardiology[6] in 2022 also underscored the lack of data, but noted withholding RASI therapy in patients with hypertension could be considered to prevent intraoperative hypotension, and continuing RASI therapy in patients with heart failure is acceptable.

We conducted the Stop-or-Not trial to compare the effect of a strategy of preoperative discontinuation of RASI therapy vs a strategy of preoperative continuation of RASI therapy on all-cause mortality and postoperative complications after major noncardiac surgery.

Key Points

Question Is a continuation strategy of renin-angiotensin system inhibitors before major noncardiac surgery associated with better postoperative outcomes than discontinuation?

Findings In this multicenter randomized clinical trial that included 2222 patients, the rate of all-cause mortality and major postoperative complications was 22% in the discontinuation group and 22% in the continuation group (risk ratio, 1.02).

Meaning In patients undergoing major noncardiac surgery and treated long-term with renin-angiotensin system inhibitors, a continuation strategy of the medication was associated with a similar rate of all-cause mortality and major postoperative complications compared with a discontinuation strategy.

Methods

Trial Design

The Stop-or-Not study was an investigator-initiated, multicenter, open-label, randomized clinical trial conducted at 40 French hospitals. The steering committee members designed the trial, gathered and analyzed the data, prepared the manuscript, and, with their coauthors, decided to submit it for publication. The detailed trial protocol was published[7] and appears in Supplement 1.

The clinical events committee reviewed and validated all primary outcome events and was blinded to study group assignment (eList in Supplement 2). The trial protocol was approved by an institutional review board (Ile de France V No. 2017-002114-30). Patients were enrolled after providing written informed consent.

Patient Selection and Randomization

Patients aged 18 years or older were enrolled if they were scheduled for elective major noncardiac surgery and if they were being treated long-term with ACEIs or ARBs for at least 3 months before surgery. Major surgery was defined as a procedure with an expected duration of more than 2 hours from surgical incision to skin closure and an expected postoperative hospital stay of at least 3 days. After enrollment, patients were randomized at a 1:1 ratio to continue or discontinue RASI therapy (**Figure 1**), with stratification by hospital site and by heart failure status (New York Heart Association stage <II or ≥II).

The exclusion criteria were emergency surgery, hyperkalemia, terminal illness (ie, death deemed inevitable within 1 month), severe kidney insufficiency (estimated glomerular filtration rate <15 mL/min/1.73 m^2 or requiring kidney replacement therapy), preoperative shock (determined by the need for vasoactive drugs before surgery), and lack of social insurance.

Description of the Strategies

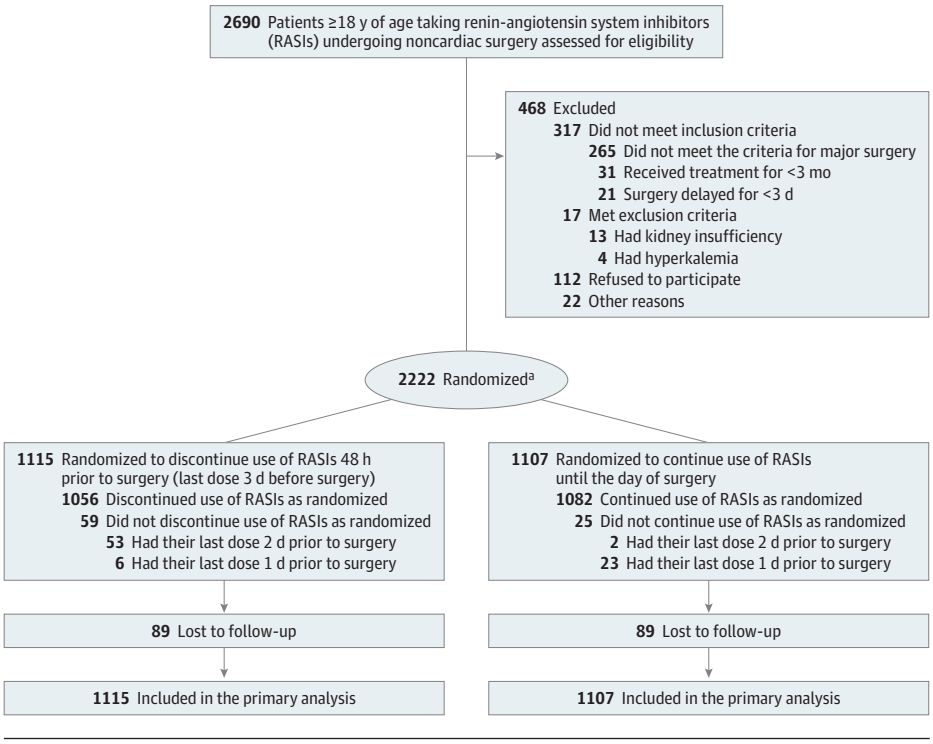
In the continuation strategy group, RASI therapy was continued until the day of the surgery. In the discontinuation strategy group, RASI therapy was stopped 48 hours prior to surgery (ie, they would take the last dose 3 days before surgery). The 48-hour window was chosen to avoid residual RAS blockage after the treatments were administered while keeping the trial pragmatic.

A prescription indicating the strategy (continue or discontinue use of RASI) was generated automatically, printed, and then handed and explained to the patient. Every patient received a phone call from a clinical research assistant 3 days before surgery to ensure a good understanding of the instructions and also received a leaflet to record daily intake of RASI pills.[7] In each study group, patients were to resume RASI therapy as soon as possible after surgery when the oral route was deemed feasible, and in the absence of hypotension or worsening kidney function.

Primary and Secondary Outcomes

The primary outcome was a composite of all-cause mortality and major postoperative complications, which included (1) postoperative major cardiovascular events (acute myocardial infarction, arterial or venous thrombosis, stroke, acute pulmonary edema, cardiogenic shock, acute severe hypertension, de novo cardiac arrhythmia requiring therapeutic intervention), (2) sepsis or septic shock (defined according to the Sepsis-3 definition[8]), (3) respiratory complications (determined by the need for reintubation or noninvasive ventilation for respiratory failure), (4) unplanned intensive care unit (ICU) admission or readmission, (5) acute kidney injury (based

Figure 1. Patient Selection, Randomization, and Flow Through the Trial



[a]Stratified by hospital site and history of chronic heart failure status (New York Heart Association stage <II or ≥II).

on the serum creatinine item of the Kidney Disease Improving Global Outcome criteria[9]), (6) hyperkalemia (serum potassium level >5.5 mmol/L requiring therapeutic intervention[10]), and (7) need for surgical reintervention within 28 days after surgery (eMethods in Supplement 2).

The secondary outcomes were intraoperative hypotension (defined as a mean arterial pressure <60 mm Hg or required treatment with vasopressors), all-cause mortality, episodes of acute kidney injury, postoperative organ failure (assessed by the maximum Sequential Organ Failure Assessment score on day 7),[11] and length of stay in the hospital and ICU during the 28 days after surgery.

Description of Parameters for Assessing Efficacy Outcomes

Patients were followed up from hospital admission until postoperative day 28. Investigators and research staff members responsible for the primary outcome assessment were unaware of group assignments. A double-blinded trial was not feasible due to the large number of RASIs available on the market, making the generation of placebos infeasible. A clinical events committee (blinded to group assignment) reviewed all adverse events to determine if the study outcome had been reached (eList in Supplement 2).

Statistical Analysis

Based on an estimated incidence of 25% for the primary outcome,[8] enrolling 2222 patients would allow 80% power to detect a relative decrease of 20% in complications in the RASI continuation group (corresponding to an absolute reduction of 5% for incidence of the primary outcome) using the χ^2 test, and considering that the 2 interim analyses led to a final test at a nominal α level of .0465 according to the O'Brien-Fleming method. The primary analysis was performed using the intention-to-treat principle, and comparing the composite outcome measures at 28 days by study group using the χ^2 test.

There was no plan to address multiplicity; therefore, hypothesis testing is limited to the primary outcome. The adjusted analysis was performed using a mixed-effects logistic regression analysis, adjusting for baseline variables (age, sex, diabetes status, heart failure status, baseline serum creatinine level, and baseline hemoglobin level), and using hospital site as a random effect.

The sample size calculation was performed using the Pro tier of nQuery version 4 (Statistical Solutions Ltd). All statistical analyses were performed using R version 3.6.2 (R Foundation for Statistical Computing). $P < .05$ was considered statistically significant. More detailed information on the statistical analysis appears in the statistical analysis plan in Supplement 3 and in the eMethods in Supplement 2.

Results

Patient Enrollment and Follow-Up

From January 2018 to April 2023, 2690 patients were assessed for enrollment at 40 hospitals (Figure 1) and 2222 were randomly assigned to a RASI discontinuation strategy (1115 patients) or a RASI continuation strategy (1107 patients). The baseline characteristics were comparable between the groups (**Table 1**). Of the 2222 patients (mean age, 67 years [SD, 10 years];

Table 1. Baseline Demographic and Perioperative Characteristics

	Discontinue use of RASIs (n = 1115)	Continue use of RASIs (n = 1107)
Age, median (IQR), y	68 (61-73)	68 (61-73)
Sex, No. (%)		
Male	730 (65)	721 (65)
Female	385 (35)	386 (35)
Body mass index, median (IQR)[a]	28 (25-32)	28 (25-32)
Coexisting medical condition, No. (%)		
Hypertension	1096 (98)	1083 (98)
Coronary artery disease	179 (16)	183 (17)
Peripheral artery disease	158 (14)	172 (16)
Obstructive sleep apnea	156 (14)	134 (12)
Chronic obstructive pulmonary disease	112 (10)	114 (10)
Chronic kidney disease	102 (9)	96 (9)
Diabetes	89 (8)	87 (8)
History of stroke	74 (7)	67 (6)
Heart failure	72 (6)	69 (6)
Currently smoke	153 (14)	179 (16)
Long-term medication use, No. (%)		
Angiotensin receptor blockers	595 (54)	594 (54)
Statins	515 (46)	473 (43)
Angiotensin-converting enzyme inhibitors	513 (46)	509 (46)
Aspirin	393 (35)	374 (34)
Calcium channel blockers	349 (31)	364 (33)
Diuretics	348 (31)	362 (33)
β-Blockers	334 (30)	354 (32)
Preoperative levels, median (IQR)		
Hemoglobin, g/dL	13.5 (12.5-14.6)	13.6 (12.5-14.6)
Creatinine, mg/dL	0.9 (0.7-1.1)	0.9 (0.7-1.1)
Preoperative hemodynamic parameters, median (IQR)		
Systolic blood pressure, mm Hg	134 (124-146)	131 (121-143)
Diastolic blood pressure, mm Hg	95 (87-103)	93 (85-101)
Ejection fraction, %	57 (49-64)	55 (45-62)
Intraoperative care, No. (%)		
Invasive blood pressure monitoring	329 (30)	334 (30)
Cardiac output or stroke volume monitoring	152 (14)	136 (12)
Central venous pressure monitoring	139 (12)	145 (13)
Neuraxial block	128 (11)	135 (12)
Type of surgery, No. (%)		
Abdominal	376 (34)	364 (33)
Thoracic	177 (16)	192 (17)
Vascular	127 (11)	131 (12)
Urological	112 (10)	106 (10)
Orthopedic	96 (9)	96 (9)
Pelvic	65 (6)	71 (6)
Neurosurgical	53 (5)	52 (5)
Liver	45 (4)	44 (4)
Other[b]	64 (6)	51 (5)
Duration of surgery, median (IQR), min	182 (130-270)	187 (126-270)

Abbreviation: RASIs, renin-angiotensin system inhibitors.

SI conversion factor: To convert creatinine to μmol/L, multiply by 88.4.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Includes otorhinolaryngology (n = 61), reconstruction surgery (n = 37), and not defined (n = 17).

Table 2. Primary and Secondary Outcomes

	No. (%)[a]				
	Discontinue use of RASIs (n = 1115)	Continue use of RASIs (n = 1107)	Between-group difference (95% CI), %[a]	Unadjusted risk ratio (95% CI)[b]	Adjusted odds ratio (95% CI)[a,c]
Primary outcome[d]					
All patients	245 (22)	247 (22)	0 (−3 to 4)	1.02 (0.83 to 1.25)	1.01 (0.82 to 1.24)
Components of the primary outcome					
All-cause mortality	11 (1)	12 (1)	0 (−1 to 1)	1.10 (0.49 to 2.48)	1.12 (0.48 to 2.58)
Type of postoperative event					
Cardiovascular[e]	52 (5)	52 (5)	0 (−2 to 2)	1.01 (0.69 to 1.47)	1.01 (0.68 to 1.50)
Sepsis	20 (2)	18 (2)	0 (−1 to 1)	0.91 (0.48 to 1.70)	0.91 (0.47 to 1.74)
Respiratory complication[f]	36 (3)	33 (3)	0 (−2 to 1)	0.92 (0.58 to 1.47)	0.94 (0.58 to 1.52)
Acute kidney injury	121 (11)	122 (11)	0 (−2 to 3)	1.02 (0.80 to 1.29)	0.98 (0.74 to 1.29)
Hyperkalemia	21 (2)	27 (2)	1 (−1 to 2)	1.30 (0.74 to 2.28)	1.34 (0.73 to 2.46)
Unplanned admission to intensive care unit	52 (5)	50 (5)	0 (−2 to 2)	0.97 (0.66 to 1.42)	0.94 (0.62 to 1.41)
Reoperation or radiological intervention	86 (8)	95 (9)	1 (−1 to 3)	1.11 (0.84 to 1.47)	1.11 (0.81 to 1.51)
Secondary outcomes					
Episodes of hypotension (required treatment with vasopressors)	417 (41)	544 (54)	13 (9 to 17)	1.31 (1.19 to 1.44)	1.78 (1.47 to 2.16)
Duration of hypotension, median (IQR), min	6 (4 to 12)	9 (5 to 16)	MD, 3.7 (1.4 to 6.0)		AMD, 3.45 (1.11 to 5.78)
Sequential Organ Failure Assessment score at 7 d, median (IQR)[g,h]	3 (1 to 5)	2 (1 to 7)	MD, −0.24 (−1.90 to 1.41)		AMD, −0.01 (−1.73 to 1.71)
Length of hospital stay, median (IQR), d	6 (3 to 8)	5 (3 to 9)	MD, −0.23 (−0.78 to 0.32)		AMD, −0.21 (−0.77 to 0.35)
Length of intensive care unit stay, median (IQR), d[g]	6 (3 to 9)	6 (3 to 10)	MD, 1.07 (−1.63 to 3.78)		AMD, 0.79 (−2.23 to 3.81)
Hospital-free days at day 28 (IQR), d	22 (20 to 25)	23 (19 to 25)	MD, 0.22 (−0.33 to 0.76)		AMD, 0.20 (−0.36 to 0.75)

Abbreviations: AMD, adjusted mean difference; MD, mean difference; RASIs, renin–angiotensin system inhibitors.

[a] Unless otherwise indicated.

[b] The 95% CIs were not adjusted for multiplicity.

[c] Adjusted for age, sex, diabetes status, heart failure status, preoperative serum creatinine level, and preoperative hemoglobin level.

[d] The primary outcome was a composite of all-cause mortality and major postoperative complications (including major cardiovascular events, sepsis or septic shock, respiratory complications, unplanned intensive care unit admission or readmission, acute kidney injury, hyperkalemia, and need for surgical reintervention) within 28 days after surgery.

[e] Included acute myocardial infarction, arterial or venous thrombosis, stroke, acute pulmonary edema, cardiogenic shock, acute severe hypertension crisis, de novo cardiac arrhythmia requiring therapeutic intervention (eTable 1 in Supplement 2).

[f] Patient needed reintubation or noninvasive ventilation for respiratory failure.

[g] Among patients with an unplanned admission to the intensive care unit.

[h] The score range is 0 to 4 points; a higher score indicates a worse predicted outcome.

65% were male), 98% were being treated for hypertension, 9% had chronic kidney disease, 8% had diabetes, and 6% had heart failure.

Treatment Strategies

Of the 2222 patients at baseline, 46% were being treated with ACEIs and 54% were being treated with ARBs. Adherence to the study instructions was excellent (96.3% of patients had complete adherence). Among the patients in the RASI continuation group, they stopped treatment at a median of 0 days (IQR, 0-0 days) before surgery compared with a median of 3 days (IQR, 3-3 days) in the RASI discontinuation group. In the RASI discontinuation group, 6 patients (1%) took their last dose 1 day before surgery and 53 patients (6%) took their last dose 2 days before surgery. In the RASI continuation group, 23 patients (2%) took their last dose 1 day before surgery and 2 patients (<1%) took their last dose 2 days before surgery (eFigure 1 in Supplement 2).

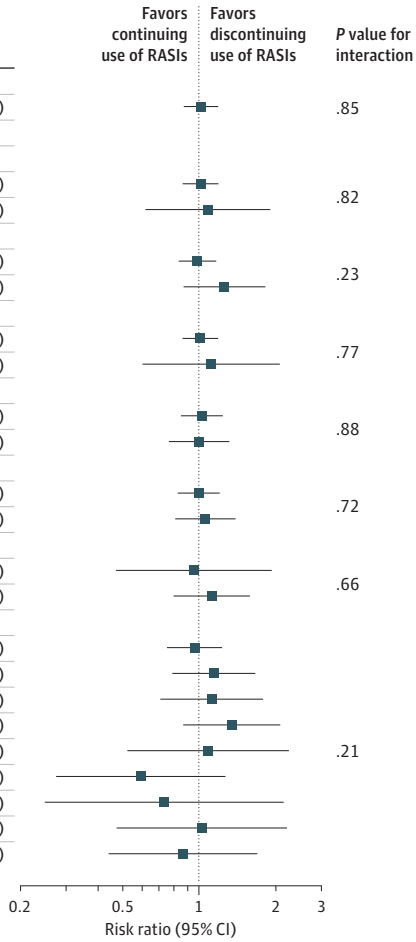
Patients in both groups resumed treatment at a median of 1 day (IQR, 1-3 day) after surgery. The volume of fluids, dose of vasopressors, and the amount of blood products that were administered to patients in each group appear in eTable 1 in Supplement 2. Patients in both groups received the same amount of crystalloids or blood transfusions. However, patients in the RASI continuation group were more likely than those in the RASI discontinuation group to receive vasopressor support (P = .02). Patients in the RASI continuation group received higher doses of vasopressors (eTable 1 in Supplement 2).

Primary Outcome

Among the patients who underwent randomization, complete 28-day outcome data were available for 2044 (92%). The median follow-up was 28 days (IQR, 28-31 days). The rate of all-cause mortality and major postoperative complications at 28 days was 22% (245 of 1115 patients) in the RASI

Figure 2. Primary Outcome for All Patients and by Individual Patient Subgroups

	Discontinued use of RASIs		Continued use of RASIs			
	No. of events	No. of patients	No. of events	No. of patients	Risk ratio (95% CI)	*P* value for interaction
Primary outcome						
All patients	245	1115	247	1107	1.02 (0.87-1.19)	.85
Patient subgroups						
Age group, y						
≤80	225	1026	230	1037	1.01 (0.86-1.19)	.82
>80	20	89	17	70	1.08 (0.61-1.90)	
History of chronic kidney disease						
No	212	1013	208	1011	0.98 (0.83-1.17)	.23
Yes	33	102	39	96	1.26 (0.87-1.82)	
History of heart failure						
No	230	1043	231	1038	1.01 (0.86-1.19)	.77
Yes	15	72	16	69	1.11 (0.60-2.07)	
Diuretic use						
No	167	767	166	745	1.02 (0.85-1.24)	.88
Yes	78	348	81	362	1.00 (0.76-1.31)	
β-Blocker use						
No	170	781	163	753	0.99 (0.82-1.20)	.72
Yes	75	334	84	354	1.06 (0.80-1.39)	
Elevated level of natriuretic peptide						
No	13	80	13	84	0.95 (0.47-1.93)	.66
Yes	42	143	47	143	1.12 (0.79-1.58)	
Type of surgery						
Abdominal	96	376	89	364	0.96 (0.75-1.23)	
Thoracic	38	177	47	192	1.14 (0.78-1.66)	
Vascular	26	127	30	131	1.12 (0.70-1.78)	
Urological	26	112	33	106	1.34 (0.86-2.08)	
Orthopedic	12	96	13	96	1.08 (0.52-2.25)	.21
Pelvic	14	65	9	71	0.59 (0.27-1.27)	
Neurosurgical	7	53	5	52	0.73 (0.25-2.15)	
Liver	8	45	8	44	1.02 (0.47-2.21)	
Other	16	64	11	51	0.86 (0.44-1.69)	



The primary outcome was a composite of all-cause mortality and major postoperative complications (including major cardiovascular events, sepsis or septic shock, respiratory complications, unplanned intensive care unit admission or readmission, acute kidney injury, hyperkalemia, and need for surgical reintervention) within 28 days after surgery.

discontinuation group and 22% (247 of 1107 patients) in the RASI continuation group (risk ratio, 1.02 [95% CI, 0.87-1.19]; *P* = .85) (**Table 2**, **Figure 2**, and eFigure 1 and eTables 2-3 in Supplement 2).

After accounting for missing data using the multiple imputation procedure, the result was consistent for the primary outcome of all-cause mortality and major postoperative complications at 28 days (risk ratio, 1.01 [95% CI, 0.91-1.11]). The results remained unchanged after adjustment for the stratification factors used during randomization and the baseline characteristics (Table 2). The effect of the RASI discontinuation strategy vs the RASI continuation strategy on the risk of all-cause mortality and major postoperative complications was consistent across subgroups (Figure 2 and eTable 3 in Supplement 2). The variability in the primary outcome across hospital sites appears in eFigure 2 in Supplement 2. The survival analysis also was not significant (**Figure 3**).

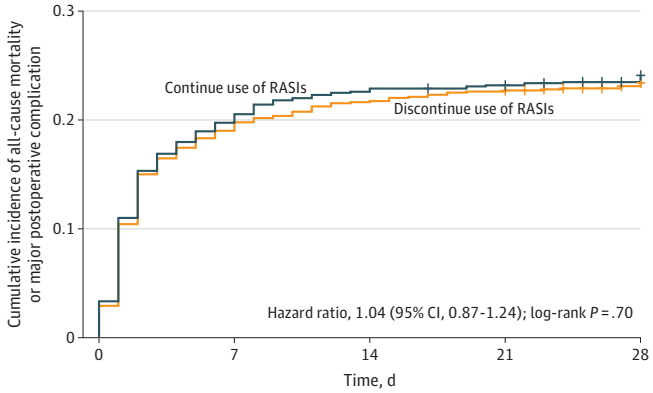
Secondary Outcomes

Episodes of hypotension during surgery occurred in 417 patients (41%) in the RASI discontinuation group and in 544 patients (54%) in the RASI continuation group (risk ratio, 1.31 [95% CI, 1.19-1.44]). The median duration of hypotension with a mean arterial pressure below 60 mm Hg was 6 minutes (IQR, 4-12 minutes) in the RASI discontinuation group and 9 minutes (IQR, 5-16 minutes) in the RASI continuation group (Table 2 and eFigure 3 and eTable 1 in Supplement 2). The mean difference in duration of mean arterial pressure below 60 mm Hg was 3.7 minutes (95% CI, 1.4-6.0 minutes).

Acute kidney injury occurred in 121 patients (11%) in the RASI discontinuation group and in 122 patients (11%) in the RASI continuation group. Kidney replacement therapy was administered to 4 patients in each group.

In the RASI discontinuation group, 129 patients (13%) were admitted to the ICU compared with 110 patients (11%) in the RASI continuation group. The length of stay in the ICU or the hospital

Figure 3. Cumulative Incidence of the Primary Outcome by Treatment Group



No. at risk

Discontinue use of RASIs	1026	831	804	794	756
Continue use of RASIs	1018	817	788	781	748

The primary outcome was a composite of all-cause mortality and major postoperative complications (including major cardiovascular events, sepsis or septic shock, respiratory complications, unplanned intensive care unit admission or readmission, acute kidney injury, hyperkalemia, or need for surgical reintervention) within 28 days after surgery. The hash marks indicate censoring. The median follow-up was 28 days (IQR, 28-31 days).

did not differ between the groups. There were no significant between-group differences in the trial outcomes (Figure 2).

Per-Protocol and As-Treated Analyses

The results for all-cause mortality and major postoperative complications were mostly the same in the per-protocol analysis (risk ratio, 1.01 [95% CI, 0.86-1.18]) and in the as-treated analysis (risk ratio, 1.00 [95% CI, 0.85-1.17]).

Sensitivity Analysis

According to the sensitivity analysis, 27% of the patients in the RASI discontinuation group with an actual surgery duration of longer than 2 hours had a complication within 28 days vs 28% in the RASI continuation group. The risk of developing a postoperative complication was not affected by the type of RASI (ACEIs or ARBs) or the type of preoperative epidural analgesia (eTable 4 in Supplement 2). The data from an exploratory subgroup analysis for the primary outcome appear in eTable 5 in Supplement 2.

Discussion

The strategy of RASI management before major surgery has long been a matter of debate, and the lack of large, randomized clinical trials has prevented the establishment of recommendations with high-quality evidence. Patients randomized to the preoperative RASI continuation strategy had a similar rate of all-cause mortality and major postoperative complications compared with patients randomized to the RASI discontinuation strategy. Patients randomized to the preoperative RASI continuation strategy had more episodes of intraoperative hypotension and these episodes lasted for a longer duration.

One of the main reasons for withholding RASIs before surgery is the possible increased risk of intraoperative hypotension, which has previously been associated with postoperative complications.[12] Patients randomized to the RASI continuation strategy in the current study had a higher rate of hypotension. A systematic review[1] of 5 randomized clinical trials and 4 cohort studies found that withholding RASIs before surgery was associated with fewer cases of intraoperative hypotension (odds ratio, 0.63 [95% CI, 0.47-0.85]). In a prospective observational cohort,[2] withholding RASIs 24 hours before surgery was associated with a lower risk of intraoperative hypotension (adjusted risk ratio, 0.80 [95% CI, 0.72-0.93]; P = .001) and fewer complications (composite outcome of all-cause mortality, stroke, and myocardial infarction; adjusted relative risk, 0.82 [95% CI, 0.70-0.96]; P = .01), but the association might have been affected by unmeasured confounders.

In a single-center trial[13] of 275 individuals, there were fewer cases of intraoperative hypotension in those randomized to omission of the final preoperative RASI dose vs continuation of RASI therapy (55% vs 69%, respectively; intraoperative hypotension was defined as systolic blood pressure <80 mm Hg), but more individuals in the omission group had postoperative hypertension. However, in a study conducted in the UK,[14] the rates of hypotension were similar in those who were randomized to continue RASI therapy before surgery (n = 132) vs those randomized to stop RASI therapy (n = 130). Likewise, in a pilot randomized clinical trial (n = 121),[15] the discontinuation of RASIs 2 days before nonemergent cardiac surgery vs continuation of RASIs did not appear to have an effect on postoperative intravenous vasopressor use (78.3% in the continuation group vs 75.4% in the discontinuation group, P = .70) or on the rates of vasoplegic shock (31.7% vs 27.9%, respectively, P = .65).

In the current trial, the higher incidence of intraoperative hypotension in the RASI continuation group did not translate into a higher risk of all-cause mortality and major postoperative complications. The reasons were likely the rapid correction of intraoperative hypertension and the overall short duration of low blood pressure. Increased awareness of the risk of prolonged hypotension has led to more liberal use of intraoperative vasopressors in recent years.[16] The rapid correction of intraoperative hypotension in the current trial likely led to a limited between-group difference in the duration of

intraoperative hypotension. Whether the difference would remain small in more resource-constrained settings is uncertain. Furthermore, previous observational studies exploring the association between hypotension and outcomes were prone to risk of residual bias.[17]

Randomized clinical trials have found inconsistent results on the effect of preventing intraoperative hypotension on postoperative outcomes.[17] In a trial by Wu et al[18] and in the INPRESS trial,[19] patients randomized to a hypotension preventive strategy had a lower incidence of postoperative complications. In a larger trial by Wanner et al,[20] a hypotension prevention strategy was not associated with fewer postoperative complications. The POISE-3 trial[21] randomized 7490 patients into a hypotension avoidance strategy vs a hypertension avoidance strategy and RASIs were withheld 2 days before surgery in the hypotension avoidance strategy group (71.7% of the patients enrolled were receiving RASI therapy). The rates for the primary outcome (a composite outcome of vascular death and nonfatal myocardial injury, stroke, and cardiac arrest) were not different between the groups.[21] However, the current trial differed from the POISE-3 trial[21] because the RASI management strategy was part of a bundle for hypotension avoidance in the POISE-3 trial. Furthermore, adherence to strategy instructions was suboptimal in the POISE-3 trial[21] (5.3% of patients took a RASI on the day of surgery in the hypotension avoidance group vs 38.3% of patients in the hypertension avoidance group).

The results of the current trial could have an effect on future guidelines. The absence of difference in postoperative outcomes makes both strategies (continuation and discontinuation) acceptable and safe. A RASI discontinuation strategy may be considered if a particular concern for profound hypotension exists in light of a potentially increased risk of intraoperative hypotension (although without a clinically meaningful longer duration of hypotension).

Limitations

This trial has limitations. First, the patients were not blinded to the RASI strategies (continuation vs discontinuation) because it would have been impractical. Second, the anesthesiologists also were aware of the RASI strategies.

Third, the trial had a pragmatic nature and included a range of surgeries, aiming for generalizability, but may have been underpowered to detect differences in some rarer primary outcome components. Fourth, there were only a limited number of patients with chronic heart failure, which limits the application of the conclusions from this study for that specific group. Fifth, the trial was performed in a single country (France), so the results might not be generalizable to other health care settings.

Conclusions

Among patients who underwent major noncardiac surgery, a continuation strategy of RASIs before surgery was not associated with a higher rate of postoperative complications than a discontinuation strategy.

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