Perioperative management of renin-angiotensin system inhibitors in hypertensive patients undergoing non-cardiac surgery

Manejo perioperatorio de inhibidores del sistema renina-angiotensina en pacientes hipertensos sometidos a cirugía no cardíaca

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Abstract

The appropriate management of renin-angiotensin system inhibitors (RASIs) in hypertensive patients facing non-cardiac surgery remains a subject of debate. This observational study evaluated 80 hypertensive patients on chronic RASI therapy, comparing outcomes between those who continued (n=40) versus discontinued (n=40) medication approximately 48 hours before surgery. Key findings demonstrated comparable safety profiles between strategies. Mortality was identical between groups (2.5% each, p=1.000), with no significant differences in major cardiovascular events, sepsis, respiratory complications, acute kidney injury (p=0.111), hyperkalemia (p=0.334), or hospital length of stay (p=0.095). However, the continuation strategy resulted in significantly higher rates of intraoperative hypotension (p=0.001), longer duration of hypotensive episodes (p<0.001), and increased vasopressor requirements (p<0.001). These results suggest that while continuing RASIs predictably increases intraoperative hemodynamic challenges, it does not lead to worse clinical outcomes. The decision to continue or discontinue RASIs should therefore be individualized, considering each patient's specific cardiovascular status and surgical risk factors. This study contributes to the growing evidence supporting both approaches as viable options in the perioperative management of hypertensive patients.

Keywords: Renin-angiotensin system inhibitors, hypertension, perioperative care, non-cardiac surgery, intraoperative hypotension

Resumen

El manejo adecuado de los inhibidores del sistema renina-angiotensina (ISRA) en pacientes hipertensos que se enfrentan a cirugía no cardíaca sigue siendo objeto de debate. Este estudio observacional evaluó a 80 pacientes hipertensos en terapia crónica con ISRA, comparando los resultados entre quienes continuaron (n=40) y quienes suspendieron la medicación (n=40) aproximadamente 48 horas antes de la cirugía. Los hallazgos clave demostraron perfiles de seguridad comparables entre las estrategias. La mortalidad fue idéntica entre los grupos (2,5% cada uno, p=1,000), sin diferencias significativas en eventos cardiovasculares mayores, sepsis, complicaciones respiratorias, daño renal agudo (p=0,111), hiperpotasemia (p=0,334) o duración de la estancia hospitalaria (p=0,095). Sin embargo, la estrategia de continuación resultó en tasas significativamente mayores de hipotensión intraoperatoria (p = 0,001), mayor duración de los episodios hipotensivos (p < 0,001) y un mayor requerimiento de vasopresores (p < 0,001). Estos resultados sugieren que, si bien la continuación de los inhibidores de la recaptación de angiotensina (IRA) aumenta previsiblemente los problemas hemodinámicos intraoperatorios, no conlleva peores resultados clínicos. Por lo tanto, la decisión de continuar o suspender los IRAS debe individualizarse, considerando el estado cardiovascular específico de cada paciente y los factores de riesgo quirúrgico. Este estudio contribuye a la creciente evidencia que respalda ambos enfoques como opciones viables en el manejo perioperatorio de pacientes hipertensos.

Palabras clave: Inhibidores del sistema renina-angiotensina, hipertensión, cuidados perioperatorios, cirugía no cardíaca, hipotensión intraoperatoria.

Introduction

The Renin-Angiotensin System (RAS) plays a critical role in regulating blood pressure, fluid balance, and cardiovascular homeostasis [1]. Renin-angiotensin system inhibitors (RASIs), including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), are first-line therapies for hypertension, heart failure, and chronic kidney disease [2,3]. Despite their proven long-term benefits, the perioperative management of these medications remains clinically challenging due to conflicting evidence and guidelines [4]. The fundamental concern regarding continuing RASIs prior to surgery revolves around their potential to cause intraoperative hypotension through inhibition of angiotensin II-mediated vasoconstriction and reduced aldosterone secretion [5]. This hypotension may compromise perfusion to vital organs, potentially increasing the risk of myocardial injury, acute kidney injury (AKI), and other complications [6]. Conversely, discontinuing RASIs might precipitate rebound hypertension, increase cardiovascular stress, and potentially lead to postoperative cardiovascular events [7].

Current guidelines offer conflicting recommendations. The American College of Cardiology/American Heart Association suggest that continuing RASIs perioperatively is reasonable, while the European Society of Cardiology guidelines recommend considering withholding these agents before non-cardiac surgery to prevent hypotension, particularly in patients without heart failure [8,9]. This discrepancy stems from a lack of conclusive evidence from large randomized trials, though recent studies have begun to address this knowledge gap [10]. The STOP-or-NOT randomized clinical trial, one of the largest studies on this topic, found no difference in the composite endpoint of all-cause mortality and major postoperative complications at 28 days between continuation and discontinuation strategies (22% in both groups) [5]. Similarly, the SPACE trial demonstrated that discontinuing RASIs did not reduce myocardial injury but might increase the risk of clinically significant acute hypertension [11]. These findings suggest that both strategies may be acceptable, with the decision requiring individualization based on patient and surgical factors.

This study aims to contribute to this evidence base by comparing the effects of continuing versus discontinuing RASIs before non-cardiac surgery on postoperative complications in an Indonesian population. By examining both hemodynamic parameters and clinical outcomes, we seek to provide practical guidance for perioperative physicians managing these common medications.

Study Design and Setting

An observational cohort study was conducted at Wahidin Sudirohusodo General Hospital, a tertiary referral center in Makassar, Indonesia [12]. The study period was December 2024, with data collection continuing until the target sample size was achieved. The study protocol was reviewed and approved by the institutional ethics committee, and all participants provided informed consent.

Participant Selection

Patients scheduled for elective non-cardiac surgery were screened for eligibility. Inclusion criteria were: (1) age ≥18 years; (2) scheduled for major non-cardiac surgery with expected duration >2 hours and anticipated hospital stay ≥3 days; and (3) ongoing treatment with ACEIs or ARBs for at least three months prior to surgery. Exclusion criteria included: emergency surgery, severe renal impairment (estimated glomerular filtration rate <15 mL/min/1.73m² or requiring renal replacement therapy), preoperative shock requiring vasopressor support, hyperkalemia (>5.5 mmol/L), terminal illness with life expectancy <1 month, and lack of social insurance coverage.

Study Groups and Intervention

Participants were stratified into two groups based on clinical decisions regarding their perioperative RASI management:

1. **RASI continuation group**: Patients continued taking their prescribed ACEIs or ARBs until the day of surgery.

2. **RASI discontinuation group**: Patients discontinued their ACEIs or ARBs approximately 48 hours before surgery (last dose taken 3 days preoperatively).

The decision to continue or discontinue RASIs was made by the treating clinical team based on individual patient factors and institutional protocols, reflecting real-world practice [13]. In both groups, RASIs were resumed postoperatively as soon as clinically appropriate, typically when oral intake was feasible and no significant hypotension or worsening renal function was present.

Data Collection and Outcomes

Data were collected through direct observation, review of medical records, and standardized data collection forms. Baseline characteristics recorded included patients' age, gender, body mass index (BMI), existing comorbidities, and the type of surgery they underwent. The primary outcomes assessed were all-cause mortality within 28 days after surgery, major adverse cardiovascular events such as myocardial infarction, stroke, arterial or venous thrombosis, acute pulmonary edema, cardiogenic shock, severe acute hypertension, or new cardiac arrhythmias requiring intervention. Additionally, occurrences of sepsis or septic shock were evaluated based on Sepsis-3 criteria, along with respiratory complications necessitating reintubation or noninvasive ventilation. Unplanned admissions or readmissions to the intensive care unit (ICU) were also tracked, as were cases of acute kidney injury defined by KDIGO criteria and episodes of hyperkalemia with serum potassium above 5.5 mmol/L that required intervention. Secondary outcomes encompassed the incidence and duration of intraoperative hypotension—characterized by a mean arterial pressure below 60 mmHg or the need for vasopressor therapy—the vasopressor requirements during surgery, and the overall lengths of hospital and ICU stays[14].

Statistical Analysis

Data were analyzed using SPSS version 26 (IBM Corp., Armonk, NY, USA) [15]. Continuous variables were assessed for normality using the Shapiro-Wilk test and presented as mean ± standard deviation or median with interquartile range, as appropriate. Categorical variables were presented as frequencies and percentages. Between-group comparisons were performed using independent t-tests for normally distributed continuous variables, Mann-Whitney U tests for non-normally distributed variables, and chi-square or Fisher's exact tests for categorical variables, as appropriate [16]. A significance level of $\alpha = 0.05$ was used for all statistical tests. Given the observational nature of the study and multiple comparisons, findings were interpreted with caution regarding potential type I error.

Baseline Characteristics

A total of 80 patients were included in the analysis, with 40 patients in both the RASI continuation and discontinuation groups. Table 1 summarizes the baseline characteristics of the study population. The groups were well-balanced in terms of age, gender distribution, and comorbidity profiles. The majority of patients were aged 51-60 years (25% in continuation group vs. 20% in discontinuation group), and most were male (27.5% vs. 32.5%). Hypertension was the most common comorbidity (37.5% vs. 33.8%), followed by hypertension with type 2 diabetes mellitus (11.3% vs. 13.8%). The mean BMI was notably higher in the discontinuation group (36.51 ± 56.96 kg/m²) compared to the continuation group (23.12 ± 4.22 kg/m²), though this difference was largely driven by extreme values in the discontinuation group. The types of surgical procedures were similar between groups, with posterior decompression and stabilization being the most common (17.5% vs. 16.3%), followed by craniectomy tumor removal (6.3% vs. 8.8%) and total thyroidectomy (7.5% vs. 6.3%).

Table 1: Baseline Characteristics of Study Participants

Characteristic	RASI Continuation (n=40)	RASI Discontinuation (n=40)
Age (years)		
≤40	1 (1%)	3 (4%)
41-50	5 (6%)	5 (6%)
51-60	20 (25%)	16 (20%)
>60	14 (18%)	16 (20%)
Gender		
Male	22 (27.5%)	26 (32.5%)
Female	18 (22.5%)	14 (17.5%)
Comorbidities		
Hypertension	30 (37.5%)	27 (33.8%)
Hypertension + Type 2 DM	9 (11.3%)	11 (13.8%)
Other	1 (1.3%)	2 (2.5%)
BMI (kg/m²)	23.12 ± 4.22	36.51 ± 56.96
Surgical Type		
Posterior Decompression & Stabilization	14 (17.5%)	13 (16.3%)
Craniectomy Tumor Removal	5 (6.3%)	7 (8.8%)
Total Thyroidectomy	6 (7.5%)	5 (6.3%)
Nephrectomy	3 (3.8%)	5 (6.3%)
Laparotomy	5 (6.3%)	3 (3.8%)
Open Bivalve Renal	3 (3.8%)	2 (2.5%)
Other	4 (5.0%)	5 (6.3%)

Primary Outcomes

Mortality: There were two deaths (2.5%) within 28 days postoperatively, one in each group. Statistical analysis showed no significant difference between groups (p=1.000) (Table 2).

Table 2: Mortality Outcomes

Group	Survived	Died	Total	p-value
RASI Continuation	39	1	40	1.000
RASI Discontinuation	39	1	40	
Total	78	2	80	

Major Adverse Cardiovascular Events: No MACE occurred in either group during the study period (p=1.000) (Table 3).

Table 3: Major Adverse Cardiovascular Events

Group	No MACE	MACE	Total	p-value
RASI Continuation	40	0	40	1.000
RASI Discontinuation	40	0	40	
Total	80	0	80	

Sepsis and Respiratory Complications: No cases of sepsis or respiratory complications requiring intervention were observed in either group (p=1.000 for both outcomes) (Tables 4 and 5).

Table 4: Sepsis Outcomes

Group	No Sepsis	Sepsis	Total	p-value
RASI Continuation	40	0	40	1.000
RASI Discontinuation	40	0	40	
Total	80	0	80	

Table 5: Respiratory Complications

Group	No Complications	Complications	Total	p-value
RASI Continuation	40	0	40	1.000
RASI Discontinuation	40	0	40	
Total	80	0	80	

ICU Readmissions: No significant difference was found in ICU readmission rates between groups (mean rank: 40.50 for both groups; p=1.000) (Table 6).

Table 6: ICU Readmissions

Group	n	Mean Rank	Sum of Ranks	p-value
RASI Continuation	40	40.50	1620.00	1.000
RASI Discontinuation	40	40.50	1620.00	
Total	80			

Acute Kidney Injury: Although the mean rank of AKI incidence was higher in the RASI continuation group (44.64) compared to the discontinuation group (36.36), this difference did not reach statistical significance (p=0.111) (Table 7).

Table 7: Acute Kidney Injury

Group	n	Mean Rank	AKI Incidence	p-value
RASI Continuation	40	44.64	0	0.111
RASI Discontinuation	40	36.36	0	
Total	80			

Hyperkalemia: No significant difference was observed in hyperkalemia incidence between groups (mean rank: 43.00 vs. 38.00; p=0.334) (Table 8).

Table 8: Hyperkalemia Incidence

Group	n	Mean Rank	Hyperkalemia Events	p-value
RASI Continuation	40	38.00	0	0.334
RASI Discontinuation	40	43.00	0	
Total	80			

Secondary Outcomes

Intraoperative Hypotension: The RASI continuation group had a significantly higher incidence of intraoperative hypotension compared to the discontinuation group (mean rank: 48.93 vs. 32.08; p=0.001) (Table 9).

Table 9: Intraoperative Hypotension

Group	n	Mean Rank	Hypotension Incidence	p-value
RASI Continuation	40	48.93	40	0.001
RASI Discontinuation	40	32.08	40	
Total	80			

Duration of Intraoperative Hypotension: The duration of hypotension was significantly longer in the RASI continuation group (mean rank: 56.64) compared to the discontinuation group (mean rank: 24.36; p<0.001) (Table 10).

Table 10: Duration of Intraoperative Hypotension

Group	n	Mean Rank	Duration (min)	p-value
RASI Continuation	40	56.64	33.85	<0.001
RASI Discontinuation	40	24.36	15.62	
Total	80			

Vasopressor Requirements: The RASI continuation group required significantly higher vasopressor doses compared to the discontinuation group (mean rank: 55.74 vs. 25.26; p<0.001) (Table 11).

Table 11: Vasopressor Requirements

Group	n	Mean Rank	Sum of Ranks	p-value
RASI Continuation	40	55.74	2229.50	<0.001
RASI Discontinuation	40	25.26	1010.50	
Total	80			

Length of Hospital and ICU Stay: No significant differences were observed in length of hospital stay (mean rank: 44.69 vs. 36.31; p=0.095) or ICU stay (mean rank: 41.33 vs. 39.68; p=0.746) between continuation and discontinuation groups (Tables 12 and 13).

Table 12: Length of Hospital Stay

Group	n	Mean Rank	Sum of Ranks	p-value
RASI Continuation	40	44.69	1787.50	0.095
RASI Discontinuation	40	36.31	1452.50	
Total	80			

Table 13: Length of ICU Stay

Group	n	Mean Rank	Sum of Ranks	p-value
RASI Continuation	40	41.33	1653.00	0.746
RASI Discontinuation	40	39.68	1587.00	
Total	80			

This observational cohort study compared continuing versus discontinuing RASIs before non-cardiac surgery and found no significant differences in mortality, cardiovascular events, sepsis, respiratory complications, AKI, hyperkalemia, or hospital length of stay. However, continuing RASIs was associated with significantly increased intraoperative hypotension, longer hypotension duration, and greater vasopressor requirements[5,17]. These findings align with recent large randomized trials and suggest that while RASI continuation affects intraoperative hemodynamics, it does not significantly impact most clinical outcomes[18].

The absence of significant differences in mortality and major cardiovascular events is consistent with the STOP-or-NOT trial, which found identical rates (22%) of the composite endpoint of all-cause mortality and major postoperative complications in both continuation and discontinuation groups[5]. Similarly, a meta-analysis by Saad et al. found no significant differences in mortality or MACE between continuation and discontinuation strategies[19]. This suggests that the theoretical concerns about rebound hypertension or cardiovascular instability after RASI discontinuation may not translate into clinically significant events in most patients, possibly due to effective perioperative monitoring and management.

The significantly higher incidence and duration of intraoperative hypotension in the RASI continuation group aligns with the known pharmacodynamic effects of these medications. RASIs impair compensatory vasoconstriction during anesthesia-induced vasodilation, potentially leading to more profound and prolonged hypotension[6,20]. The STOP-or-NOT trial reported intraoperative hypotension in 54% of continuation patients versus 41% in discontinuation patients (risk ratio 1.31)[5], while our study found hypotension in all continuation patients versus all discontinuation patients, though with significant differences in duration and severity. This discrepancy may reflect differences in patient population, surgical procedures, or anesthetic techniques.

Despite increased intraoperative hypotension, we found no significant difference in AKI incidence between groups. This contrasts with some previous studies that suggested an association between intraoperative hypotension and AKI but aligns with the STOP-or-NOT trial which found no difference in AKI rates between groups[5]. This may suggest that the duration and severity of hypotension in our study, though statistically different, were not sufficient to cause renal injury, or that compensatory mechanisms preserved renal perfusion. Additionally, the meta-analysis by Palmer et al. found that withholding RASIs was associated with reduced AKI risk (OR=0.88)[17], though this effect was not observed in our smaller cohort.

The lack of difference in hyperkalemia incidence between groups is noteworthy, as RASIs are known to potentially cause hyperkalemia through inhibition of aldosterone secretion. This may reflect appropriate patient selection (exclusion of patients with severe renal impairment or baseline hyperkalemia), adequate perioperative monitoring, or prompt resumption of therapy postoperatively. These findings align with those reported in the SPACE trial, which found no significant difference in hyperkalemia between groups[11]. The similar lengths of hospital and ICU stay between groups suggest that the hemodynamic effects of RASI continuation, while statistically significant, may not translate into clinically meaningful differences in recovery time or resource utilization. This is consistent with the findings of the STOP-or-NOT trial, which reported no differences in these secondary outcomes[5].

Several limitations should be considered when interpreting our results. First, the observational design introduces potential selection bias, as the decision to continue or discontinue RASIs was not randomized. However, this reflects real-world clinical practice and decision-making[13]. Second, the sample size was relatively small, limiting statistical power to detect differences in less common outcomes such as mortality or MACE. Third, the single-center design may limit generalizability to other settings or populations. Fourth, neither patients nor clinicians were blinded to treatment allocation, potentially introducing performance bias. Finally, the study population had relatively low rates of heart failure and advanced kidney disease, which may limit applicability to higher-risk populations.

Our findings, consistent with recent larger trials, support individualizing perioperative RASI management based on patient and surgical factors rather than adopting a universal approach[5,11,18]. For patients at particular risk of hypotension (e.g., those with baseline hypotension, undergoing procedures with significant fluid shifts, or requiring deep anesthesia), temporary discontinuation of RASIs may be prudent. Conversely, for patients with well-controlled hypertension or heart failure where continuity of therapy is prioritized, continuing RASIs may be reasonable with appropriate preparedness to manage intraoperative hypotension. This tailored approach is increasingly supported by the literature[19,20].

Conclusions

In patients undergoing non-cardiac surgery, continuing RASIs until the day of surgery significantly increases the risk, duration, and severity of intraoperative hypotension and vasopressor requirements compared to discontinuing these medications 48 hours preoperatively. However, this hemodynamic effect does not translate into significant differences in mortality, major cardiovascular events, renal dysfunction, hyperkalemia, or length of stay. These findings align with recent randomized trials and suggest that both strategies may be acceptable, with the decision requiring individualization based on patient-specific factors and surgical context. Future studies with larger sample sizes should focus on identifying patient subgroups that might benefit preferentially from one strategy over another, particularly those with heart failure, reduced ejection fraction, or chronic kidney disease. Additionally, research exploring protocolized hemodynamic management strategies tailored to RASI continuation status may help optimize outcomes for these patients.

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