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Heart Connections

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Meta-analysis & systematic reviews

Continuing versus Withholding Renin–Angiotensin–Aldosterone System Antagonists Before Noncardiac Surgery: A Systematic Review and Meta-Analysis

Poursuite versus arrêt des antagonistes du système rénine-angiotensine-aldostérone en préopératoire de chirurgie non cardiaque : Revue systématique et méta-analyse

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Abstract

Background: It remains unclear whether to continue or withdraw angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEI) before noncardiac surgery to reduce perioperative morbidity. This systematic review and meta-analysis aimed to analyze the consequences of continuing ARB or ACEi in the incidence of intraoperative hypotension and postoperative complications.

Methods: This systematic review and meta-analysis followed the PRISMA 2020 guidelines and was registered in the PROSPERO database. We conducted a comprehensive search in several bibliographic databases for studies comparing continuing versus withholding renin angiotensin aldosterone system antagonists before noncardiac surgery. Primary outcomes included the incidence of intraoperative hypotension, while secondary outcomes covered the intraoperative use of the vasoactive agent, the incidence of severe hypotension, intraoperative and postoperative hypertension, the incidence of acute kidney injury (AKI), 30-day postoperative all-cause mortality, and the incidence of major cardiocerebral events (MACCE).

Results: Five randomized controlled trials, three nonrandomized controlled trials, and four retrospective case-control studies were included that involved 50184 patients. Meta-analysis revealed that continuing ACEI or ARBs before surgery increased the incidence of intraoperative hypotension (OR = 1.96, 95%CI [1.30, 2.96] p=0.001). Heterogeneity was substantial across studies but was significantly reduced in subgroup analyses. Furthermore, the use of vasoactive agents and the incidence of severe hypotension were significantly higher in the continuing group. No significant differences in intraoperative hypertension and the incidence of AKI and MACCE at 30 days after the operation.

Conclusions: Continued ACEI or ARBs before non-cardiac surgery increases the incidence of intraoperative hypotension, without reducing the incidence of both AKI and MACCE postoperatively. More research is necessary to explore the appropriate perioperative management of ACE-I and ARB.

Keywords: angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, noncardiac surgery, intraoperative hypotension

Résumé

Introduction : La nécessité de poursuivre ou d'interrompre le traitement par antagonistes des récepteurs de l'angiotensine (ARA) et inhibiteurs de l'enzyme de conversion de l'angiotensine (IEC) avant une intervention chirurgicale non cardiaque afin de réduire la morbidité péri-opératoire reste incertaine. Cette revue systématique et méta-analyse visait à analyser les conséquences de la poursuite du traitement par ARA ou IEC sur l'incidence de l'hypotension peropératoire et des complications postopératoires.

Méthodes : Cette revue systématique et méta-analyse a suivi les recommandations PRISMA 2020 et a été enregistrée dans la base de données PROSPERO. Nous avons effectué une recherche exhaustive dans plusieurs bases de données bibliographiques afin d'identifier des études comparant la poursuite ou l'arrêt du traitement par ARA avant une intervention chirurgicale non cardiaque. Le critère de jugement principal était l'incidence de l'hypotension peropératoire, tandis que les critères d'évaluation secondaires étaient l'utilisation peropératoire de l'agent vasoactif, l'incidence de l'hypotension sévère, l'hypertension peropératoire et postopératoire, l'incidence de l'insuffisance rénale aiguë (IRA), la mortalité toutes causes confondues à 30 jours postopératoires et l'incidence des événements cardio-cérébraux majeurs (ECCM).

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Résultats : Cinq essais contrôlés randomisés, trois essais contrôlés non randomisés et quatre études cas-témoins rétrospectives ont été inclus, portant sur 50 184 patients. Une méta-analyse a révélé que la poursuite du traitement par IEC ou ARA II avant la chirurgie augmentait l'incidence d'hypotension peropératoire (OR = 1,96, IC à 95 % [1,30, 2,96], p = 0,001). L'hétérogénéité était importante entre les études, mais était significativement réduite dans les analyses de sous-groupes. De plus, l'utilisation d'agents vasoactifs et l'incidence d'hypotension sévère étaient significativement plus élevées dans le groupe poursuivant le traitement. Aucune différence significative n'a été observée concernant l'hypertension peropératoire et l'incidence d'IRA et d'ECCM à 30 jours après l'opération.
Conclusions : La poursuite du traitement par IEC ou ARA II avant une chirurgie non cardiaque augmente l'incidence d'hypotension peropératoire, sans réduire l'incidence d'IRA et d'ECCM en postopératoire. Des recherches supplémentaires sont nécessaires pour explorer la prise en charge périopératoire appropriée des IEC et des ARA II.

Mots clés : Antagonistes des récepteurs aux angiotensines, inhibiteurs de l'enzyme de conversion de l'angiotensine, chirurgie non cardiaque, hypotension peropératoire.

Introduction

The Renin-angiotensin-aldosterone system inhibitor (RAAS) is a widely used treatment. Approximately one-third of surgical patients are on antihypertensive drugs annually, particularly RAAS inhibitors(1,2). However, evidence supporting the use or discontinuation of angiotensin receptor blockers (ARB) and angiotensin-converting enzyme inhibitors (ACEI) on the day of surgery is still lacking. Perioperative use of ACEIs and ARBs has been associated with early post-induction hypotension requiring the use of vasopressors under general anesthesia (3,4). This can result in acute renal injury, myocardial injury, or stroke as postoperative complications. However, the potential association between perioperative ACEI / ARB and major morbidity has not been elucidated (5–8). Furthermore, the continuation of ACE-I / ARB in the perioperative period may also be associated with improved outcomes in vascular surgical patients who have sustained a perioperative myocardial infarction (9). Consequently, in this meta-analysis we aimed to study the incidence of intraoperative and postoperative hemodynamic instability in patients treated with RAAS inhibitors undergoing noncardiac surgery, settled by the incidence of hypotension, hypertension, use of vasoactive agents, hospital length of stay (LOS), acute kidney injury (AKI), 30-day postoperative all-cause mortality, and incidence of major cardio-cerebral events (MACCE).

Methods

This systematic review and meta-analysis follows the 2020 Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) Guidelines (10) and was checked according to the AMSTAR 2 (Assessing the methodological quality of systematic reviews) guidelines (11). The protocol is registered in the PROSPERO database (ID: CRD42024519162). and described in a previously published article (12).

Bibliographic sources

We conducted an electronic search of the relevant literature and limited our search to data published until June 1, 2024. We did not use language restrictions. We sought trials in the United States National Library of Medicine, the Cochrane Database of Systematic Reviews (CDSR), and the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, National Institutes of Health PubMed/MEDLINE, Web of Science and Google Scholar databases. The MEDLINE and Embase strategies were run simultaneously as a multifile search in Ovid, and the results were duplicated using the Ovid duplication tool. We used the following keywords: 'angiotensin converting enzyme inhibitors ACEIs", "angiotensin-converting enzyme inhibitors ACEI', 'renin-angiotensin system inhibitor", "renin-angiotensin-aldosterone system inhibitor', 'continuing', 'withholding', 'preoperative' and "non-cardiac surgery". We manually checked the reference list of included trials to identify additional studies. Additionally, we searched for several clinical trial registries (ClinicalTrial.gov, Current Controlled Trials, Australian New Zealand Clinical Trials Registry (www.actr.org.au), Prospero registration, and the University Hospital Medical Information Network Clinical Trials Registry (www.umin.ac.jp/ctr) to identify ongoing trials.

Study selection

Two authors performed independent and blinded record screening. Disagreements were resolved by discussion after consulting a third member of the review team. The full texts of all selected studies were then selected according to predefined inclusion and exclusion criteria. The included studies were case-control studies, cohort studies, non-randomized controlled trials, and randomized controlled trials (RCT). Only articles published in peer-reviewed journals were considered. Data from noncomparative studies, review articles, editorial letters, abstracts only, comments, and case series (fewer than ten cases) were excluded.

Assessment of Risk of bias

The Cochrane tool for bias assessment was used to assess the risk of bias in RCTs (RoB2) (13). We evaluated bias in five distinct domains (A. randomization process, B. deviations from intended interventions, C. bias in the measurement of outcome, D. bias to missing outcome data, and E. bias in selecting the reported results). Within each domain, one or more signaling questions lead to judgments of "low risk of bias," "some concerns," or "high risk of bias". Regarding controlled clinical trials, the Newcastle-Ottawa Scale (NOS) was used.

Data extraction and outcomes

Data, including the first author's name, year of publication, country, type of study, age, sex (female / male), population, sample size (continuing group versus withholding group), angiotensin system inhibitors, outcomes, and duration of follow-up. We conducted our search based on the Population, Intervention, Comparator and Outcome (PICO) approach. In case of unclear bias domains or missing primary outcomes information, authors were contacted by email.

Population: adult patients (aged ≥ 18 years), who were chronically using ACEIs or ARBs chronically due to chronic hypertension, who underwent scheduled or emergency noncardiac surgery.

Intervention: Continue to receive ACEIs or ARBs to the day of surgery (< 12 hours preoperatively)

Control group: Patients who did not receive these treatments on the day of surgery (> 12 hours preoperatively)

Outcomes: The primary outcome was the incidence of intraoperative hypotension. Secondary outcomes were intraoperative use of vasoactive agent (incidence, dose of ephedrine (mg) and dose of phenylephrine (ng)), incidence of severe hypotension, hospital stay (LOS), intraoperative and postoperative hypertension, incidence of acute kidney injury (AKI), 30-day postoperative all-cause mortality and incidence of major cardiocerebral events (MACCE).

Statistical analysis

We used the RevMan 5.4 statistical package from the Cochrane Collaboration for meta-analysis (14). We selected the mean difference (MD) as an effective measure for continuous data. Odds ratios (OR) with 95% confidence intervals (95% CI) were calculated for dichotomous variables. The random-effects model was used and the significance threshold was fixed at 0.05. When the mean and standard deviation (SD) were not reported, they were estimated from the range (R) and median based on the formula described by Hozo et al. (15).

Assessment of Heterogeneity

To assess heterogeneity, three strategies were used:

1. The Cochrane Chi² test (Q test), Tau2, which is the variance of true effects, and the 95% predictive interval (index of dispersion) to estimate the degree of heterogeneity (16). We calculate the predictive interval using a comprehensive meta-analysis prediction interval. Values less than 25% indicated no heterogeneity, between 25% and 50% indicated moderate heterogeneity, and more than 50% indicated substantial heterogeneity.
2. Graphical exploration with funnel plots (17).
3. Sensitivity analysis with a subgroup analysis when applicable (18). Subgroup analyzes were carried out, if feasible, to assess potential sources of heterogeneity.

Results

Bibliographic Research

The literature search identified 2538 articles, of which 21 were selected for full-text review, and finally 12 studies (1,19-29). The detailed PRISMA flow diagram is presented in Figure 1. Nine articles were excluded for the following reasons: two studies were protocols (30,31), two studies were systematic reviews and meta-analyses (32,33), four studies included nonhypertensive patients in the control group (34-37), and one study evaluated inadequate outcomes (38). The demographic data of the retained studies are presented in Table 1. The risk of bias assessment using the RoB 2 and Newcastle-Ottawa Scale (NOS) is presented in Table 2. A total of 50184 patients (16292 patients in the continuing group (CG) versus 33892 patients in the withholding group (WG)) were included in this study. These studies were published from September 2000 to February 2024. Five studies were randomized controlled trials, three studies were nonrandomized controlled trials, and four studies were retrospective case-control.

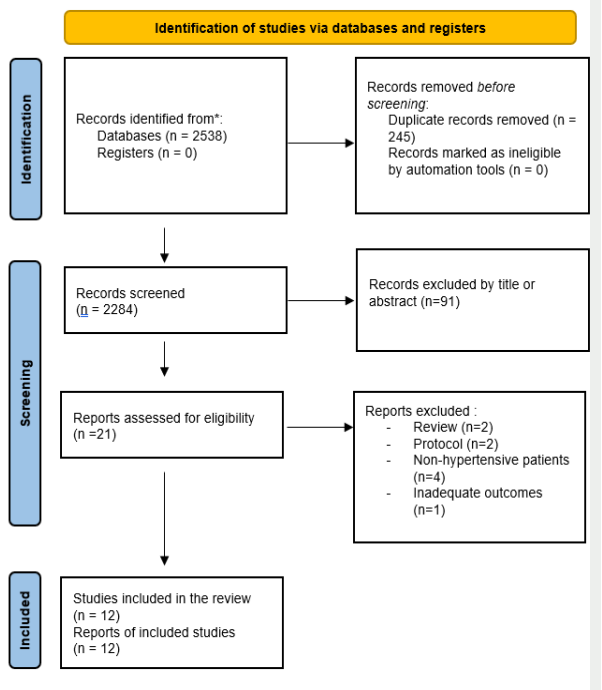

Figure 1. PRISMA 2020 flow diagram of the retained studies

Incidence of intraoperative hypotension

Eight studies reported data on the incidence of intraoperative hypotension (1,19-23,25,29). It was reported in 1304 out of 4122 patients in the continuing group (31.6%) and 482 out of 1770 patients in the withholding group (27.2%). The pooled results showed that the incidence of intraoperative hypotension was significantly higher in the continuing group but with high heterogeneity (OR = 1.96, 95% CI [1.30, 2.96] p=0.001; Tau^2=0.18) (Figure 2).

Table 1. Demographic data from the retained studies

Authors (year)	Country	Type of study	Age	Gender (female/ male)	Population	Sample size (CG vs WG)	Angiotensin system inhibitors	Outcomes	Follow-up
1-Takeuchi et al (2022)	Japan	RCT	69.35± 8.7	96/10	ASA II patients aged 20 – 80 years with primary hypertension undergoing minor abdominal or urological surgery under general anesthesia	106 patients. (54 vs 52)	ARB/CCB combination tablets	-incidence of hypotension (SBP<80 mmhg) -vasoactive agents	3 days
2-Zainudheen et al (2017)	Australia	Retrospective case-control	69.8± 7.8	151/137	Adult patients undergoing total knee or hip replacement, receiving a single blood pressure lowering agent	258 patients. (129 vs 129)	ACE-I or ARB	-incidence of hypotension (SBP<90 mmHg) -perioperative AKI	3 days
3-Comfere et al (2005)	USA	No-RCT	66.5± 4.25	117/147	Adult patients undergoing elective surgery	267 patients. (144 vs 123)	ACE-I or ARB	-incidence of hypotension (SBP<85 mmHg) -incidence of severe hypotension	24 hours
4-Drake et al (2018)	UK	No-RCT	70.2± 10.45	332/ 617	Adult patients undergoing elective major abdominal surgery	949 patients. (376 vs 573)	ACE-I or ARB	-postoperative AKI -mortality	30 days
5-Roshanov et al (2016)	Canada	No-RCT	68.8± 10.8	2389/ 2413	Patients > 45 years undergoing noncardiac surgery	4802 patients. (3557 vs 1245)	ACE-I or ARB	-mortality -cardiovascular complications -incidence of hypotension (SBP<90 mmHg)	30 days
6-Calloway et al (2014)	USA	Retrospective case-control	66.15± 3.45	35/25	Patients aged 60 to 75 years who underwent elective orthopedic surgery under neuraxial anesthesia	60 patients (37 vs 23)	ACE-I or ARB	-incidence of hypotension (SBP<85 mmHg) -vasopressor requirements; -postoperative complications	-
7-Ackland et al (2024)	UK	RCT	71.5± 2.5	126/134	ASA III patients aged > 60 years undergoing elective non-cardiac surgery	262 patients. (132 vs 130)	ACE-I or ARB	-myocardial injury; -incidence of hypotension	30 days
8-Yoon et al (2021)	USA	Retrospective case-control	65± 11	165/184	Patients aged 18 to 80 years undergoing non-cardiac surgery	349 patients. (153 vs 196)	ACE-I or ARB	-intraoperative hypotension; -vasopressor requirements	24 hours
9-Bertrand et al (2001)	France	RCT	68± 12	7/30	Patients undergoing elective major vascular surgery	37 patients (19 vs 18)	Angiotensin II antagonists	-intraoperative hypotension	-
10-Twersky et al (2013)	USA	RCT	61.5± 15.75	347/215	ASA II or III patients undergoing ambulatory and same-day surgery	562 patients. (264 vs 262)	ACE-I or ARB	-incidence of hypertension (SBP>140 mmhg) -incidence of hypotension (SBP<90 mmhg)	24 hours
11-Shirmer et al (2007)	Germany	RCT	65.5± 12	51/49	Patients undergoing ear, nose, and throat surgery and ophthalmology	100 patients (50 vs 50)	ACE-I or ARB	-Incidence of hypotension	-
12-Kim et al (2024)	Republic of Korea	Retrospective cohort study	64.9± 9.85	22864/ 19568	Patients aged > 18 years undergoing elective non-cardiac surgery	42432 patients (11377 vs 31055)	ACE-I or ARB	-Cardiovascular complications -Mortality	30 days

CG: continuing group; **WG**: withholding group; **RCT**: randomized controlled trial; **ARB**: angiotensin receptor blockers; **CCB**: calcium channel blockers; **ACEI**: angiotensin converting enzyme inhibitors; **SBP**: systolic blood pressure; **AKI**: acute kidney injury

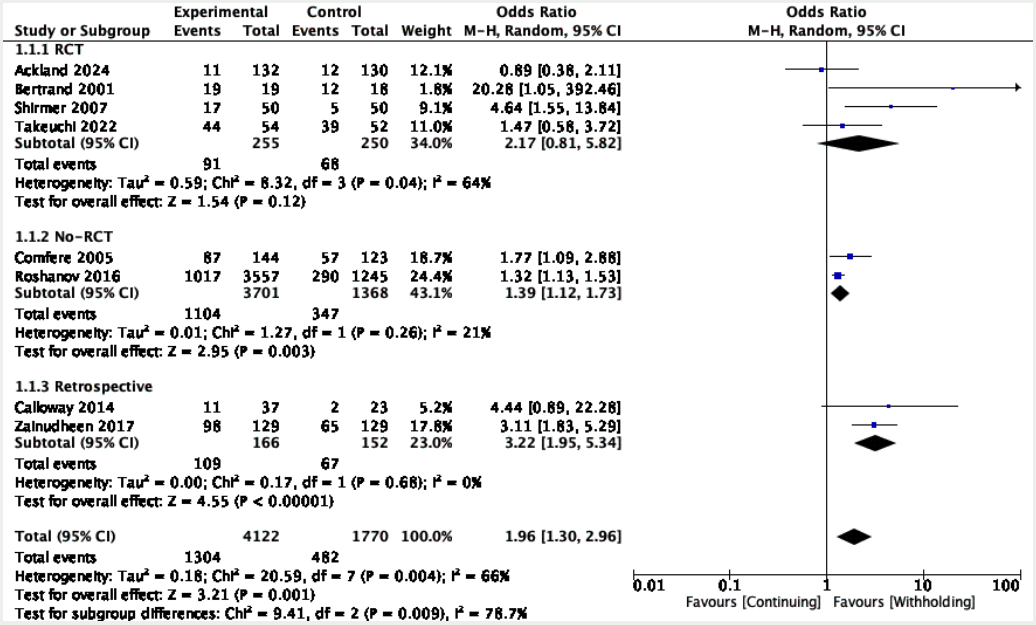

Figure 2. Forest plot of intraoperative hypotension

Subgroup analyzes demonstrated that within the RCT subgroup, continuing ACEIs or ARB did not significantly impact the incidence of intraoperative hypotension, but heterogeneity remained substantial (OR = 2.17, 95% CI [0.81, 5.82], p=0.12; Tau²=0.59). In contrast, in the non-RCT and retrospective groups, the continued ACEI or ARB markedly increased the incidence of intraoperative hypotension, and heterogeneity was reduced, (OR = 1.39, 95% CI [1.12, 1.73] p=0.003; Tau²=0.01) and (OR = 3.22, 95% CI [1.95, 5.34] p < 0.001; Tau²=0), respectively.
Secondary outcomes:

Intraoperative Vasoactive Agents

Six studies evaluated data on the use of intraoperative vasoactive agents (20-22,24,25,27). It was used in 3073 out of 11859 patients in the continuing group (25.9%) versus 2390 out of 31544 patients in the withholding group (7.6%). They showed that in the continuation group, the use of vasoactive agents was significantly higher (OR = 2.33, 95% CI [1.28, 4.24] p=0.006; Tau²=0.42) (Figure 3A). The dose of ephedrine was reported in five studies (20,21,23,24,26). The pooled results showed that the mean dose of ephedrine was higher in the continuing group compared to the withholding group (MD = 3.66, 95% CI [0.78, 6.55], p=0.01; Tau²=9.47) (Figure 3B). The dose of phenylephrine was reported in only four studies (18,20,23,24). They showed that there was no significant difference between both groups, but heterogeneity was high (MD = -60.27, 95% CI [-138.66, 18.13], p=0.13; Tau²=3145.11).

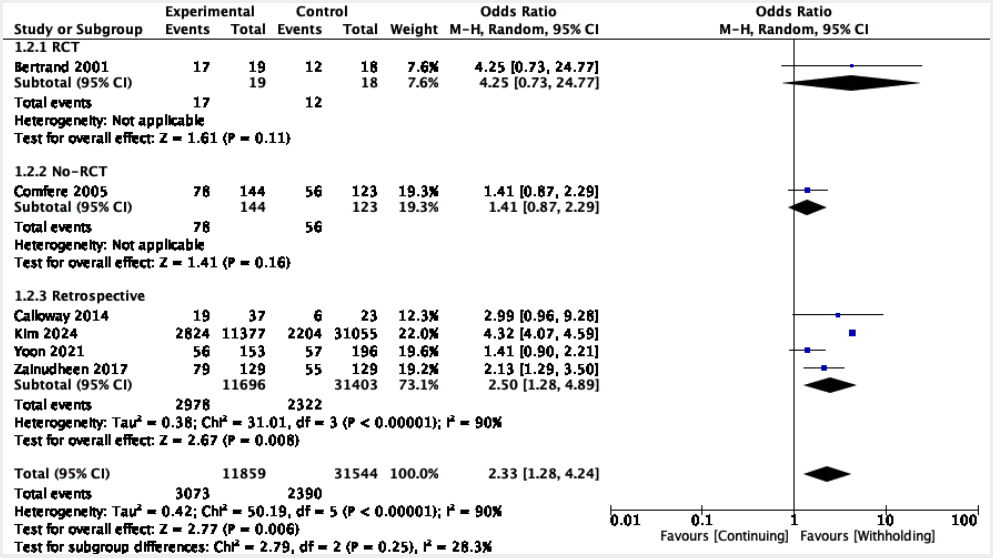

Figure 3. Forest plots of secondary outcomes: **3A.** Intraoperative use of vasoactive agents

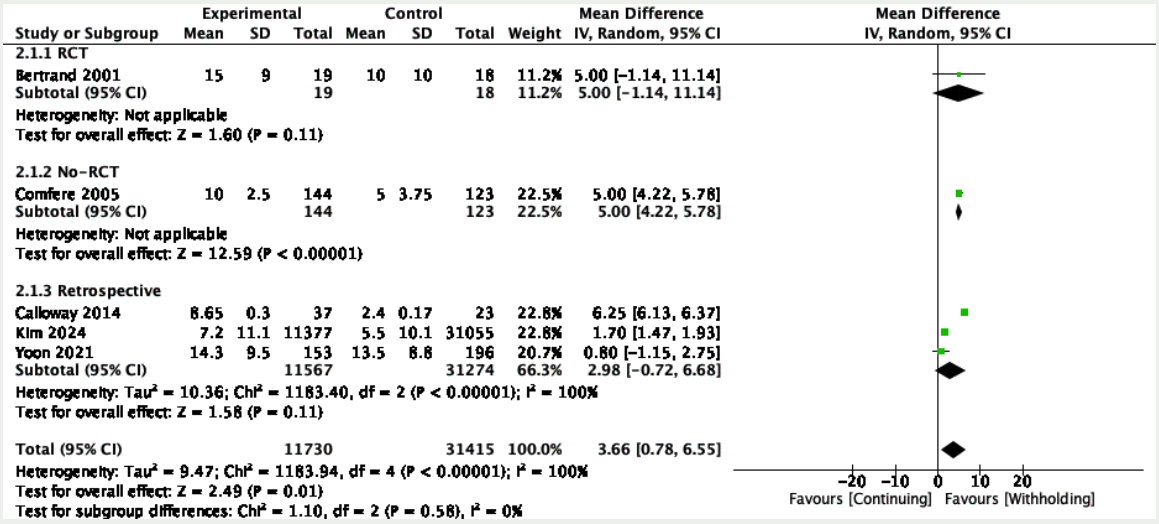

Figure 3. Forest plots of secondary outcomes: **3B.** dose of ephedrine

Incidence of severe hypotension

Only three studies reported data on the incidence of severe hypotension (19,21,22). It was reported in 65 of 235 patients in the continuing group and 41 of 198 patients in the withholding group. The combined results showed that the continuation of ACEI or ARB was significantly associated with a higher incidence of severe hypotension (OR = 2.03, 95% CI [1.04, 3.97], p=0.04; Tau^2=0.09) (Figure 3C).

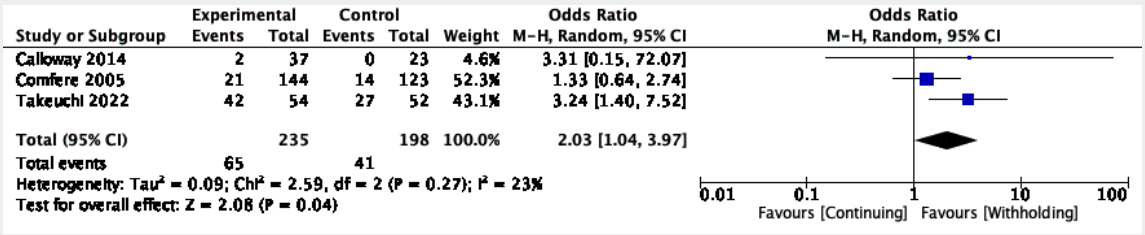

Figure 3. Forest plots of secondary outcomes: **3C.** Incidence of severe hypotension

LOS of the hospital

Four studies evaluated data on hospital LOS (19-22). It was reported in 364 patients in the continuation group versus 327 patients in the withholding group. There was no significant difference between the two groups (MD = -0.29, 95% CI [-0.91, 0.34], p=0.37; Tau^2=0.0.33).

Intraoperative and postoperative hypertension

Five studies reported data on the incidence of intraoperative and postoperative hypertension (19,23,25-27). It was reported in 2336 out of 11846 patients in the continuing group versus 2673 out of 31517 patients in the withholding group. The pooled results did not show significant differences between the two groups (OR = 0.82, 95% CI [0.33, 2.04], p=0.68; Tau^2=0.89).

Incidence of postoperative AKI

Five studies reported data on the incidence of postoperative AKI (20-23,28). It was reported in 95 of 818 patients in the continuing group and 126 of 978 patients in the withholding group. The pooled results did not show significant differences between the group (OR = 1.20, 95% CI [0.48, 3.02], p=0.39, Tau^2=0.52) (Figure 3D).

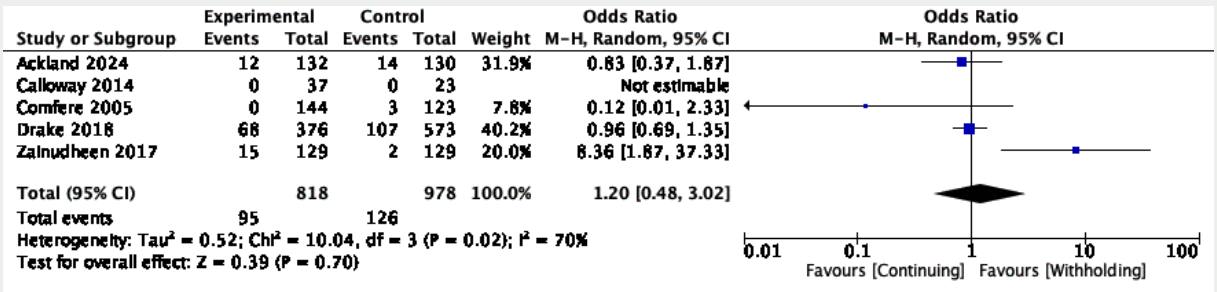

Figure 3. Forest plots of secondary outcomes: **3D.** Incidence of acute postoperative kidney injury

30-day postoperative mortality

Six studies evaluated data on the incidence of 30-day postoperative causes of mortality (1,21,22,26-28). It was reported in 107 out of 15755 patients in the continuing group and 128 out of 33281 patients in the withholding group. There was no significant difference between the two groups, with low heterogeneity (OR = 0.90, 95% CI [0.67, 1.21], p=0.48; Tau^2=0) (Figure 3E).

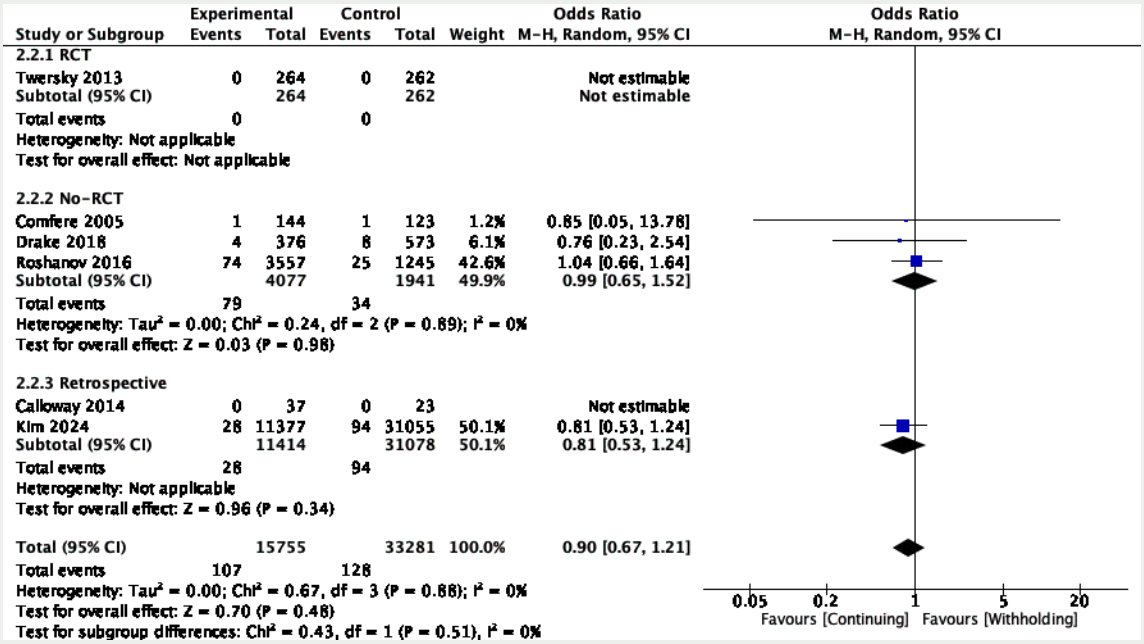

Figure 3. Forest plots of secondary outcomes: **3E.** 30-day mortality

Incidence of postoperative MACCE

Six studies reported data on the incidence of postoperative MACCE (1,20-22,26,27). It was reported in 921 out of 11543 patients in the continuing group and 2181 out of 31207 patients in the withholding group. The pooled results did not show significant differences between the two groups, with low heterogeneity (OR = 1.13, 95% CI [0.92, 1.38], p=0.24; Tau^2=0.02) (Figure 3F).

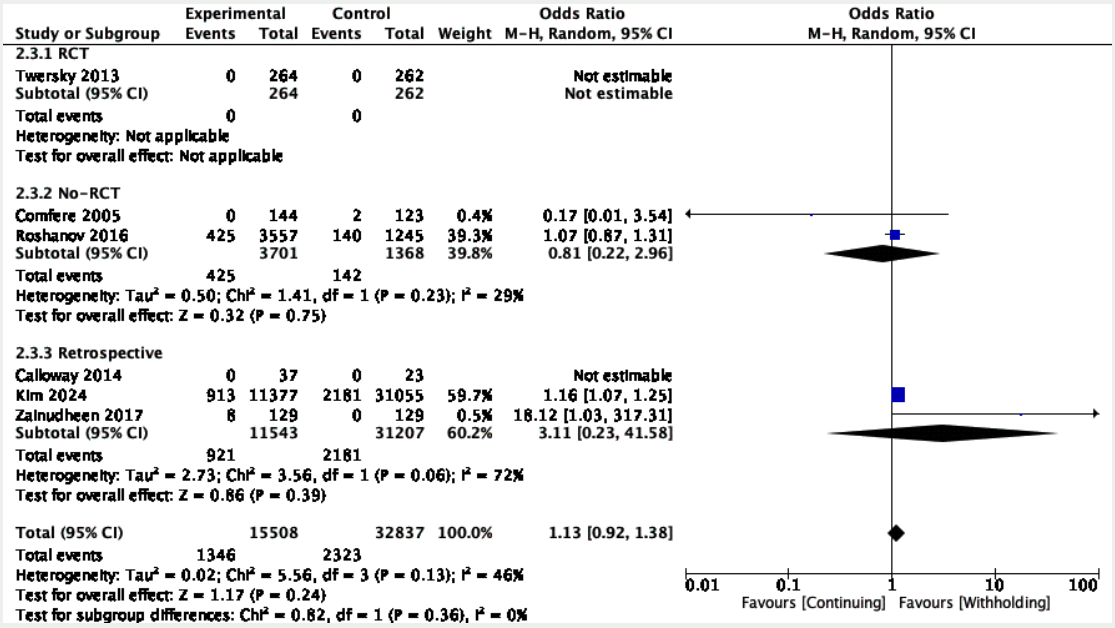

Figure 3. Forest plots of secondary outcomes: **3F.** Incidence of postoperative MACCE

Discussion

Our study aimed to analyze the incidence of intraoperative and postoperative hemodynamic instability and its consequences in patients undergoing noncardiac surgery treated with RAAS inhibitors. Taking into account all the included studies, we showed that the incidence of intraoperative hypotension was significantly higher in the continuing group, but with high heterogeneity (OR = 1.96, 95% CI [1.30, 2.96] p=0.001; Tau^2=0.18). There were no differences in the incidence of intraoperative hypotension in the analysis (OR = 2.17, 95% CI [0.81, 5.82], p=0.12; Tau^2=0.59). Consequently, continuing treatment with RAAS inhibitors was associated with a higher risk of severe hypotension and increased use of vasopressors. There was no difference in the incidence of hypertension, AKI, 30-day mortality, and new MACCE.

Intraoperative hypotension has been widely described in patients undergoing RAAS inhibitor treatment. Anesthesia is known to induce sympatholytic effects, and the maintenance of arterial blood pressure depends on the regulation of RAAS during the intra-operative period (7,39). The common belief is that stopping RAAS inhibitors before surgery prevents intraoperative hypotension, but this is mainly based on observational studies or small samples of RCT trials (40). The subgroup analysis of RCT included in our study did not demonstrate an increase in the risk of hypotension. Two previous meta-analyses found an increased risk of intraoperative hypotension, but no subgroup analysis including only RCTs was performed (41,42). Furthermore, the SPACE trial, a robust and recent RCT study that established the duration of cessation prior to surgery with respect to the pharmacokinetics of each drug, was not included in those meta-analyses (43). Our findings provide interesting details on the evidence of hypotension associated with continued RAAS inhibitors before surgery. However, studies included suffered high heterogeneity in both patients, including protocol of anesthesia and scheduled surgery: orthopedic surgery under general or neuraxial anesthesia (44,45), elective abdominal and urology surgery under general anesthesia (7,43,46-49), or major vascular surgery under general anesthesia (50).

In our study, we showed an increased risk of intra-operative severe intraoperative hypotension and use of vasopressor in the continuing group. Severe hypotension was reported in three studies, including Two of them did not find an increased risk (7,44). The third was a comparison of a combination treatment of RAAS inhibitor and calcium channel blocker (CCB) versus no treatment, and significant hypotension was defined as an SBP < 80 mmHg (47). Regarding the use of vasopressor, only one study specified a protocol for the use of vasopressor (44), which could have led to an overrepresentation of the necessity of hemodynamic support in the continuing group in other studies (7,45,50-52). On the contrary, we found no increased risk of mortality, new MACCE, or AKI at 30 days during the postoperative period. In the same way, MACCE had a different definition between studies: increase in the non-high-sensitivity cardiac troponin T value (cTnT) (48,51), raising of troponin and new ST-T wave or Q wave on electrocardiogram (44,45,53-55), congestive cardiac failure, cardiac arrhythmias, cerebrovascular events confirmed on brain imaging (45), or non-specified (56). The definition of AKI was based on serum creatinine elevation, with a threshold issued from the RIFLE or KDIGO classification, which is quite comparable (57). Although there is evidence for an increased risk of ischemic events up to 30 days after surgery (58), the end of follow-up at discharge from the operative room or post-anesthesia care unit and before 72 h in four studies may have underestimated the incidence of MACCE and AKI (7,44,45,56). No protective role has been demonstrated.

Several limitations have been identified in the current meta-analysis. First, the results suffer from a high heterogeneity between the studies, including a wide range of surgeries and patients. We could not measure the incidence of hypotension depending on the protocol of anesthesia used (general anesthesia vs. locoregional anesthesia), which could have provided interesting data regarding the continuation or discontinuation of RAAS inhibitors. The large variations in the definition of hypotension and the absence of a standard protocol for the use could have influenced the study findings. As a result, it is appropriate to classify the results as exploratory.

Conclusions

We may consider that the absence of a protective role and the possible existence of an increase in perioperative complications related to hypotension induced by ACE inhibitors should lead to a case-by-case approach, depending on the molecule used and the planned surgery. More large-scale randomized controlled trials are needed to confirm the results.

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