ANESTHESIA & ANALGESIA® Infographic

Take It or Leave It:
A Meta-analysis of Perioperative ACE Inhibitors and ARBs

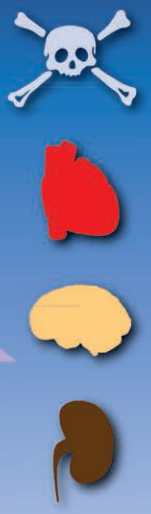
~33%
of patients > 45 years old presenting for surgery are taking an ACE-I or ARB

These medications have been associated with intraoperative hypotension. A meta-analysis in this issue pooled available data in non-cardiac surgical patients.[1] The aim was to uncover potential postoperative outcomes associated with continuation of this common drug class.

1816 patients withheld their ACE-I/ARB

4206 patients continued their ACE-I/ARB

No differences were seen between the two groups with respect to mortality, MACE, CVA or AKI. Of note, sample sizes were under-powered for these outcomes.



30% relative risk ↑ in hypotension

Current suggestions from:

ACC/AHA
Reasonable to continue drugs but if withheld should be restarted as soon as possible

CCS
Withhold drugs for 24 hours prior to surgery

ESC/ESA
Withhold drugs for 24 hours prior if used for HTN, continue drugs if used for heart failure

More high quality randomized trials are needed to determine perioperative ACE-I/ARB outcomes.

The continuation of ACE inhibitors and angiotensin receptor blockers perioperatively has been associated with intraoperative hypotension. To date, it has remained unclear whether definitive outcomes emerge from the decision to withhold them on the morning of surgery. In this issue, Hollmann et al offer a systematic review and meta-analysis pooling roughly 6000 patients across 9 studies in the noncardiac surgical population that either continued their medication or had it withheld. The results substantiate the association of intraoperative hypotension and continuation of ACE-I/ARBs. No differences in mortality, cardiac events, stroke, acute kidney injury, or length of stay were found between the 2 groups. However, limitations of this analysis include lack of uniformity of the definitions of hypotension, inconsistent anesthetic regimens, and several other elements that reduce the power to elucidate statistical significance in outcomes. The reader is encouraged to review this article for further depth of understanding.

ACC/AHA indicates American College of Cardiology/American Heart Association; ACE-I, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; CCS, Canadian Cardiovascular Society; CVA, cerebrovascular accident; ESC/ESA, European Society of Cardiology/European Society of Anaesthesiology; MACE, major adverse cardiac event.

The Infographic is composed by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine (n-nathan@northwestern.edu). Illustration by Naveen Nathan, MD.

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1. Hollmann C, Fernandes NL, Biccard BM. A systematic review of outcomes associated with withholding or continuing angiotensin-converting enzyme inhibitors and angiotensin receptor blockers before noncardiac surgery. *Anesth Analg*. 2018;127:678–687.

IARS International Anesthesia Research Society

Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers Before Elective Noncardiac Surgery: An Ongoing Dilemma

Sudarshan Setty, MD, Daniela Orza, MD, and Kumar G. Belani, MBBS, MS

Angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARBs) are potent and ubiquitous antihypertensive medications.[1] Multiple guidelines suggest that ACE-I/ARB drugs be omitted on the morning of surgery, commensurate with a host of clinical experience detailing profound hypotension after the routine induction of anesthesia during noncardiac surgery when ACE-I or ARB drugs are continued. Moreover, the resulting hypotension may be distressingly resistant to routine rescue doses of vasopressors such as phenylephrine, ephedrine, vasopressin, norepinephrine, and other drugs.[2–4] Thus, continuation of these specific antihypertensive drugs in surgical patients often elicits significant angst for surgeons and anesthesiologists alike. Interestingly, Hollmann et al[5] provide clinicians with contrarian results regarding this conundrum based on the conclusions of a meta-analysis that focuses on major cardiovascular and cerebrovascular outcomes—and not simply the magnitude of change for intraoperative blood pressure.

Their analysis examined major cardiovascular outcomes of over 6000 patients aggregated from a combination of 9 randomized clinical trials and cohort studies. Validating many clinicians' experience, Hollmann et al[5] confirmed an overall 30% increase in the relative risk of hypotension (corresponding to an absolute risk increase of 6.5%, from 23.4% to 29.9%) associated with continued therapy. Thus, the "solution" seems clear —to mitigate this risk, simply withhold all ACE-I and ARB drugs the morning of surgery. Indeed, this is the conclusion of the frequently cited VISION study.[6] The Vascular Events in Non-cardiac Surgery Patients Cohort Evaluation (VISION) analyzed data from 14,687 patients undergoing noncardiac surgery of which 4802 were on ACE-I/ARB in a prospective cohort study. Patients who withheld ACE-I/ARBs in the 24 hours before surgery had a lower incidence of all-cause death, stroke, or myocardial injury (12% in the withheld group versus 12.9% in the continued group with an adjusted relative risk of 0.82, 95% CI, 0.70–0.96, and a *P* value of .01). But is withholding these specific antihypertensive drugs always necessary, or even prudent? Strikingly, meta-analysis by Hollmann et al[5] did not demonstrate an association between continued administration of ACE-I/ARB therapy and patient mortality (odds ratio = 0.97; 95% CI, 0.62–1.52) or major adverse cardiac events (MACEs; odds ratio = 1.12; 95% CI, 0.82–1.52) despite the frequent occurrence of intraoperative hypotension.

So, what is the most prudent approach for clinicians at this time? What are the likely long-term consequences from continuing ACE-I/ARB therapy versus withholding them? Should all patients have their ACE-I/ARB medication withheld on the day scheduled for surgery, or just select subsets (eg, cardiac versus noncardiac surgery)? Is a 24-hour hold sufficient, or is even more time required for those medications to be eliminated?

ACE-I and ARB pharmacology is complex and may provide some insights into the discrepant findings of the meta-analysis by Hollmann et al.[5] Most of the ACE-I are prodrugs, which are metabolized in the liver and kidneys, with the exception of lisinopril, which is excreted unchanged in urine. Factors like congestive heart failure, kidney, or liver dysfunction can affect the half-life of the ACE-I.[7] It is therefore important that the practitioner evaluates the type and time of the last dose of the ACE-I or ARB that has been prescribed, as each drug has a different pharmacokinetic and pharmacodynamic profile (Table).[8,9] For example, captopril has an elimination half-life of 4–6 hours and enalapril, which is longer acting than captopril, is deesterified in the liver and kidneys to its active form enalaprilat. The elimination half-life of enalaprilat is normally about 5 hours but increases in patients with congestive heart failure to 6–8 hours, and with repeated doses the elimination half-life increases to 11 hours. Thus, whether and when you stop ACE-I may well depend on several comorbidities.

But even after accounting for the complexity of ACE-I/ARB drug pharmacology, 2 questions remain:

1. How can we account for the consistent occurrence of hypotension but the lack of association with increased mortality or morbidity in the meta-analysis by Hollmann et al[5] (unlike prior studies)?
2. While the VISION trial[6] accounts for 97.4% weightage for the mortality analysis, the meta-analysis by Hollmann et al[5] comes to a discrepant conclusion regarding MACE outcomes. How do we explain this?

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Table. Select Pharmacokinetic Parameters of Some of the ACE-I and ARBs

Drug (ACE Inhibitor)	Clearance CL (L/h)	Drug (ARB)	Half-Life (h)
Benazeprilat	1.79	Losartan	2
Cilaaprilat	12.3	Valsartan	9
Fosinopril acid	2.34	Irbesartan	11–15
Lisinopril	6.36 (renal)	Candesartan	3.5–4.0
Pentopril	12.78 (renal)	Telmisartan	24
Perindopril	9.36	Eprosartan	5–7
Ramiprilat	6.0 (renal)	Olmesartan	13 (approximately)

Data were derived from Song and White[8] and Barreras and Gurk-Turner.[9]
Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARBs, angiotensin II receptor blockers; CL, clearance.

First, clinicians should consider key components and implications of the statistical meta-analysis itself. While this unique tool can lend powerful insights to summarizing disparate findings surrounding a specific medical intervention, the conclusions are potentially susceptible to a host of limitations.[10] For instance, critics opine that the technique is encumbered if authors combine different types (ie, "apples and oranges") of studies—indeed, the underlying studies of Hollmann et al[5] combined 5 randomized controlled trials with 4 cohort studies. Potential differences in reliability between these 2 study formats can be difficult to discern, and the analysis by Hollmann et al[5] was not broken out by each study type. Moreover, the meta-analysis did not adjust for key baseline factors, increasing the likelihood of underestimating a treatment outcome. Any meta-analysis may also be influenced by major discrepancies in study size. Here, the results of the single study by Roshanov et al[6] (Table 1 in Hollmann et al[5]) accounted for 80% of the combined patient data—more than all the other studies combined. Finally, an inherent limitation in some of the original studies included in the meta-analysis is that MACEs were unreported. Indeed, the mortality data appear to be drawn from a minority of the studies. Moreover, one could speculate that smaller studies without serial troponin and/or electrocardiogram monitoring missed substantial numbers of myocardial infarctions or at least myocardial injury.

As expected, the 9 selected studies in the meta-analysis by Hollmann et al[5] include a host of different ACE-I/ARB drugs, the interval from last dose to surgery, the definition of hypotension, and the methods used to treat hypotension in the operating room. Only 3 of the 9 studies included in the meta-analysis by Hollmann et al reported which of the ACE-I/ARBs were administered (or withheld),[11–13] and only 1 reported that they included ARB drugs, but did not specify which ones.[14] Depending on the specific study, the ACE-I/ARB drugs might be withheld for >10 hours,[13] 12–24 hours,[11] 24 hours,[12] or were simply held the day before surgery[6,14,15] without specifying the exact number of hours (Table 2 in Hollmann et al). Thus, there is wide variation in time from last dose and the different type of ACE-I/ARB medications in the meta-analysis.

In addition, 9 studies varied widely in the duration for which the blood pressure was reported, the treatment of hypotension, and the very definition of what constitutes hypotension (surprisingly none of the studies reported the duration of hypotension). The definition of hypotension varied widely from a systolic blood pressure <80[14] or 85 mm Hg[9,11,13] lasting longer than a minute, a systolic blood pressure <90 mm Hg that prompted a clinical intervention,[6] or a systolic blood pressure <90 mm Hg for any duration.[11] Only 1 study defined hypotension as mean arterial pressure of <60 mm Hg.[16] Treatment for hypotension also varied from vasopressors[12,14,16] to intravenous fluids[15] or intravenous fluids with vasopressors[11] to a multimodal approach.[6]

Realistically, all clinicians worry about not just the degree of hypotension, but also its duration. For instance, we know that prolonged hypotension with mean arterial pressures of <55 mm Hg for longer than 20 minutes results in increased mortality, and adverse renal and cardiac outcomes.[17] Thus, the absence of this information (the duration of intraoperative hypotension in the analysis) leaves us to wonder whether the continuation of ACE-I and ARB drugs on the day of surgery causes only transient hypotension (insufficient to cause mortality or MACE), or that these clinicians were very adept and proficient at its correction.

Finally, one is left to reconcile why the Hollmann et al meta-analysis reports no change in mortality regardless of whether ACE-I/ARBs were continued on the day of surgery (odds ratio = 0.96), while the largest single study included in the data set (the VISION study[6]) reported a lower risk of mortality, myocardial injury, and stroke associated with withholding ACE-I/ARB drugs. Perhaps the inability of the current meta-analysis to fully adjust for baseline factors and covariates is critical, whereas Roshanov et al[6] adjusted for a host of potential confounders in their study.[6] Additionally, the VISION study reported results from a modified Poisson regression in the context of adjusted relative risks rather than pooled estimates of the odds ratio as done in the Hollmann et al meta-analysis.

Regardless, the meta-analysis by Hollmann et al[5] provides additional insights and uncertainties while addressing the vital decision about preoperative medications during the preparation of adult hypertensive surgical patients. We agree that a large randomized controlled trial is required to finalize the elusive answer regarding the safety of continuing or withholding ACE-I/ARB drugs on the day of surgery. The current literature both supports withholding ACE-I/ARBs the day before surgery (Roshanov et al[6]) and questions it (Hollmann et al[5]). For now, we encourage clinicians to consider all aspects of the literature along with unique characteristics of each patient in reaching optimal care decisions.

DISCLOSURES

Name: Sudarshan Setty, MD.
Contribution: This author helped review the manuscript referenced by this editorial and accepted by *Anesthesia & Analgesia*. This author provided a review and summary of other studies relevant to this article. This author also commented on the statistics used in the meta-analysis. This author was thus able to draft the editorial. The final editorial was reviewed and approved by this author.
Name: Daniela Orza, MD.
Contribution: This author helped review the manuscript referenced by this editorial and accepted by *Anesthesia & Analgesia*. This author provided summary points including conducting an analysis of the statistics used. This information was used in putting together the editorial. The final editorial was reviewed and approved by this author.

Name: Kumar G. Belani, MBBS, MS.
Contribution: This author helped finalize the editorial after reviewing the manuscript referenced in this editorial and accepted by *Anesthesia & Analgesia*. This author used the inputs provided by Dr Setty and Orza to finalize the manuscript and provided the table.
This manuscript was handled by: Richard C. Prielipp, MD.

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META-ANALYSIS

A Systematic Review of Outcomes Associated With Withholding or Continuing Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers Before Noncardiac Surgery

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BACKGROUND: The global rate of major noncardiac surgical procedures is increasing annually, and of those patients presenting for surgery, increasing numbers are taking either an angiotensin-converting enzyme inhibitor (ACE-I) or an angiotensin receptor blocker (ARB). The current recommendations of whether to continue or withhold ACE-I and ARB in the perioperative period are conflicting. Previous meta-analyses have linked preoperative ACE-I/ARB therapy to the increased incidence of postinduction hypotension; however, they have failed to correlate this with adverse patient outcomes. The aim of this meta-analysis was to determine whether continuation or withholding ACE-I or ARB therapy in the perioperative period is associated with mortality and major morbidity.

METHODS: This meta-analysis was prospectively registered on PROSPERO (CRD42017055291). A comprehensive search of MEDLINE (PubMed), CINAHL (EBSCO host), ProQuest, Cochrane database, Scopus, and Web of Science was conducted on December 6, 2016. We included adult patients >18 years of age on chronic ACE-I or ARB therapy who underwent noncardiac surgery in which ACE-I or ARB was either withheld or continued on the morning of surgery. Primary outcomes included all-cause mortality and major cardiac events (MACE). Secondary outcomes included the risk of congestive heart failure, acute kidney injury, stroke, intraoperative/postoperative hypotension, and the length of hospital stay.

RESULTS: After abstract review, the full text of 25 studies was retrieved, of which 9 fulfilled the inclusion criteria: 5 were randomized control trials, and 4 were cohort studies. These studies included a total of 6022 patients on chronic ACE-I/ARB therapy before noncardiac surgery. A total of 1816 patients withheld treatment the morning of surgery and 4206 continued their ACE-I/ARB. Preoperative demographics were similar between the 2 groups. Withholding ACE-I/ARB therapy was not associated with a difference in mortality (odds ratio [OR], 0.97; 95% confidence interval [CI], 0.62–1.52; $I^2 = 0\%$) or MACE (OR, 1.12; 95% CI, 0.82–1.52; $I^2 = 0\%$). However, withholding therapy was associated with significantly less intraoperative hypotension (OR, 0.63; 95% CI, 0.47–0.85; $I^2 = 71\%$). No effect estimate could be pooled concerning length of hospital stay and congestive heart failure.

CONCLUSIONS: This meta-analysis did not demonstrate an association between perioperative administration of ACE-I/ARB and mortality or MACE. It did, however, confirm the current observation that perioperative continuation of ACE-I/ARBs is associated with an increased incidence of intraoperative hypotension. A large randomized control trial is necessary to determine the appropriate perioperative management of ACE-I and ARBs. (Anesth Analg 2018;127:678–87)

KEY POINTS

- **Question:** Is the withholding or continuation of angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs) before noncardiac surgery associated with perioperative mortality or major morbidity?
- **Findings:** The continuation of ACE-Is/ARBs on the morning of noncardiac surgery is associated with increased intraoperative hypotension; however, an association with mortality and major adverse cardiac events remains unclear.
- **Meaning:** Large randomized trials are needed to adequately assess for an association between perioperative ACE-I/ARB use and major morbidity in noncardiac surgery.

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More than 280 million surgeries are performed globally each year[1]; of these patients, approximately one-third are ≥45 years and are on either an angiotensin-converting enzyme inhibitor (ACE-I) or an angiotensin receptor blocker (ARB) before surgery.[2] Controversy exists as to whether ACE-Is/ARBs should be continued in the perioperative period because continuation has been associated with both harm and benefit. Intraoperative hypotension secondary to continuation of ACE-I and ARB therapy in the perioperative period[3,4] may be associated with major perioperative morbidity[2] and has led some clinicians to withhold therapy. Conversely, continuation of ACE-Is/ARBs in the perioperative period may also be associated with improved outcomes, in which preoperative ACE-I has been associated with improved outcomes in vascular surgical patients who have sustained a perioperative myocardial infarction (MI).[5] This is potentially important considering a 30-day mortality rate after a perioperative MI after noncardiac surgery of approximately 10%.[6] However, these cardiovascular benefits have not consistently been demonstrated in the literature.[7] It is for these reasons that the potential harms or benefits associated with continuing or withholding ACE-I and ARBs in the perioperative period remain unclear.

It is not surprising that the current perioperative guidelines vary in the recommendations made regarding perioperative continuation or withholding of ACE-Is/ARBs. The 2014 American College of Cardiology/American Heart Association guidelines[8] state that it is reasonable to continue therapy preoperatively, and if withheld, therapy may be reinstituted as soon as clinically feasible, while the most recent guidelines by the Canadian Cardiovascular Society[9] suggest omitting therapy 24 hours before surgery (strong recommendation, low quality of evidence). In contrast, the European Society of Cardiology/European Society of Anaesthesiology[10] bases its recommendations on the indication for treatment with an ACE-I/ARB, recommending discontinuation for 24 hours before surgery if prescribed for hypertension, and continuation if prescribed for heart failure and left ventricular systolic dysfunction.[10] Furthermore, should these patients not be on ACE-I/ARB therapy before surgery, guidelines recommend instituting ≥1 week before surgery.[10] Unfortunately, the evidence for the American, European, and Canadian guidelines is limited.

Two previous meta-analyses[11,12] have provided information concerning perioperative ACE-I/ARB therapy and the impact on mortality and major morbidity. Unfortunately, both cardiac and noncardiac data were used in both, with main results revealing no significant difference in MI or mortality[12] and a 50% increase in the incidence of postinduction hypotension[11] associated with treatment continuation. These meta-analyses and numerous previous studies are therefore underpowered to address potential associations between perioperative ACE-I/ARBs and major morbidity,[3,4,13–15] despite a clear demonstration of increased incidence of intraoperative hypotension. Associations with MI, acute kidney injury (AKI), death, or stroke remain unknown. Considering the uncertainty in the current literature concerning the clinical consequences associated with continuing or withholding of ACE-I/ARBs in the perioperative period, and the absence of a recent meta-analysis addressing this problem, an updated review of the literature is needed to accurately inform the decision on whether to withhold or continue perioperative ACE-I/ARB therapy.

The objectives of this meta-analysis were therefore to estimate and assess the mortality and major morbidity associated with withholding or continuation of ACE-I/ARBs before noncardiac surgery.

METHODS

Protocol and Registration

This systematic review and meta-analysis was registered with PROSPERO (international prospective register for systematic reviews CRD42017055291). The review was approved by the ethics board at the University of Cape Town, and the need for consent waived as all data extracted was in the public domain. We adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analysis[16] guidelines.

Eligibility Criteria

The aim of this systematic review was to report on important patient outcomes associated with withholding or continuing ACE-Is/ARBs on the morning of noncardiac surgery. Study eligibility was determined by the participants or population, interventions, comparisons, outcomes, and study design criteria. Eligible populations included all adult patients (>18 years of age) who were chronically receiving either ACE-I/ARB and undergoing noncardiac surgery. The intervention included withholding of ACE-I/ARB therapy either on the day of surgery or the day before surgery, with the comparator group continuing treatment through the perioperative period. Primary outcomes included all-cause mortality and major cardiac events (MACE). We used the included study definitions of MACE in the analyses. Secondary outcomes included the incidence of AKI, congestive heart failure (CHF), cerebrovascular accident (CVA), intraoperative and postoperative hypotension, and length of hospital stay (LOS). We included the following study designs: randomized controlled trials (RCTs) or observational studies in which patients in both treatment arms were on chronic ACE-I/ARB therapy before surgery. Case reports and case–control studies were excluded. We evaluated ACE-Is/ARBs as a treatment group and did not attempt to evaluate the effects of specific classes of ACE-I or ARB drugs. We included all human studies regardless of language, sample size, publication status, or date of publication.

Information Sources and Search

We searched 6 electronic databases through December 6, 2016: MEDLINE (PubMed), CINAHL (EBSCO host), ProQuest, Cochrane database, Scopus, and Web of Science. The search terms included the following: Angiotensin Type II Receptor Antagonists (MESH term) or Angiotensin-Converting Enzyme Inhibitors (MESH term) and Withholding Treatment (MESH term) and Surgical Procedures, Operative (MESH term) not Cardiac Surgical Procedures (MESH term). Limits included human studies only. The search strategy is shown in Supplemental Digital Content 1, Appendix 1, http://links.lww.com/AA/C251.

Study Selection Process

The title and abstract of each citation were independently screened by 2 authors (C.H. and N.L.F.) to identify potentially eligible studies. Study patients were excluded if: (1) the study patients were undergoing cardiac surgery; (2) ACE-Is/ARBs were not withheld before surgery; (3) patients were not on chronic ACE-I/ARB therapy before surgery; and (4) nonhuman studies. We excluded reviews, case reports, and duplicate publications. Potentially relevant studies were retrieved for full-text evaluation.

Data Collection Process

Full texts of all potentially relevant studies were independently evaluated by 2 reviewers (C.H. and N.L.F.) to determine eligibility. Disagreements were resolved by consensus. If no consensus could be reached, a third reviewer (B.M.B.) made the final decision. A manual search of the reference lists of all included papers was also conducted. We attempted to contact the authors of included studies if further data were required.

Data Items

A standardized data extraction sheet was used to extract population demographics, surgery, and outcome data from the included studies by C.H. and N.L.F. We extracted the definition of each outcome and time to outcome, the duration of withholding ACE-Is/ARBs, and type of ACE-I/ARB therapy. No further data were obtained from authors, and, hence, all the data presented were extracted from the publications only.

Risk of Bias in Individual Studies

The quality of each randomized trial was assessed using the Cochrane Collaboration risk of bias tool,[17] assessing selection bias, concealment bias, performance bias, detection bias, attrition bias, and other biases. Observational studies were assessed using the Newcastle Ottawa Quality Assessment Scale.[18] All assessments of bias of individual studies were conducted by 2 authors (C.H. and N.L.F.) independently, and disagreements were resolved with the third reviewer (B.M.B.).

Summary Measures and Statistical Analysis

A meta-analysis was conducted using Review Manager Version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2014). Pooled dichotomous outcomes were reported as odds ratios (ORs) and 95% confidence intervals (CIs). Heterogeneity between studies was assessed using the I^2 statistic, which describes the percentage of variation across studies that is due to heterogeneity and not chance. We considered an I^2 test of >25% to represent significant heterogeneity. Because a high degree of clinical heterogeneity and between-study variance was expected, we used a random-effects model to assess all relevant outcomes. The results are presented as forest plots where applicable. Because standard RevMan (version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) software ignores 0 events, studies with 0 outcome events were excluded from the MACE and mortality analyses.

Additional Analyses

We planned 2 sensitivity analyses: a sensitivity analysis of RCTs only for the outcomes of mortality, MACE, and intraoperative and postoperative hypotension; and a second sensitivity analysis of studies assessing major noncardiac surgery alone.

We also conducted a trial sequential analysis (TSA) to determine the total required sample size using Trial Sequential Analysis software[19] version 0.9.5.9 Beta (Copenhagen Trial Unit; Rigshospitalet, Dept 7812, The Copenhagen University Hospital, Copenhagen, Denmark). An O'Brien-Fleming α-spending analysis with a 2-sided 5% boundary was used, and a futility analysis was included. We used a 25% relative risk reduction in the analyses and included a model-based variance heterogeneity correction when calculating the required information size calculation. A continuity correction factor of 0.5 was applied to the TSA for MACE and mortality to confirm findings from the RevMan software and the exclusion of 0 events.

RESULTS

A total of 900 citations were retrieved from the initial search, of which 12 abstracts were selected and full articles retrieved. The reference lists of retrieved articles were further screened, and 13 additional articles were added for full-text review. Of the excluded studies, 7 had no comparator group,[13,20–25] 4 were case reports,[26–29] 1 included cardiac data (from which we could not extract the noncardiac data or contact the authors),[30] 1 was a multicenter-based questionnaire,[31] 1 only considered preoperative blood pressure (BP),[32] and 2 only considered postoperative nonresumption of ACE-I/ARB.[33,34] Nine studies fulfilled the eligibility criteria and were selected for inclusion in the meta-analysis.[2–4,14,35–39] One of the included studies was a German publication, which required translation for data extraction.[37]

We were unsuccessful in obtaining further data from the authors of 3 of the studies.[30,32,36] As a result, 2 of these studies were excluded. Vijay et al[30] conducted an observational study on 323 patients undergoing noncardiac and cardiac surgery; however, noncardiac data only could not be extracted from the pooled results. Griffin et al[32] reported on preoperative BP only, with no documentation on intraoperative or postoperative outcomes. A detailed flow diagram of the excluded and included trials is shown in Figure 1.

Study Characteristics

Of the 9 included studies, 5 were RCTs[3,4,36,37,39] and 4 were cohort studies,[2,14,35,38] with a total of 6022 patients on chronic ACE-I/ARB therapy. A total of 1816 withheld treatment on the morning of surgery, and 4206 continued their ACE-I/ARB therapy. The patient demographics and comorbid diseases are presented in Table 1, and the type of ACE-I/ARB, duration of withholding therapy, and the outcomes measured and time to outcomes are presented in Table 2. The individual study outcome definitions used for the primary and secondary outcomes in the meta-analysis are shown in Supplemental Digital Content 2 and 3, Table 1, http://links.lww.com/AA/C252, Table 2, http://links.lww.com/AA/C253, respectively.

Six studies omitted ACE-Is/ARBs on the day before surgery,[2,4,35–37,39] and 2 studies omitted therapy ≥10 hours before surgery.[14,38] In 1 study, captopril was omitted 12 hours before surgery and enalapril 24 hours before surgery,[3] based

on the difference in the half-lives of the respective agents. There was no published information on when ACE-I/ARB therapies were resumed. There was large variability in the duration of follow-up between studies, ranging from the day of hospital discharge to 30 days after surgery.[2]

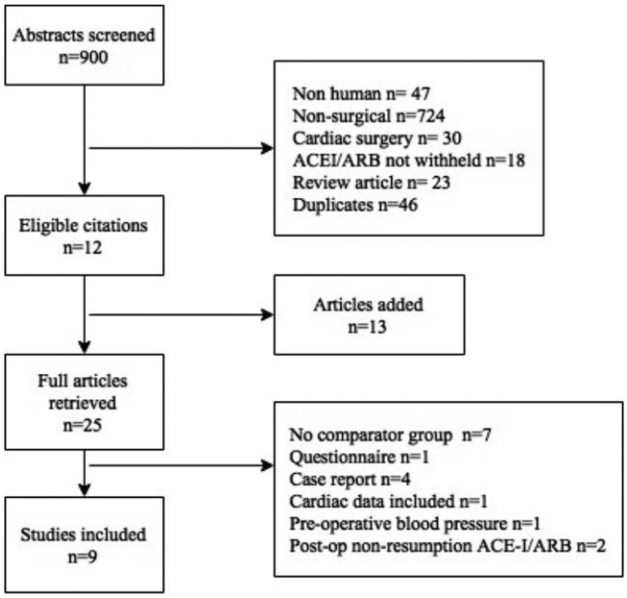

Figure 1. Flowchart of study identification and inclusion. ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Risk of Bias Within Studies

The risk of bias of the 5 RCTs is shown in Supplemental Digital Content 4, Figure 1, http://links.lww.com/AA/C254. Three[4,36,39] trials had low selection bias, with unclear randomization in 2 RCTs.[3,37] Concealment was unclear in all trials, and most experienced performance bias due to unblinded participants[3,4,39] or anesthesiologists.[39] Two trials were assessed as having had selective reporting, in which 1 did not report all the patients for their secondary outcome of postoperative hypertension,[39] and the other study did not report on outcomes of patients treated intraoperatively with ephedrine.[36] Overall, the observational studies performed well in terms of selection, comparability, and outcomes (Supplemental Digital Content 5, Table 3, http://links.lww.com/AA/C255). The funnel plots representing the possibility of publication bias associated with MACE and intraoperative hypotension are shown in Supplemental Digital Content 6 and 7, Figure 2, http://links.lww.com/AA/C256, Figure 3, http://links.lww.com/AA/C257, respectively. Results suggest minimal bias, although the analysis includes few studies.

Results of Individual Studies and Meta-analysis

Mortality. Five studies assessed mortality as an outcome, of which 1671 patients were in the ACE-I/ARB withholding group and 4021 in the continuation group (Figure 2). There was no difference in the mortality between patients who withheld or continued ACE-I/ARB (OR, 0.97; 95% CI, 0.62–1.52). No evidence of heterogeneity was observed with

Table 1. Demographics of Patients in the Included Studies

Reference	Patients (n)	Type of Surgery	Age (y), mean (±SD)	Hypertension, n (%)	Coronary Artery Disease, n (%)
Randomized trials					
Coriat et al[3]	W: 30 C: 21	Vascular	W: enalapril, 69 (±8) C: enalapril, 70 (±8) W: captopril, 66 (±6) C: captopril, 68 (±7)	NR	W: 4 (13.3) C: 2 (9.5)
Rajgopal et al[36]	W: 30 C: 30	NR	Between 40 and 60	NR	NR
Bertrand et al[4]	W: 18 C: 19	Vascular	W: 68 (±11) C: 68 (±13)	W: 18 (100) C: 19 (100)	W: angina, 1 (5.6) History of MI, 5 (27.7) Previous PCI, 3 (16.7) C: angina, 1 (5.2) History of MI, 1 (5.2) Previous PCI, 1 (5.2)
Schirmer and Schürmann[37]	W: 50 C: 50	ENT and ophthalmology	W: 64 (±13) C: 67 (±11)	NR	NR
Twersky et al[39]	W: 262 C: 264	Ambulatory and same day surgery	W: 61 (SD NR) C: 62 (SD NR)	NR	W: 32 (12) C: 33 (13)
Cohort studies					
Calloway et al[35]	W: 23 C: 37	Orthopedic	W: 65.7 (±2.9) C: 66.6 (±4)	NR	W: 3 (13) C: 6 (16)
Roshanov et al[2]	W: 1245 C: 3557	All major noncardiac surgery (emergent and elective)	W: 69 (±11.1) C: 68.8 (±10.8)	NR	W: 302 (24.2) C: 777 (21.8)
Comfere et al[14]	W: 123 C: 144	Elective noncardiac surgery	W: 67 C: 66	NR	W: 29 (23.6) C: 36 (25)
Trentman et al[38]	W: 35 C: 84	Orthopedic	W: 65.9 (±9.8) C: 66.3 (±8.4)	NR	NR

Abbreviations: C, continued; ENT, ear, nose, and throat; MI, myocardial infarction; n, number; NR, not reported; PCI, percutaneous coronary intervention; SD, standard deviation; W, withheld.

Table 2. Characteristics of Included Studies Assessing Type and Duration of Withholding ACE-I/ARBs and Primary and Secondary Outcomes Measured in Studies

Reference	Type of ACE-I/ARB	Duration of Withholding ACE-I/ARB	Length of Follow-up	Outcomes Measured
Randomized trials				
Coriat et al[3]	Captopril/enalapril	Captopril = 12 h Enalapril = 24 h	Study ended at skin incision	SBP on induction and shortly afterward. PCEI, PRA, and catecholamine levels before surgery, preinduction and postinduction
Rajgopal et al[36]	NR	DBS	Study ended 60 min postinduction	SBP, DBP, and MAP pre- and postinduction
Bertrand et al[4]	ARB only, type NR	DBS	Until hospital discharge	Postinduction hypotension and need for vasopressors
Schirmer and Schürmann[37]	NR	DBS	NR	Postinduction hypotension and vasopressor usage
Twersky et al[39]	NR	24 h (mean time =1405 min)	NR	HTN immediately before surgery, surgical cancellations 2nd to HTN, prolonged hospitalization, adverse clinical events, and postoperative HTN
Cohort studies				
Calloway et al[35]	ACE-I = benazepril/ enalapril/lisinopril/ quinapril/ramipril ARB = candesartan/irbesartan/ losartan/ olmesartan/telmisartan/ valsartan	24 h before surgery	Until hospital discharge	SBPs and MAPs pre- and intraoperatively, vasopressor use. Morbidity: MI, stroke, acute kidney injury, ICU admission, and mortality
Roshanov et al[2]	NR	DBS	30 d after surgery	Primary: all-cause death, stroke, or myocardial injury. Secondary: intraoperative/postoperative hypotension
Comfere et al[14]	ACE-I = benazepril, benazeprilat, enalapril, enalaprilat, lisinopril, quinapril, fosinopril, fosinoprilat, ramipril ARBs = candesartan, losartan, valsartan	≥10 h before surgery	Until hospital discharge	Development of moderate or severe hypotension at 0–30 and 31–60 min after induction
Trentman et al[38]	NR	≥10 h before surgery	NR	Total number of hypotensive episodes during intraoperative period. Secondary: vasopressor usage and fluid administered

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; DBS, day before surgery; HTN, hypertension; ICU, intensive care unit; MAP, mean arterial pressure; MI, myocardial infarction; NR, not reported; PCEI, plasma-converting enzyme inhibitor; PRA, plasma renin activity; SBP, systolic blood pressure.

this outcome (I^2 = 0%). Of these studies, only 2 were RCTs, totaling 563 patients, with no reported mortality.

Major Cardiac Events. Five studies reported MACE with no significant difference between the groups (OR, 1.12; 95% CI, 0.82–1.52; P = .78) (Figure 3). One study assessed both MI and myocardial injury after noncardiac surgery (MINS)[2]; however, only data of those patients fulfilling the MI definition were included in the meta-analysis. No evidence of heterogeneity was observed (I^2 = 0%).

Congestive Heart Failure. Only 1 study[4] reported on the development of CHF during hospital admission, although no events were reported in the study. It was therefore not possible to determine a pooled effect for ACE-I/ARBs on CHF.

Cerebrovascular Complications. Four studies[2,14,35,39] assessed the incidence of CVAs with 1653 in the withdrawal group and 4002 in the continuation group (Supplemental Digital Content 8, Figure 4, http://links.lww.com/AA/C258). Outcome events were reported only in 2 studies, with no difference between the groups (OR, 0.95; 95% CI, 0.44–2.06), and no evidence of heterogeneity between the studies observed (I^2 = 0%).

Acute Kidney Injury. Two studies reported on the incidence of AKI,[14,35] with a small sample of 146 patients in the withholding group and 181 in the continuation group (Supplemental Digital Content 9, Figure 5, http://links.lww.com/AA/C259). Only 3 events were reported in the withholding group (OR, 8.39; 95% CI, 0.43–164.12).

Intraoperative Hypotension. Eight studies evaluated the effect of ACE-Is/ARBs on intraoperative hypotension. One study[36] reported only mean and standard deviation in the assessment of postinduction hypotension compared to preoperative BPs, and because we were unable to contact these authors to establish the absolute number of patients who experienced intraoperative hypotension, these data are not included in the meta-analysis. They did, however, show

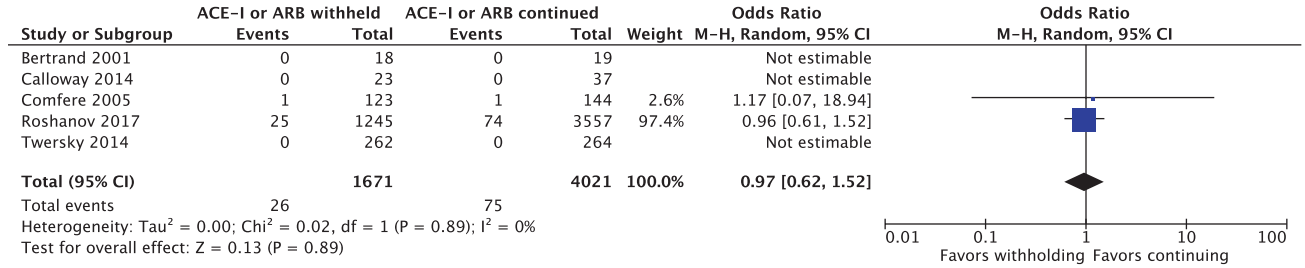

Figure 2. Mortality associated with withholding or continuing ACE-I or ARB therapy. Zero arm events not included. ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; M–H, Mantel-Haenszel.

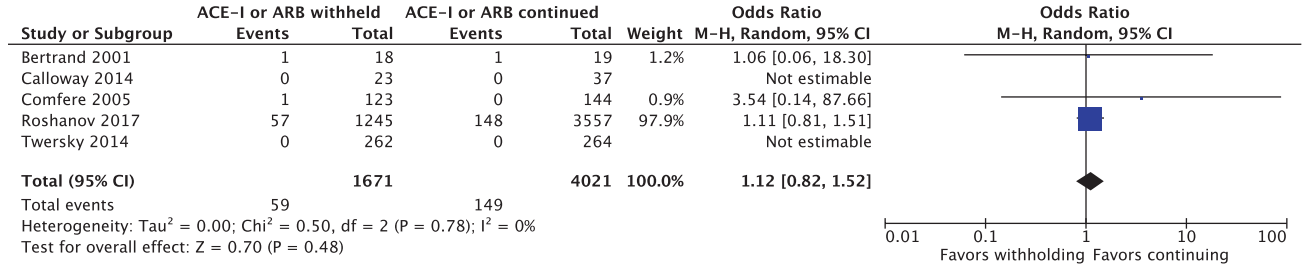

Figure 3. Major adverse cardiac events associated with withholding or continuing ACE-I or ARB therapy. Zero arm events not included. ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; M–H, Mantel-Haenszel.

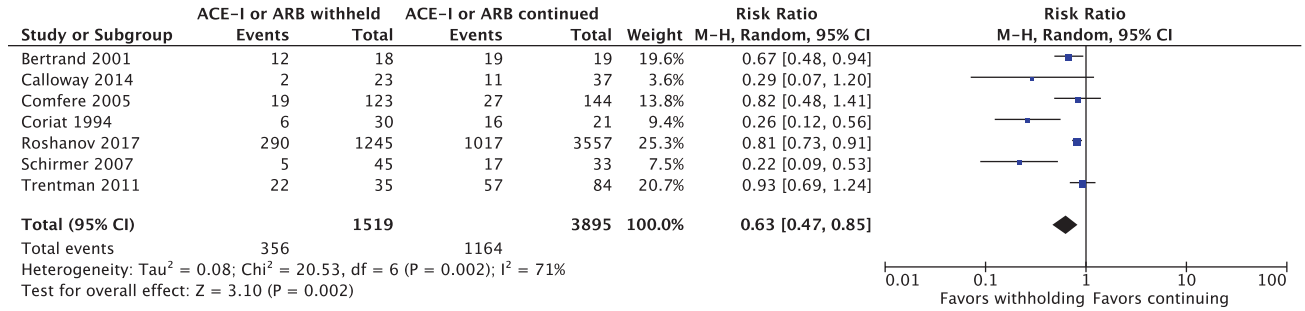

Figure 4. Intraoperative hypotension associated with withholding or continuing ACE-I or ARB therapy. ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; M–H, Mantel-Haenszel.

that intraoperative hypotension was significantly increased for up to 60 minutes after induction in the patients who continued ACE-Is/ARBs. Seven studies totaling 5414 patients examined the effect of withholding or continuing ACE-I/ARB therapy on intraoperative hypotension and are included in the meta-analysis. The incidence of intraoperative hypotension was 30% (Figure 4). Withholding of ACE-I/ARB was associated with significantly less hypotension (OR, 0.63; 95% CI, 0.47–0.85), although there was marked heterogeneity between studies ($I^2 = 71\%$).

Postoperative Hypotension. Three studies[2,14,35] reported on postoperative hypotension (Supplemental Digital Content 10, Figure 6, http://links.lww.com/AA/C260), of which 1 was up to 3 days postoperatively[2] and 2 were in the postanesthesia high-care unit.[14,35] There was no difference in treatment effect (OR, 0.95; 95% CI, 0.81–1.12; $P = .52$), and no evidence of heterogeneity was observed between the groups.

Length of Hospital Stay. Only 2 studies reported on postoperative LOS.[14,35] One study reported a median length of 3 days in the withholding group and 2 days in the continuation group,[14] and the other study only reported LOS data for the entire cohort, and not individual groups.[36] Neither study reported a significant difference in the length of postoperative stay between withholding and continuing ACE-Is/ARBs. It was therefore not possible to determine a pooled effect for ACE-I/ARBs on LOS.

Additional Analyses

Randomized Trials. A sensitivity analysis of MACE and intraoperative hypotension was conducted (Supplemental Digital Content 11, Table 4, http://links.lww.com/AA/C261) for RCTs only. For the outcome of MACE, no significant difference was identified between groups withholding or continuing therapy (OR, 1.06; 95% CI, 0.06–18.30; $P = .97$), and a significant increased risk of intraoperative hypotension was observed with treatment continuation (OR, 0.09; 95% CI, 0.04–0.22; $P \leq .00001$). We could not conduct a sensitivity analysis of RCTs for mortality (because no outcome events were reported) or postoperative hypotension (because no RCTs reported this outcome).

Major Surgery. Two studies[3,4] included major surgery only, and both assessed outcomes in vascular surgical patients. For the outcomes of mortality, CHF, AKI, and LOS, it was not

possible to determine pooled effects because the outcomes were either not assessed or no events were reported. For the outcome of MACE, 1 trial could be included,[4] with no difference between the groups. For intraoperative hypotension, pooled data revealed a significantly increased risk of intraoperative hypotension associated with treatment continuation (OR, 0.07; 95% CI, 0.02–0.25; $I^2 = 0\%$; $P < .0001$).

Trial Sequential Analysis. The results of the required information size and crossing of 5% significance or futility boundaries are shown in Supplemental Digital Content 12, Table 5, http://links.lww.com/AA/C262. The TSA for intraoperative hypotension crosses the boundary line and thus favors significantly less hypotension associated with withholding ACE-I/ARB therapy (Supplemental Digital Content 13, Figure 7, http://links.lww.com/AA/C263). The analysis for intraoperative hypotension is adequately powered when the larger analysis of randomized and nonrandomized trials is included. However, all the analyses are underpowered when considering only randomized trials.

The sensitivity analysis for both arm 0 events revealed unchanged ORs and CIs for MACE and mortality when a continuity correction factor of 0.5 was applied to both arm 0 events.

DISCUSSION

The main findings in this meta-analysis are that there is no difference in mortality, MACE, CHF, AKI, or CVA between patients withholding or continuing chronic ACE-I/ARB therapy before surgery in the published literature. However, the total sample size remains small and is underpowered for all these outcomes. Concerning intraoperative hypotension, this meta-analysis demonstrated that continuing ACE-I/ARBs on the morning of surgery is associated with approximately 30% relative risk increase in hypotension (and an absolute risk increase of 6.5%, from 23.4% to 29.9%), but not postoperative hypotension. No difference in LOS was demonstrated between the groups.

This is the most comprehensive meta-analysis of outcomes associated with noncardiac surgery after withholding or continuing ACE-Is/ARBs therapy to date. Further, the population included is >10 times larger than that of the previous meta-analysis conducted in 2008,[11] in which a 50% relative increase in intraoperative hypotension was demonstrated. Because only noncardiac studies were assessed in the current analysis, it clarifies the impact of continuing ACE-Is/ARBs on intraoperative hypotension in this patient group alone.

Considering the variation in hypotensive response to ACE-I/ARB therapy among individuals, it may be important to assess the impact of treatment discontinuation on the incidence of intraoperative hypotension between differing racial or ethnic groups. Previous data have confirmed that hypertensive African American patients have decreased plasma renin activity,[40,41] increased β-adrenergic receptors,[42] increased adrenergic responses to catecholamines,[43] and reduced efficacy of BP reduction by ACE-I therapy.[41,44,45] Twersky et al[39] were the only authors to present race in their published data; however, there were no differences in the effect of withholding or continuing ACE-Is/ARBs on the preoperative BP between African Americans and non--African Americans. Unfortunately, no assessment of intraoperative hemodynamics was made, and the impact of therapy withdrawal on mortality was not assessed. Because personalized medicine may provide better outcomes for an individual than a 1-size-fits-all approach, future studies may therefore need to assess the impact of ethnicity and perioperative ACE-I/ARB therapy on patient-relevant outcomes.

Several limitations have been identified in the current meta-analysis. These include a lack of uniform definitions for morbidity outcomes, such as MACE and hypotension across the studies. Thresholds for hypotension varied as some reported a systolic BP <80 mm Hg[4] and others a mean arterial pressure <60 mm Hg[37] as hypotension. All hypotensive episodes were treated according to the study hypotensive thresholds, with some studies aiming to keep BP within 20% of baseline,[35] and the actual duration of hypotension was not reported in any of the studies. This is a major limitation because an intraoperative mean BP <55 mm Hg exceeding 20 minutes in duration[46] has been associated with increased mortality and adverse renal and cardiac outcomes. It is possible that the earlier treatment of hypotension in our included studies may have mitigated against hypotensive-associated MACE and AKI in the included RCTs. Standardized anesthetic protocols were used in only 4 studies,[3,4,36,37] and, hence, intraoperative BPs in the remaining 5 studies may have been affected by differing anesthetic practices and anesthetic agents.

For the assessment of MACE, our meta-analysis included only data for MI and not for MINS. Diagnostic criteria for MI were based on either electrophysiological findings or biochemical investigations[2,4,14,35] in all studies except for one,[39] in which MI was not defined and no events were reported. Active surveillance was performed in only 2 of these studies.[2,4] In one study, MACE was detected using twice-daily 12-lead electrocardiography and daily cardiac troponin I surveillance until day 3 postoperatively;[4] in the other, daily troponin I surveillance was taken until day 3.[2] Because >65% of perioperative MIs are asymptomatic,[6] it is possible that some episodes of MACE may have been missed in the studies that did not include postoperative troponin surveillance. Importantly, postoperative troponin elevation is independently associated with 30-day mortality, independent of a diagnosis of MI.[47,48] Of the individual studies, the largest prospective cohort[2] of 4802 patients showed a 16% reduction in the relative risk of MINS (adjusted relative risk, 0.84; 95% CI, 0.7–0.998) associated with withholding therapy; however, the meta-analysis showed no difference in the outcome for MACE, although it is underpowered. This remains an important finding considering the adverse prognosis associated with MINS,[48] and it needs further investigation.

Concerning study methodology, considerable variation was identified between the studies in terms of study design, bias, and definition of outcomes. Significant bias was identified in terms of performance, and in 2 studies, it included selective outcome reporting.[36,39] Although the funnel plots suggest little potential for publication bias associated with MACE and intraoperative hypotension, there are few studies, hence, we cannot adequately assess for publication bias. All outcomes were underpowered when considering

randomized trials alone with the exception of intraoperative hypotension. The inclusion of nonrandomized studies in the meta-analysis to increase the power of the pooled analysis introduces bias and may have limited the reliability of results. The lack of uniformity in the definition of specific outcomes (stroke, MACE, and intraoperative hypotension) is also undesirable and may have contributed to the heterogeneity associated with the incidence of intraoperative hypotension when continuing ACE-Is or ARBs. We were unable to contact 3 authors[30,32,36] of articles that contained data that may have been included in the meta-analysis for intraoperative hypotension[32,36] and possibly for other outcomes in which it was not possible to separate cardiac and noncardiac surgeries.[30]

Although we present noncardiac surgical outcomes, it is possible that the severity of the noncardiac surgery may be an important factor associated with outcomes after withholding or continuing ACE-Is/ARBs. Previous propensity score-matched studies[22,49,50] and retrospective reviews[51,52] have ranged from either minimally invasive to major vascular surgery,[50] in which ACE-Is/ARBs have been associated with an increased incidence of hypotension[22] and AKI in low-risk surgeries,[51,52] but not mortality,[49] and a 5-fold risk increase in mortality in major vascular surgery.[50] In the current meta-analysis, a sensitivity analysis for vascular surgery demonstrated an increased incidence of intraoperative hypotension associated with treatment continuation. However, pooled data included only 2 RCTs,[3,4] of which population sizes remained small and studies were underpowered for other outcomes.

Finally, evidence exists for adverse renal and cardiac outcomes associated with intraoperative hypotension,[46] yet it remains unclear whether the hypotension associated with continuation of ACE-Is/ARBs is associated with these adverse outcomes. Furthermore, preoperative hypotension itself has recently been linked to the increased incidence of postoperative mortality,[53] and thus, the impact of continuing regular ACE-I/ARB therapy in the light of preoperative hypotension is unknown. The current data would suggest that it is both ethical and necessary to proceed with a large randomized control trial of withholding or continuing ACE-I/ARB to determine which approach is safer for patient outcomes. It would need a standardized definition of intraoperative hypotension[54] and intraoperative treatment thresholds.

CONCLUSIONS

This comprehensive meta-analysis of 5 RCTs and 4 cohort studies provides the current evidence for withholding or continuing chronic ACE-I/ARB therapy in the perioperative period in noncardiac surgery. It confirms previous observations that continuation of ACE-I/ARBs is associated with intraoperative hypotension; however, it was unable to demonstrate an association between perioperative ACE-I/ARB administration and mortality or MACE. Furthermore, it remains unclear whether this intraoperative hypotension is associated with major postoperative patient morbidity and whether perioperative ACE-I/ARB therapy is associated with major morbidity, independent of any associated hypotension. Finally, the influence of pharmacogenomics on outcomes associated with perioperative ACE-I/ARB remains unanswered. A large randomized trial is needed to address these questions.

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DISCLOSURES

Name: Caryl Hollmann, MBChB, DA(SA).
Contribution: This author helped with data search and extraction, bias extraction, and first draft manuscript preparation.
Conflicts of Interest: C. Hollmann is the primary author.
Name: Nicole L. Fernandes, MBChB, DA(SA).
Contribution: This author helped with data search and extraction, bias extraction, and critical review of the manuscript.
Conflicts of Interest: None.
Name: Bruce M. Biccard, MBChB, FCA, PhD.
Contribution: This author helped with original hypothesis, data analysis, and critical review of the manuscript.
Conflicts of Interest: None.
This manuscript was handled by: Richard C. Prielipp, MD.

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