A systematic review of outcomes associated with withholding or continuing angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) prior to noncardiac surgery.

by

Dr Caryl Hollmann
Student no: HLLCAR014

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Supervisor: Professor Bruce M Biccard, M.B., Ch.B., FCA, Ph.D

Department of Anaesthesia and Perioperative Medicine, Groote Schuur Hospital and University of Cape Town, South Africa

DECLARATION

I, *Dr Caryl Hollmann*, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Date: 22/01/2018

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List of abbreviations

ACE-I	Angiotensin converting enzyme inhibitor
ARB	Angiotensin receptor blocker
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analysis
PICOS	Population,Interventions,Comparisons,Outcomes and Study design
BP	Blood pressure
MAP	Mean Arterial Pressure
MI	Myocardial Infarction
MACE	Major Adverse Cardiac Events
MINS	Myocardial Injury after Noncardiac Surgery
CHF	Congestive Heart Failure
CVA	Cerebrovascular accident
AKI	Acute Kidney Injury
LOS	Length Of hospital Stay
CI	Confidence Interval
OR	Odds Ratio
SD	Standard Deviation
ACC/AHA	American College of Cardiology/ American Heart Association
ESC/ESA	European Society of Cardiology/European Society Anaesthesiology
CH	Caryl Hollmann
NF	Nicole Fernandes
BB	Bruce Biccard
RCT	Randomized Control Trial
TSA	Trial Sequential Analysis
RAS	Renin Angiotensin System

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Title Page

Title

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First name, middle initial, and last name of each author, with their highest academic degree (M.D., Ph.D., etc.), and institutional affiliations.

Caryl Hollmann M.B.,Ch.B., DA (SA)

Nicole L Fernandes M.B.,Ch.B., DA (SA)

Bruce M Biccard, M.B., Ch.B., FCA, Ph.D, Department of Anaesthesia and Perioperative Medicine, Groote Schuur Hospital and University of Cape Town, South Africa

Name, mailing address, phone number, and e-mail address of the corresponding author.

Corresponding author

Caryl Hollmann

Email- carylhollmann@gmail.com

Phone – (+27) 21 4045001

University of Cape Town

D23, Department of Anaesthesia and Perioperative Medicine

Groote Schuur Hospital

Observatory, 7925

Cape Town

South Africa

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Dr NL Fernandes – This co-author helped with data search and extraction, bias extraction, critical review of manuscript

Prof BM Biccard – This author is responsible for original hypothesis, data analysis and critical review of manuscript

Abstract

Introduction

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 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 post induction hypotension, however 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 06 December 2016. We included adult patients >18years, on chronic ACE-I or ARB therapy who underwent noncardiac surgery, where 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 (CHF), acute kidney injury, stroke, intra/postoperative hypotension and the length of hospital stay (LOS).

Results

Following abstract review, the full text of 25 studies were retrieved, of which nine fulfilled the inclusion criteria; five were randomized control trials (RCTs) and four cohort studies. These studies included a total of 6022 patients on chronic ACE-I/ARB therapy prior to noncardiac surgery. 1816

patients withheld treatment the morning of surgery and 4206 continued their ACE-I/ARB. Pre-operative demographics were similar between the two 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%). Withholding therapy was however associated with significantly less intra-operative 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 CHF.

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 intra-operative hypotension. A large randomized control trial is necessary to determine the appropriate perioperative management of ACE-I and ARBs.

Key Points summary

- **Question:** Is the withholding or continuation of angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) before noncardiac surgery associated with perioperative mortality or major morbidity?
- **Findings**: The continuation of ACE-I/ARBs on the morning of noncardiac surgery is associated with increased intra-operative 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

Introduction

More than 280 million surgeries are performed globally each year,[1] of which approximately a third of patients are 45 years or older and are on either an angiotensin receptor inhibitor (ACE-I) or an angiotensin receptor blocker (ARB) prior to surgery.[2] Controversy exists as to whether ACE-I/ARBs should be continued in the perioperative period, as continuation has been associated with both harm and benefit. Intra-operative 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-I/ARBs in the perioperative period may also be associated with improved outcomes, where preoperative ACE-I have 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 following a perioperative MI after non cardiac 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-I/ARBs. The 2014 American College of Cardiology/ American Heart Association (ACC/AHA) 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 prior to surgery (Strong Recommendation, Low Quality of Evidence). In contrast, the European Society of Cardiology/European Society of Anaesthesiology (ESC/ESA)[10] base their recommendations on the indication for treatment with an ACE-I/ARB, recommending discontinuation for 24 hours prior to 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 prior to surgery, guidelines recommend instituting ≥1 week prior to 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 utilized in both with main results revealing no significant difference in MI or mortality[12], and a 50% increase in the incidence of post induction 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 intra-operative 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 prior to 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 (PRISMA)[16] guidelines.

Eligibility criteria:

The aim of this systematic review was to report on important patient outcomes associated with withholding or continuing ACE-I/ARBs on the morning of noncardiac surgery. Study eligibility was determined by the participants or population, interventions, comparisons, outcomes, and study design (PICOS) criteria. Eligible populations included all adult patients (>18 years), 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 prior to 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), intra- and postoperative hypotension and length of hospital stay. We included the following study designs; randomized controlled trials (RCTs) or observational studies where patients in both treatment arms were on chronic ACE-I/ARB therapy prior to surgery. Case reports and case-control studies were excluded. We evaluated ACE-I/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 six electronic databases MEDLINE (PubMed), CINAHL (EBSCO host), ProQuest, Cochrane database, Scopus and Web of Science up to 6 December 2016. The search terms included: 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 Appendix 1**.**

Study selection process:

The title and abstract of each citation were independently screened by two authors (CH, NF) to identify potentially eligible studies and excluded if; i) the study patients were undergoing cardiac surgery ii) ACE-I/ARB were not withheld prior to surgery iii) patients were not on chronic ACE-I/ARB therapy prior to surgery, and iv) non-human 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 two reviewers (CH, NF) to determine eligibility. Disagreements were resolved by consensus. If no consensus could be reached, a third reviewer (BB) 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 was required.

Data items:

A standardized data extraction sheet was used to extract population demographics, surgery, and outcomes data from the included studies by CH and NF. We extracted the definition of each outcome and time to outcome, the duration of withholding ACE-I/ARBs, and type of ACE-I/ARB therapy. No further data was obtained from authors, and hence all the data presented was 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 bias. Observational studies were assessed using the Newcastle Ottawa Quality Assessment Scale.[18] All assessments of bias of individual studies were conducted by two authors (CH and NF) independently and disagreements were resolved with the third reviewer (BB).

Summary measures and statistical analysis:

A meta-analysis was conducted using Review Manager Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.). Pooled dichotomous outcomes were reported as odds ratios (OR) and 95% confidence intervals (CI). 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. As 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. As standard RevMan software ignores zero events, studies with zero outcome events were excluded from the MACE and mortality analyses.

Additional analyses:

We planned two sensitivity analyses; a sensitivity analysis of RCTs only for the outcomes of mortality, MACE, intra- 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 Copenhagen Trial Unit's Trial Sequential Analysis software[19] version 0.9.5.9 Beta. An O'Brien-Fleming α-spending analysis with a two-sided 5% boundary was used, and a futility analysis

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, in order to confirm findings from the RevMan software and the exclusion of zero events.

Results

A total of 900 citations were retrieved from the initial search of which a total of 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 seven had no comparator group,[13,20-25] four were case reports,[26-29] one included cardiac data (from which we could not extract the noncardiac data, or contact the authors),[30] one was a multicentre based questionnaire,[31] one only considered preoperative blood pressure,[32] and two only considered postoperative non-resumption 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 three of the studies.[30,32,36] As a result, two 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 blood pressure only, with no documentation on intra- or postoperative outcomes. A detailed flow diagram of the excluded and included trials is shown in Figure 1.

Insert Figure 1 near here

Study characteristics

Of the nine included studies, five were randomized controlled trials[3,4,36,37,39] and four cohort studies,[2,14,35,38] with a total of 6022 patients on chronic ACE-I/ARB therapy. 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 Supplementary table 1 and 2 respectively.

Six studies omitted ACE-I/ARBs on the day before surgery[2,4,35-37,39] and two studies omitted therapy ≥ 10 hours before surgery.[14,38] In one study captopril was omitted 12 hours before surgery and enalapril 24 hours prior to 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 a large variability in the duration of follow up between studies, ranging from the day of hospital discharge to 30 days post surgery.[2]

Risk of bias within studies

The risk of bias of the five RCTs is shown in Supplementary figure 1. Three[4,36,39] trials had low selection bias, with unclear randomization in two RCTs.[3,37] Concealment was unclear in all trials and, most suffered from performance bias due to unblinded participants[3,4,39] or anesthesiologists.[39] Two trials were assessed as having had selective reporting, in which one 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 intra-operatively with ephedrine.[36] Overall the observational studies performed well in terms of selection, comparability and outcomes (Supplementary table 3). The funnel plots representing the possibility of publication bias associated with MACE and intra-operative hypotension are shown in Supplementary figures 2 and 3 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 this outcome ($I^2 = 0\%$). Of these studies, only two were RCTs, totalling 563 patients, with no reported mortality.

Insert figure 2 near here

Major cardiac events

Five studies reported MACE with no significant difference between the groups (OR 1.12, 95% CI 0.82- 1.52; P= 0.78) (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. ($I^2 = 0\%$).

Insert Figure 3 near here

Congestive Heart Failure

Only one 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 (Supplementary figure 4). Outcome events were only reported in two studies, with no difference between the groups (OR 0.95, 95% CI 0.44 -2.06), with 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 (Supplementary figure 5). Only three events were reported in the withholding group (OR 8.39, 95% CI 0.43-164.12).

Intra-operative hypotension

Eight studies evaluated the effect of ACE-I/ARBs on intra-operative hypotension. One study[36] reported only mean and standard deviation (SD) in the assessment of post induction hypotension as compared to preoperative blood pressures, and as we were unable to contact these authors in order to establish the absolute number of patients who suffered intra-operative hypotension, these data are not included in the meta-analysis. They did however show that intra-operative hypotension was significantly increased for up to 60 minutes following induction in the patients who continued ACE-I/ARBs. Seven studies totalling 5414 patients, examined the effect of withholding or continuing ACE-I/ARB therapy on intra-operative hypotension, and are included in the meta-analysis. The incidence of intra-operative 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%).

Insert Figure 4 near here

Postoperative hypotension

Three studies[2,14,35] reported on postoperative hypotension (Supplementary figure 6), of which one was up to three days postoperatively[2] and two reported only in the post anesthesia high-care unit.[14,35] There was no difference in treatment effect (OR 0.95, 95% CI 0.81,1.12, P=0.52), and no evidence

of heterogeneity observed between the groups.

Length of hospital stay

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

Additional analyses

Randomized trials

A sensitivity analysis of MACE and intra-operative hypotension was conducted (Supplementary table 4) 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=0.97), and a significant increased risk of intra-operative hypotension observed with treatment continuation (OR 0.09, 95% CI 0.04 - 0.22, P=<0.00001). We could not conduct a sensitivity analysis of randomized controlled trials for mortality (as no outcome events were reported) or postoperative hypotension (as 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 as the outcomes were either not assessed or no events reported. For the outcome of MACE, one trial could be included[4] with no difference between the groups. For intra-operative hypotension pooled

data revealed a significantly increased risk of intra-operative hypotension associated with treatment continuation (OR 0.07, 95% CI 0.02 -0.25, I^2=0% P<0.0001)

Trial Sequential Analysis (TSA)

The results of the required information size and crossing of 5% significance or futility boundaries are shown in Supplementary table 5. The TSA for intra-operative hypotension crosses the boundary line and thus favours significantly less hypotension associated with withholding ACE-I/ARB therapy (Supplementary figure 7). The analysis for intra-operative 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 zero events revealed unchanged odds ratios and confidence intervals for MACE and mortality when a continuity correction factor of 0.5 was applied to both arm zero events.

Discussion

The main findings in this meta-analysis is that there is no difference in mortality, MACE, CHF, AKI or CVA between patients withholding or continuing chronic ACE-I/ARB therapy prior to surgery in the published literature. However, the total sample size remains small and is underpowered for all these outcomes. Concerning intra-operative 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 length of hospital stay was demonstrated between the groups.

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

Considering the variation in hypotensive response to ACE-I/ARB therapy amongst individuals, it may be important to assess the impact of treatment discontinuation on the incidence of intra-operative hypotension between differing racial or ethnic groups, as 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 blood pressure 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-I/ARBs on the preoperative blood pressure between African-Americans and non-

African-Americans. Unfortunately, no assessment of intra-operative hemodynamics was made and the impact of therapy withdrawal on mortality not assessed. As personalized medicine may provide better outcomes for an individual than a one-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 pressure (SBP) < 80mmHg[4] and others a mean arterial pressures (MAP) <60mmHg[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, as an intra-operative mean blood pressure < 55 mmHg 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 four studies,[3,4,36,37] and hence intra-operative blood pressures in the remaining five studies may have been affected by differing anesthetic practices and anesthetic agents.

For the assessment of MACE, our meta-analysis included only data for myocardial infarction and not MINS. Diagnostic criteria for MI were based on either electrophysiological findings or biochemical investigations[2,4,14,35] in all studies excepting one[39] in which MI was not defined and no events reported. Active surveillance was performed in only two of these studies.[2,4] In one, MACE was detected using twice daily 12-lead ECG, and daily cardiac troponin I surveillance until day 3 postoperativily,[4] and in the other, daily troponin I surveillance until day 3.[2] As more than 65% of perioperative MI's are asymptomatic,[47] it is possible that some episodes of MACE may have been

missed in the studies which did not include postoperative troponin surveillance. Importantly, postoperative troponin elevation is independently associated with 30 day mortality, independent of a diagnosis of MI.[48,49] Of the individual studies, the largest prospective cohort[2] of 4802 patients, showed a 16% reduction in the relative risk of myocardial injury after noncardiac surgery (MINS) (adjusted relative risk(ARR) 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,[49] and 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 two studies included selective outcome reporting.[36,39] Although the funnel plots suggest little potential for publication bias associated with MACE and intra-operative hypotension, there are few studies and hence we cannot adequately assess for publication bias. All outcomes were underpowered when considering randomized trials alone with the exception of intra-operative 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 intra-operative hypotension) are also undesirable, and may have contributed to the heterogeneity associated with the incidence of intra-operative hypotension when continuing ACE-I or ARBs. We were unable to contact three authors[30,32,36] of articles that contained data that may have been included in the meta-analysis, for intra-operative hypotension[32,36] and possibly for other outcomes where 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 following withholding or continuing ACE-I/ARBs. Previous propensity score matched studies[22,50,51] and retrospective reviews[52,53] have ranged from either minimally invasive to major vascular surgery,[51] where ACE-I/ARBs have been associated with an increased incidence of hypotension[22] and AKI in lower risk surgeries,[52,53] but not mortality,[50] and a five fold risk increase in mortality in major vascular surgery.[51] In the current meta-analysis, a sensitivity analysis for vascular surgery demonstrated an increased of intra-operative hypotension associated with treatment continuation. However pooled data included only two RCTs,[3,4] of which population sizes remained small and studies underpowered for other outcomes.

Finally, evidence exists for adverse renal and cardiac outcomes associated with intra-operative hypotension,[46] yet it remains unclear if the hypotension associated with continuation of ACE-I/ARBs is associated with these adverse outcomes. Furthermore preoperative hypotension itself has recently been linked to the increased incidence of postoperative mortality,[54] and thus the impact of continuing regular ACE-I/ARB therapy in the light of preoperative hypotension 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 intra-operative hypotension[55] and intra-operative 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 intra-operative hypotension, however was unable to demonstrate an association between perioperative ACE-I/ARB administration and mortality or MACE. Furthermore it remains unclear whether this intra-operative 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. Lastly, the influence of pharmacogenomics on outcomes associated with perioperative ACE-I/ARB remain unanswered. A large randomized trial is needed to address these questions.

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Figure 1 – Flow chart of study identification and inclusion

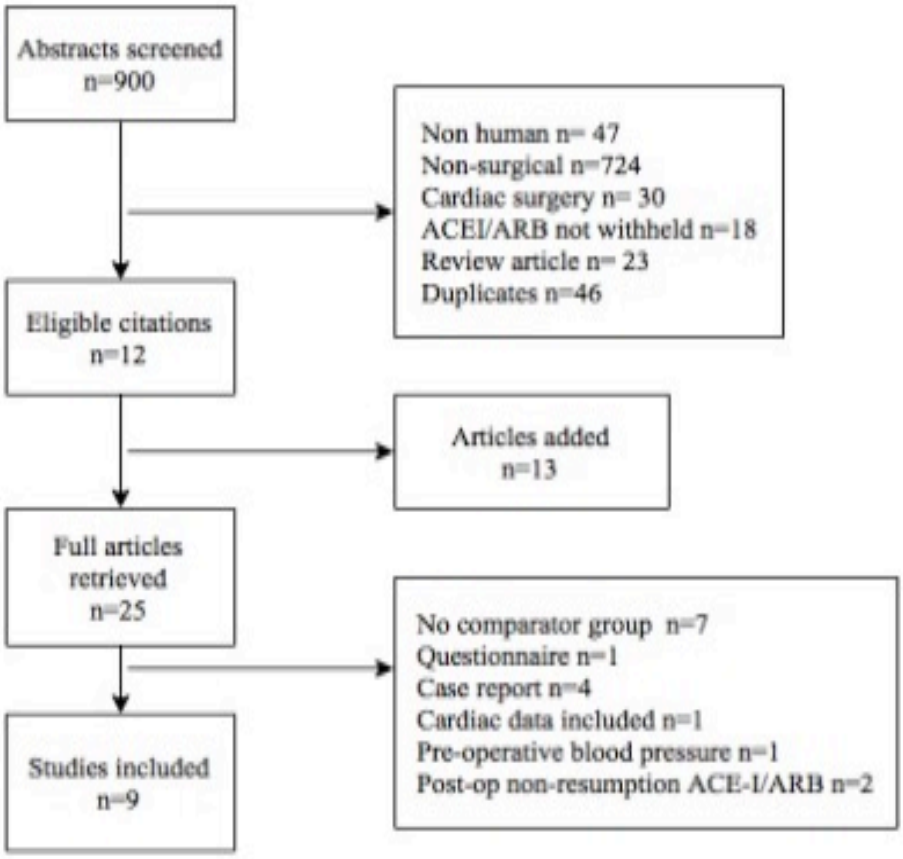


Figure 2 – Mortality associated with withholding or continuing ACE-I or ARB therapy

(Footnote)

Zero arm events not included

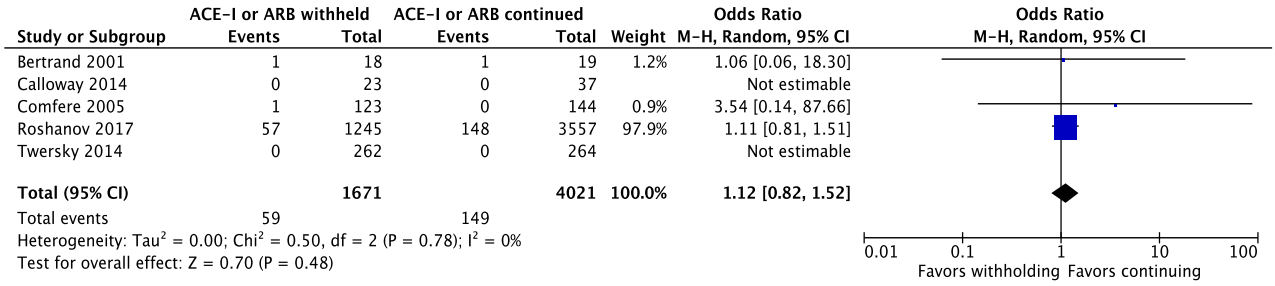


Figure 3 – Major adverse cardiac events associated with withholding or continuing ACE-I or ARB therapy

(Footnote)

Zero arm events not included

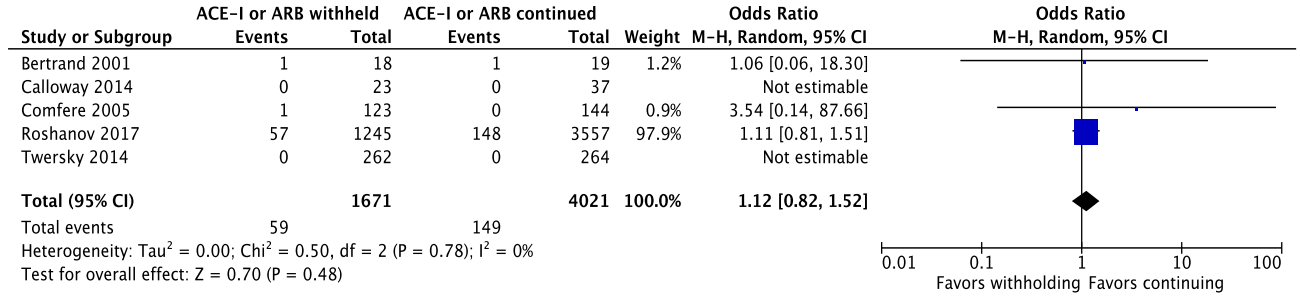


Figure 4 – Intra-operative hypotension associated with withholding or continuing ACE-I or ARB therapy

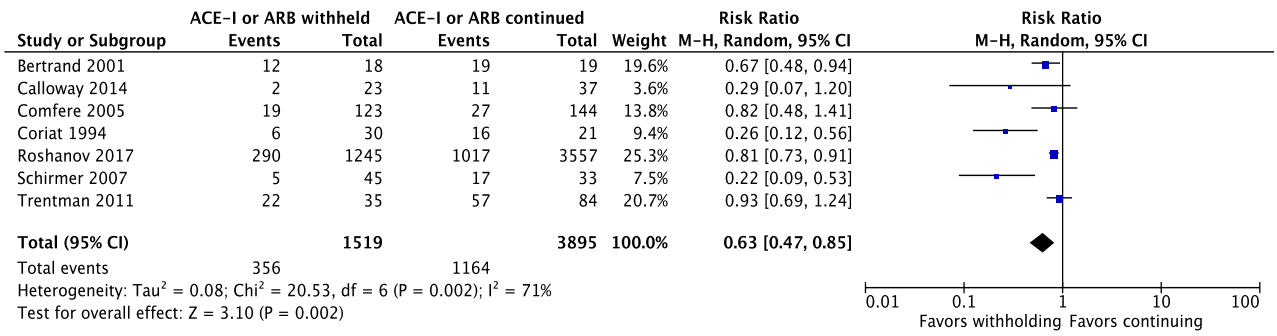


Table 1 – Demographics of patients in the included studies

Author/year	Patients (n)	Type of surgery	Age (year) mean (±SD)	Hypertension n (%)	Coronary artery disease n (%)
Randomized trials					
Coriat 1994[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 2014[36]	W: 30 C: 30	NR	Between 40-60	NR	NR
Bertrand 2001[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 2007[37]	W: 50 C: 50	ENT & Ophthalmology	W: 64 (±13) C: 67 (±11)	NR	NR
Twersky 2014[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 2014[35]	W: 23 C: 37	Orthopedic	W: 65.7 (±2.9) C: 66.6 (±4)	NR	W: 3 (13%) C: 6 (16%)
Roshanov 2017[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 2005[14]	W: 123 C: 144	Elective noncardiac surgery	W: 67 C: 66	NR	W: 29 (23.6%) C: 36 (25%)
Trentman 2011[38]	W: 35 C: 84	Orthopedic	W: 65.9 (±9.8) C: 66.3 (± 8.4)	NR	NR

SD standard deviation, MI myocardial infarction, PCI percutaneous coronary intervention, NR not reported, W withheld, C continued, n Number

Table 2 - Characteristics of included studies

Author/year	Type of ACE-I/ARB	Duration of withholding ACE-I/ARB	Length of follow-up	Outcomes measured
Randomized trials				
Coriat 1994[3]	Captopril/Enalapril	Captopril= 12hr Enalapril= 24hr	Study ended at skin incision	SBP on induction & shortly afterwards. PCEI, PRA and catecholamine levels before surgery, preinduction and postinduction
Rajgopal 2014[36]	NR	DBS	Study ended 60 minutes post induction	SBP,DBP and MAP pre- and postinduction
Bertrand 2001[4]	ARB only, type NR	DBS	Until hospital discharge	Post induction hypotension & need for vasopressors
Schirmer 2007[37]	NR	DBS	NR	Post induction hypotension & vasopressor usage
Twersky 2014[39]	NR	24 hrs (mean time =1405min)	NR	HTN immediately before surgery, surgical cancellations 2nd to HTN, prolonged hospitalization, adverse clinical events and postoperative HTN
Cohort studies				
Calloway 2014[35]	ACEI= benazepril/enalapril/ lisinopril/quinapril/ramipril ARB=candesartan/irbesartan/ losartan/olmesartan/telmisartan/ valsartan	24 hours before surgery	Until hospital discharge	SBP's and MAP's pre- and intraoperatively, vasopressor use. Morbidity; MI, stroke, acute kidney injury, ICU admission and mortality
Roshanov 2017[2]	NR	DBS	30 days after surgery	Primary; all-cause death, stroke or myocardial injury. Secondary; intra/postoperative hypotension
Comfere 2005[14]	ACEI= Benazepril, Benazeprilat, Enalapril, Enalaprilat, Lisinopril, Quinapril, Fosinopril, Fosinoprilat, Ramipril ARB's=Candesartan, Losartan, Valsartan	≥ 10hrs before surgery	Until hospital discharge	Development of moderate or severe hypotension at 0-30min & 31-60min after induction

ACE-I Angiotensin Converting Enzyme Inhibitor, ARB Angiotensin Receptor Blocker, NR Not Reported, DBS Day Before Surgery, SBP Systolic Blood Pressure, PCEAI Plasma Converting Enzyme Inhibitor, PRA Plasma Renin Activity, DBP Diastolic Blood Pressure, MAP Mean Arterial Pressure, HTN Hypertension, MI Myocardial infarction, ICU Intensive Care Unit, Min Minutes, hrs Hours

Appendix 1- Example of search strategy conducted for Systematic Review (MEDLINE)

Step 1

Search ((((((("Angiotensin-Converting Enzyme Inhibitors"[Mesh]) OR angiotensin-converting enzyme inhibitors[Title/Abstract]) OR Angiotensin Converting Enzyme Inhibitors[Title/Abstract]) OR Angiotensin-Converting Enzyme Antagonists[Title/Abstract]) OR ACE Inhibitors[Title/Abstract]) OR ACE-I[Title/Abstract])

Step 2

Search (((((Angiotensin II Receptor Blockers[Title/Abstract]) OR Angiotensin Receptor Blockers[Title/Abstract]) OR Angiotensin II Receptor Antagonists[Title/Abstract]) OR Angiotensin Receptor Antagonists[Title/Abstract]) OR (("Angiotensin Receptor Antagonists"[Mesh]) AND "Angiotensin II Type 1 Receptor Blockers"[Mesh]

Step 3

Search (((((((Angiotensin II Receptor Blockers[Title/Abstract]) OR Angiotensin Receptor Blockers[Title/Abstract]) OR Angiotensin II Receptor Antagonists[Title/Abstract]) OR Angiotensin Receptor Antagonists[Title/Abstract]) OR (("Angiotensin Receptor Antagonists"[Mesh]) AND "Angiotensin II Type 1 Receptor Blockers"[Mesh])))) OR (((((((("Angiotensin-Converting Enzyme Inhibitors"[Mesh]) OR angiotensin-converting enzyme inhibitors[Title/Abstract]) OR Angiotensin Converting Enzyme Inhibitors[Title/Abstract]) OR Angiotensin-Converting Enzyme Antagonists[Title/Abstract]) OR ACE Inhibitors[Title/Abstract]) OR ACE-I[Title/Abstract]

Step 4

Search (operative OR surgical OR surgery OR "Surgical Procedures, Operative"[Mesh])

Step 5

Search (((operative OR surgical OR surgery OR "Surgical Procedures, Operative"[Mesh]))) AND ((((((((Angiotensin II Receptor Blockers[Title/Abstract]) OR Angiotensin Receptor Blockers[Title/Abstract]) OR Angiotensin II Receptor Antagonists[Title/Abstract]) OR Angiotensin

Receptor Antagonists[Title/Abstract]) OR (("Angiotensin Receptor Antagonists"[Mesh]) AND "Angiotensin II Type 1 Receptor Blockers"[Mesh]))))) OR (((((("Angiotensin-Converting Enzyme Inhibitors"[Mesh]) OR angiotensin-converting enzyme inhibitors[Title/Abstract]) OR Angiotensin Converting Enzyme Inhibitors[Title/Abstract]) OR Angiotensin-Converting Enzyme Antagonists[Title/Abstract]) OR ACE Inhibitors[Title/Abstract]) OR ACE-I[Title/Abstract])

Step 6

Search (((((operative OR surgical OR surgery OR "Surgical Procedures, Operative"[Mesh]))) AND ((((((((Angiotensin II Receptor Blockers[Title/Abstract]) OR Angiotensin Receptor Blockers[Title/Abstract]) OR Angiotensin II Receptor Antagonists[Title/Abstract]) OR Angiotensin Receptor Antagonists[Title/Abstract]) OR (("Angiotensin Receptor Antagonists"[Mesh]) AND "Angiotensin II Type 1 Receptor Blockers"[Mesh]))))) OR (((((("Angiotensin-Converting Enzyme Inhibitors"[Mesh]) OR angiotensin-converting enzyme inhibitors[Title/Abstract]) OR Angiotensin Converting Enzyme Inhibitors[Title/Abstract]) OR Angiotensin-Converting Enzyme Antagonists[Title/Abstract]) OR ACE Inhibitors[Title/Abstract]) OR ACE-I[Title/Abstract])))) NOT (Cardiac surgical procedures OR heart surgery OR cardiac surgery OR "Cardiac Surgical Procedures"[Mesh])

Step 7

Search (((((((operative OR surgical OR surgery OR "Surgical Procedures, Operative"[Mesh]))) AND ((((((((Angiotensin II Receptor Blockers[Title/Abstract]) OR Angiotensin Receptor Blockers[Title/Abstract]) OR Angiotensin II Receptor Antagonists[Title/Abstract]) OR Angiotensin Receptor Antagonists[Title/Abstract]) OR (("Angiotensin Receptor Antagonists"[Mesh]) AND "Angiotensin II Type 1 Receptor Blockers"[Mesh]))))) OR (((((("Angiotensin-Converting Enzyme Inhibitors"[Mesh]) OR angiotensin-converting enzyme inhibitors[Title/Abstract]) OR Angiotensin Converting Enzyme Inhibitors[Title/Abstract]) OR Angiotensin-Converting Enzyme Antagonists[Title/Abstract]) OR ACE Inhibitors[Title/Abstract]) OR ACE-I[Title/Abstract])))) NOT (Cardiac surgical procedures OR heart surgery OR cardiac surgery OR "Cardiac Surgical Procedures"[Mesh]))) AND ((((((((((discontinuing) OR omission) OR discontinue) OR cease) OR stop) OR withhold) OR stopping) OR Withholding)) OR "Withholding Treatment"[Mesh])

Supplementary table 1 -Definition of primary outcomes in included studies

Author/year	Mortality	Major Adverse Cardiac Events
Randomized trials		
Coriat 1994[3]	NR	NR
Rajgopal 2014[36]	NR	NR
Bertrand 2001[4]	Cardiac death	New Q-wave or ST-T depression longer than 48hr on twice daily 12-lead ECG, associated or not with clinical findings such as circulatory failure with the need for catecholamines, or a decrease in global or regional function on echocardiography, or cTnI >0.5ng/ml
Schirmer 2007[37]	NR	NR
Twersky 2014[39]	All-cause	ND
Cohort studies		
Calloway 2014[35]	All-cause	Elevation of troponin based on laboratories' upper limit range (≥ 0.05) plus confirmatory new ST-T wave or Q wave changes on ECG
Roshanov 2017[2]	All-cause	Occurrence of A, B or C A. A typical rise of troponin/typical fall of an elevated troponin detected at its peak post surgery in a patient without a documented alternative explanation for an elevated troponin (e.g., pulmonary embolism). This criterion also required that 1 of the following must also exist: i. ischemic signs or symptoms (i.e., chest, arm, neck or jaw discomfort; shortness of breath; pulmonary edema), OR ii. development of pathologic Q waves present in any two contiguous leads that are ≥ 30 milliseconds, OR iii. ECG changes indicative of ischemia (i.e., ST segment elevation [≥ 2 mm in leads V1, V2, or V3 OR ≥ 1 mm in the other leads], ST segment depression [≥ 1 mm], or symmetric inversion of T waves ≥ 1 mm) in at least two contiguous leads, OR iv. coronary artery intervention (i.e., PCI or CABG surgery), OR v. new or presumed new cardiac wall motion abnormality on echocardiography or new or presumed new fixed defect on radionuclide imaging. B. Pathologic findings of an acute or healing myocardial infarction C. Development of new pathological Q waves on an ECG if troponin levels were not obtained or were obtained at times that could have missed the clinical event.
Comfere 2005[14]	All-cause	New appearance of Q waves at least 0.04 seconds wide and 1 mm in depth on ECG or an elevation of creatine phosphokinase MB fraction consistent with myocardial infarction.
Trentman 2011[38]	NR	NR

NR Not Reported, ND Not Defined, ECG Electrocardiogram, PCI Percutaneous Intervention, CABG Coronary Artery Bypass Graft, cTnI Cardiac Troponin I

Supplementary table 2 - Definition of secondary outcomes in included studies

Author/year	AKI	CHF	CVA	Intra-operative hypotension	Post-operative hypotension	LOS
Randomized trials						
Coriat 1994[3]	NR	NR	NR	Lowest BP after induction/ during 10min mechanical ventilation without surgical stress	NR	NR
Rajgopal 2014[36]	NR	NR	NR	SBP <85 mmHg	NR	NR
Bertrand 2001[4]	NR	NR	NR	SBP < 80mmHg lasting > 1min. Refractory; SBP that did not remain> 100 mmHg after 6mg-24mg of ephedrine (if HR < 60 bpm) and/or 100mcg- 300mcg of phenylephrine (if HR > 60bpm)	NR	NR
Schirmer 2007[37]	NR	NR	NR	MAP < 60mmHg	NR	NR
Twersky 2014[39]	NR	NR	ND	NR	NR	NR
Cohort studies						
Calloway 2014[35]	Doubling of baseline serum creatinine based on RIFLE criteria	NR	Acute neurologic deficits & confirmatory abnormal findings on neuroimaging.	Moderate; SBP ≤85 mmHg, Severe; SBP ≤65 mmHg	Same as for intraoperative	NR
Roshanov 2017[2]	NR	NR	A new focal neurological deficit thought to be vascular in origin with signs and symptoms lasting > 24 hours.	SBP <90 mmHg for any duration for which intervention was initiated (IV fluids, vasopressors/inotropes, blood transfusion, or intra-aortic balloon pump therapy)	Same as for intraoperative	
Comfere 2005[14]	Postoperative creatinine increase of 0.5 mg/dL	NR	New and medically documented CVA, TIA or neurological deficit of central origin	Moderate; SBP≤ 85 mmHg Severe; SBP ≤65 mmHg	ND	ND
Trentman 2011[38]	NR	NR		Single SBP ≤ 85mmHg	NR	NR

AKI Acute Kidney Injury, CHF Congestive Heart Failure, CVA Cerebrovascular Accident, LOS Length OF hospital Stay, NR Not Reported, BP Blood Pressure, SBP Systolic Blood Pressure, HR Heart Rate, MAP Mean Arterial Pressure, ND Not Defined, CVA Cerebrovascular Accident, TIA Transient Ischemic Attack

Supplementary table 3- Risk of bias of cohort studies using Newcastle-Ottawa Scale

Study	**Selection** (max 4 stars)	**Comparability** (max 2 stars)	**Outcome** (max 3 stars)
Calloway 2014[35]	****	**	**
Roshanov 2017[2]	****	**	***
Comfere 2005[14]	***	*	***
Trentman 2011[38]	**	*	***

Selection

1) Representativeness of the exposed cohort a) truly representative of the average in the community * b) somewhat representative of the average in the community * c) selected group of users d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort a) drawn from the same community as the exposed cohort * b) drawn from a different source c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure a) secure record (e.g. surgical records) * b) structured interview * c) written self report d) no description

4) Demonstration that outcome of interest was not present at start of study a) yes * b) no

Comparability

1) Comparability of cohorts based on the design or analysis a) study controls for age, comorbid status, sex* b) study controls for any additional factor *

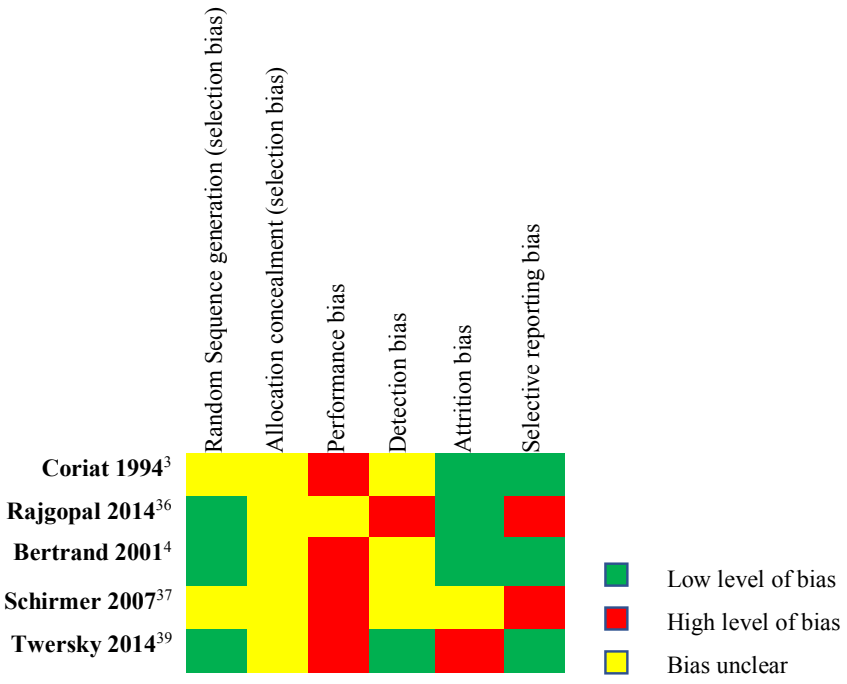
Outcome

1) Assessment of outcome a) independent blind assessment * b) record linkage * c) self report d) no description

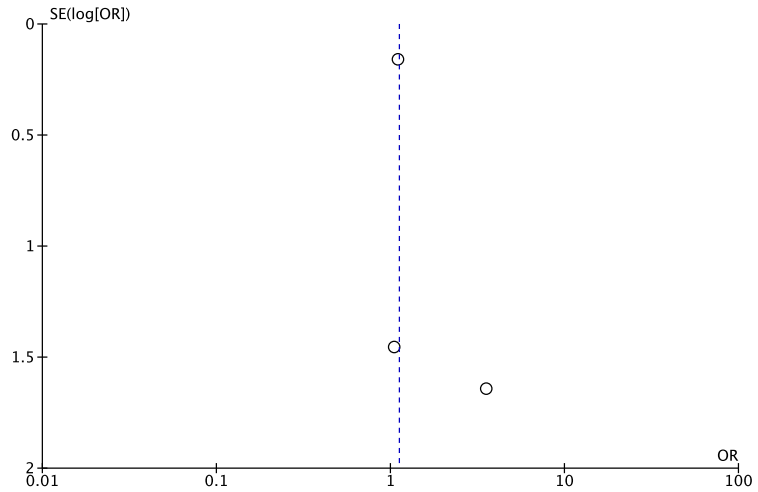
2) Was follow-up long enough for outcomes to occur a) yes (until hospital discharge for secondary outcome and 30 days post surgery for primary outcome* b) no

3) Adequacy of follow up of cohorts a) complete follow up - all subjects accounted for * b) subjects lost to follow up unlikely to introduce bias - small number lost * c) follow up rate < 90% and no description of those lost) no statement

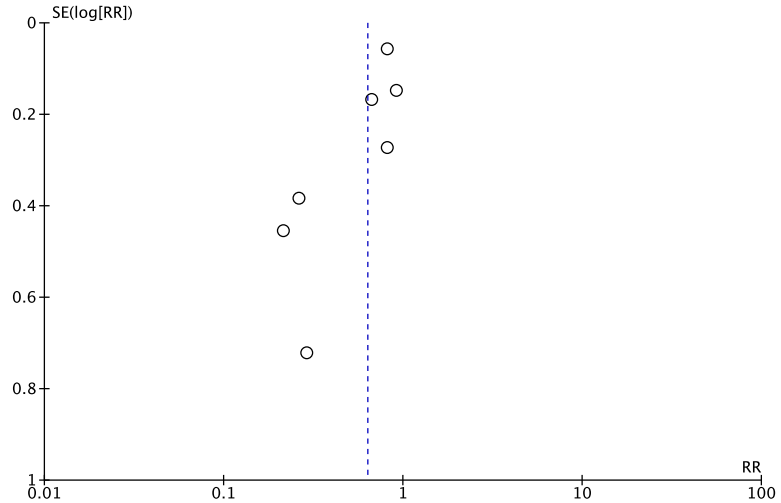
Supplementary figure 1 – Risk of bias of randomized trials using the Cochrane Collaboration tool



Supplementary figure 2 – Funnel plot representing publication bias for the outcome of MACE



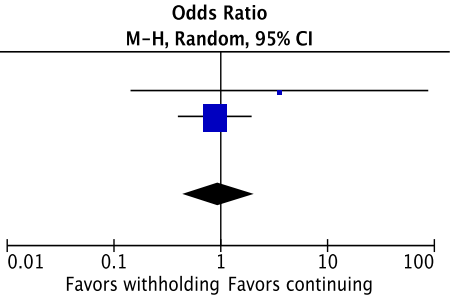
Supplementary figure 3 – Funnel plot representing publication bias for the outcome of Intra-operative hypotension



Supplementary figure 4 – Cerebrovascular complications associated with withholding or continuing ACE-I or ARB therapy

Study or Subgroup	ACE-I or ARB withheld Events	Total	ACE-I or ARB continued Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Calloway 2014	0	23	0	37		Not estimable
Comfere 2005	1	123	0	144	5.8%	3.54 [0.14, 87.66]
Roshanov 2017	8	1245	26	3557	94.2%	0.88 [0.40, 1.95]
Twersky 2014	0	262	0	264		Not estimable
Total (95% CI)		**1653**		**4002**	**100.0%**	**0.95 [0.44, 2.06]**
Total events	9		26			

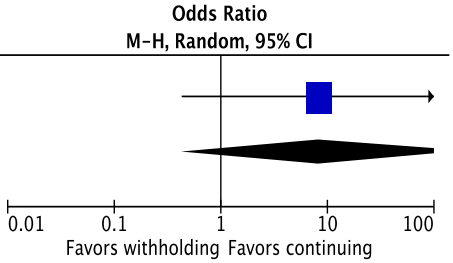
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.68$, df = 1 (P = 0.41); $I^2 = 0\%$
Test for overall effect: Z = 0.12 (P = 0.90)



Supplementary figure 5 – Acute kidney injury associated with withholding or continuing ACE-I or ARB therapy

Study or Subgroup	ACE-I or ARB withheld Events	Total	ACE-I or ARB continued Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Calloway 2014	0	23	0	37		Not estimable
Comfere 2005	3	123	0	144	100.0%	8.39 [0.43, 164.12]
Total (95% CI)		**146**		**181**	**100.0%**	**8.39 [0.43, 164.12]**
Total events	3		0			

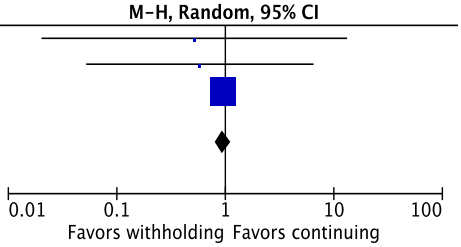
Heterogeneity: Not applicable
Test for overall effect: Z = 1.40 (P = 0.16)



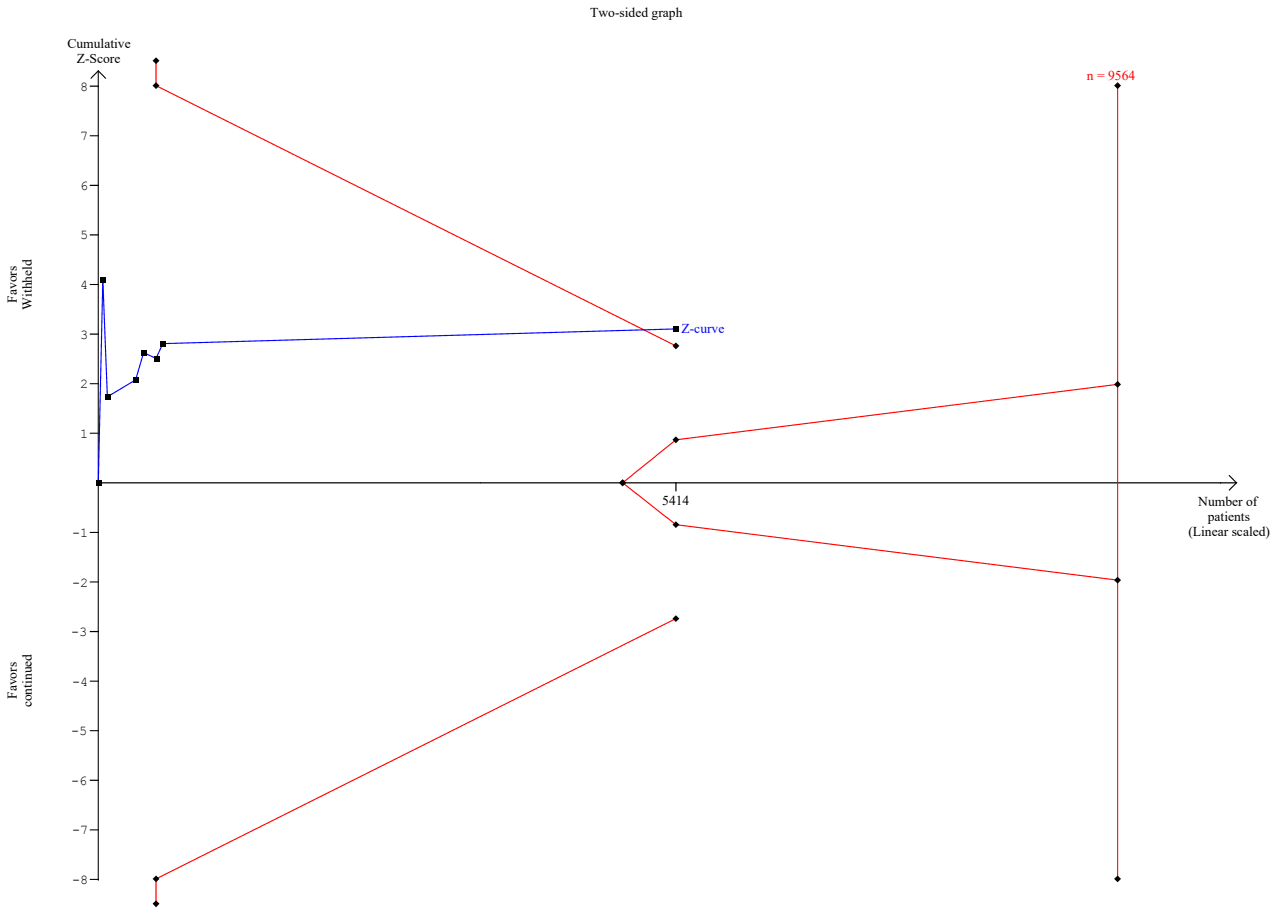
Supplementary figure 6 – Postoperative hypotension associated with withholding or continuing ACE-I or ARB therapy

Study or Subgroup	ACE-I or ARB withheld Events	Total	ACE-I or ARB continued Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Calloway 2014	0	23	1	37	0.2%	0.52 [0.02, 13.25]
Comfere 2005	1	123	2	144	0.5%	0.58 [0.05, 6.50]
Roshanov 2017	242	1245	719	3557	99.3%	0.95 [0.81, 1.12]
Total (95% CI)		**1391**		**3738**	**100.0%**	**0.95 [0.81, 1.12]**
Total events	243		722			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.29$, df = 2 (P = 0.86); $I^2 = 0\%$
Test for overall effect: Z = 0.64 (P = 0.52)



Supplementary figure 7 - Trial Sequential Analysis of intra-operative hypotension



Supplementary table 4 - Sensitivity analyses of randomized controlled trials only

Outcome	*OR (95% CI)*	*P-value*	I^2
MACE	1.06 (0.06 -18.30)	0.97	NA
Intra-operative hypotension	0.09 (0.04 - 0.22)	<0.00001	0%

OR Odds Ratio; CI Confidence Interval; MACE Major adverse cardiac event, NA Not Applicable
(Footnote)
Trials with zero arm events not included.
Not applicable as only one trial reports an outcome event.

Supplementary table 5 – Trial Sequential Analysis (TSA) to determine the required sample size, and whether a significance or futility boundary has been crossed in the existing studies

Outcome	**Total sample size**	**Cross 5% boundary**	**Cross futility boundary**
Mortality	23270	No	TLI
MACE	11364	No	No
CHF	NE	NE	NE
CVA	69506	No	TLI
AKI	NE	NE	NE
Intra-operative hypotension	9564	Yes	No
Postoperative hypotension	1889	No	TLI

MACE Major Adverse Cardiac Event, CHF Congestive Heart Failure, CVA Cerebrovascular Accident, AKI Acute Kidney Injury, NE Not estimable, TLI Too little information
Total sample size – Total sample size needed for adequately powered analysis (both treatment arms included)
Yes- benefit to withhold ACE-I/ARB therapy
(Footnote)
ACE-I Angiotensin converting enzyme inhibitor ARB angiotensin receptor blocker

PRISMA checklist for journal submission (Anesthesia &Analgesia)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	10
Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13-16
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21

Part B: Supporting documents

HREC approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338
Email: lamees.emjedi@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

02 December 2016

Dr C Hollmann
Department of Anaesthesia
D23
NGSH

Dear Prof Biccard

A systematic review of outcomes associated with withholding angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) prior to noncardiac surgery

The HREC note that the proposed study is a systematic review.

As the systematic review involves published literature available through publically accessible electronic databases, research ethics review and approval is not required.

This is in accordance with Section 1.1.8 of the Department of Health's Ethics in Health Research: Principles, Processes and Structures (South African Department of Health, 2015), which states: *"Research that relies exclusively on publicly available information or accessible through legislation or regulation usually need not undergo formal ethics review. This does not mean that ethical considerations are irrelevant to the research."*

The HREC recommend that researchers refer to the PRISMA website, for the PRISMA statement and checklist, to facilitate the reporting of systematic reviews and meta-analyses. For more information, please refer to http://www.prisma-statement.org/.

Further, fundamental ethical principles for health-related research should be considered in the objectives and methods of the systematic review. See, for example, the Declaration of Helsinki (Fortaleza, Brazil, 2013) and the Department of Health's Ethics in Health Research: Principles, Processes and Structures (South African Department of Health, 2015)

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Anesthesia & Analgesia Instructions for Authors

***Anesthesia & Analgesia* and *A&A Case Reports* Instructions for Authors**

Anesthesia & Analgesia and *A&A Case Reports* have specific **Instructions for Authors** for submitting articles, which are found below. We strongly encourage all authors to read these instructions completely and carefully, and to prepare their manuscripts in accordance with these instructions.

Articles that are not submitted in accordance with our instructions may be returned for revision prior to peer-review or rejected outright.
Brevity is crucial for a well-written and effective scholarly article. Particular attention should thus be paid to the listed word count, reference count, and table/figure limits for each article type, both for an initial submission and any subsequent revisions.
The word count, reference count, and table/figure limits will be strictly enforced, resulting in a manuscript being returned to the author(s) for revision prior to any initial or a subsequent peer-review.

Occasionally, authors will be asked by the Journal Editorial Board to resubmit their work as a different article type. If so, this subsequent manuscript will be handled as an entirely new submission, with a corresponding new assigned manuscript number.
Any changes (additions or deletions) of authors will need to be justified and clearly communicated. See below, **Section 8.A. Role of Authors and Contributors**.

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Narrative and Systematic Review Articles

- A **Narrative Review Article** or **Systematic Review Article** synthesizes previously published material into an integrated presentation of the current understanding of a topic.
- A Narrative Review can be either **focused** or **comprehensive**, based on its topic and scope.
- A Narrative Review Article should describe aspects of a topic about which scientific and evidence-based consensus exists, as well as aspects that remain controversial and are thus topics for ongoing and future research.
- A duly noted and entitled **Consensus Practice Guideline** is considered a specific type of a **focused Narrative Review**.
- A duly noted and entitled **Statistical Grand Rounds** is another specific type of a **focused Narrative Review** of the conventional or novel application of contemporary quantitative sciences (i.e., statistics, epidemiology, or database management) to issues of concern to anesthesia, critical care or pain researchers. Here the inclusion of programing code and/or illustrative datasets as online supplemental material is encouraged.
- For a Systematic Review, a formal strategy to search and to critically evaluate the medical literature should be applied and well-described. Such explicit methods are used in a Systematic Review to minimize bias in its content and findings.
- All Review Articles include a Title Page and an unstructured Abstract with no more than **400 words**.
- The Introduction section should be focused and contain no more than **400 words**.
- The Discussion section should also be focused and contain no more than **1,000 words**.
- A Review Article ranges in total length from **1,500 to 5,000 words** (not counting the Abstract and references), with up to **150 references** and **4-6 tables and/or figures**. Online supplemental material can be provided when appropriate.
- Exceptions to these word count, reference count, and table/figure limits may be granted at the discretion of the Journal Editorial Board for a **Consensus Practice Guideline** manuscript.

- Study Reporting Requirement (EQUATOR)
- Instructions for Manuscript preparation
- Instructions for Figure preparation
- Instructions for Table preparation
- Instructions for Supplemental Material

Meta-Analysis

- A **Meta-Analysis** uses analytic techniques to combine the quantitative results from existing individual studies, which are initially identified via a **Systematic Review**, thereby (a) allowing for a more precise estimate of the magnitude of benefit or harm of an intervention and/or (b) increasing the applicability of the results to a broader range of patients.
- A Meta-Analysis should not be written and submitted as a Systematic Review Article but as a separate submission type.
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- A "Key Points" summary is also provided, which describes the Question, Findings, and Meaning, each composed of **one sentence**
- These manuscripts are divided into four sections: Introduction, Methods, Results, and Discussion.
- The Introduction section should be focused and contain no more than **400 words**.
- The Discussion section should also be focused and contain no more than **1,000 words**.
- A Meta-Analysis ranges in total length from **1,500 to 5,000 words** (not counting the Abstract and references), with no more than **150 references** and **4-6 tables and/or figures**. Online supplemental material can be provided when appropriate.
- Study Reporting Requirement (EQUATOR)
- Instructions for Manuscript preparation
- Instructions for Figure preparation
- Instructions for Table preparation
- Instructions for Supplemental Material

Manuscript Organization

ALL articles should be arranged in the following order.

1. Manuscript, as a single file, consisting of Title Page, Abstract (not required for all article types – see Articles At A Glance), Body Text, References

2. Tables (each Table should be a separate .doc file or placed at the end of the manuscript file)
3. Figure Legends (placed consecutively, in numerical order, all on the same page)
4. Figures (each Figure should be uploaded as a separate file)
5. Appendices (each Appendix should be a separate file)

Title Page

- Article Title
- First name, middle initial, and last name of each author, with their highest academic degree (M.D., Ph.D., *etc.*), and institutional affiliations.
- Name, mailing address, phone number, and e-mail address of the corresponding author.
- Disclosure of funding received for the work from National Institutes of Health (NIH), Wellcome Trust, Howard Hughes Medical Institute (HHMI), and all other financial support, including departmental or institutional funding. If no funding received, state Financial Disclosures: None
- Please list any conflicts of interest the authors have had within the 36 months of submission. If no conflicts, state Conflicts of interest: None
- Clinical trial number and registry URL, if applicable.
- **List the word count of the Abstract, Introduction, and Discussion. Also list the overall word count for the entire body of text (excluding Abstract and References).**
- Abbreviated Title (running head) that states the essence of the article (< 50 characters). This is not required for all article types (see above).
- List each author's individual contribution to the manuscript. For each author, please list the individual contribution using the following text: "Author Name: This author helped…"

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For **Original Clinical/Laboratory Research Reports** and Meta-Analyses, a "Key Points" summary should be included directly underneath the structured abstract. The key points summary should describe the Question, Findings, and Meaning, each composed of one sentence. Please format the summary as three bullet points:

- Question: [One Sentence Text]
- Findings: [One Sentence Text]
- Meaning: [One Sentence Text]

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The body of the manuscript should typically be divided into four parts (does not apply to all article types – See Article Types At A Glance):

- Textual material (body text, tables, figure legends etc.) should be submitted as a .doc or .docx word processing file
- 12 point Arial or Times New Roman font
- Introduction (new page). This should rarely exceed one page in length.
- Should ideally contain only 4 to 5 short paragraphs: (1) significance, (2) background, (2) rationale, and (3) the study's aims or objectives and if applicable, (5) primary study hypothesis, and if appropriate, the secondary study hypothesis.
- Avoid the temptation and frequent tendency to provide an extensive literature review in the Introduction.
- Methods (new page)
- A statement that the study was approved by the appropriate IRB/Research Ethics Committee and written informed patient consent was obtained, or that the requirement for written informed consent was waived. (See section C Protection of Human Subjects).
- If applicable, authors should include their clinical trial registration number, registry, principle investigator and date of registration. (See section G Registration of Clinical Trials)
- A statement indicating the author has followed the appropriate EQUATOR guidelines should be included in the Methods section.
- ▪ Example: "This manuscript adheres to the applicable CONSORT guidelines."
- A subsection entitled "Statistical Analysis" should appear at the end of the Methods section when appropriate
- Results (new page)
- Discussion (new page). Focuses on the findings in the current work

Acknowledgements

For acknowledgement of individuals or organizations, provide complete name, degrees, academic rank, department, institutional affiliation, city, state, and country. Add description of the contribution to the study.

References

- *Anesthesia & Analgesia* and *A&A Case Reports* follow the American Medical Associate (AMA) citation style; Consult the American Medical Association Manual of Style, 10th ed., New York, Oxford University Press, 2007, for style.
- Number references (as superscripts) in the sequence they appear in the text.
- In text, tables, and legends, identify references with superscript Arabic numerals.
- If there are 6 or fewer authors/editors, list all 6; if there are more than 6, list the first 3 followed by "et al."
- Abbreviate names of journals according to the journals abbreviation list maintained by PubMed
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- *Anesthesia & Analgesia* and *A&A Case Reports* follow the American Medical Associate (AMA) table format.
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- Use a separate page for each table.
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- For any table that exceeds two typed pages and cannot be divided into a new table, the table should be submitted as a supplemental digital content file (see formatting requirements for Supplemental Digital Content files below).
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- Each table should have a brief title.
- Each column in a table should have a brief column header name.
- Use footnotes (not table titles or column headings) for explanatory matter and definitions of abbreviations. Abbreviations must be described with footnotes even if they are defined in the text or in other tables.
- For footnotes within a Table, use lower-case italicized letters in sequential alphabetical order.
- If you include a block of data, a table, or a figure from another source, whether published or unpublished, acknowledge the original source.

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   Use metric units. The units for pressures are mmHg or cmH2O. Diagonal slashes are acceptable for simple units, *e.g.*, mg/kg; when more than two items are present, negative exponents should be used, *i.e.*, ml · kg-1 · min-1 instead of ml/kg/min.

2. Abbreviations

   Define all abbreviations except those approved by the International System of Units for length, mass, time, temperature, amount of substance, *etc.* Do not create new abbreviations for drugs, procedures, experimental groups, *etc.*

3. Drug Names and Equipment

   Use generic names. If a brand name must be used, insert it in parentheses after the generic name. Provide manufacturer's name, city, state, and country. Be careful about the use of trademarked terms (*e.g.*, ThrombelastographyTM, TEGTM, *etc.*).

4. Statistical Analysis

   Detailed statistical methodology must be reported. Describe randomization procedures and the specific tests used to examine each part of the results; do not simply list a series of tests. Care should be taken with respect to a) parametric vs. nonparametric data, b) corrections for multiple comparisons, and c) rounding errors (summary statistics should not contain more significant digits than the original data). Median range (or percentiles) is preferred for nonparametric data.

5. Patient Identification

   Do not use patients' names, initials, or hospital numbers. An individual (other than an author) must not be recognizable in photographs unless written consent of the subject has been obtained and is provided at the time of submission.

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Editor Response 1:

Sep 06 2017 02:50PM

Caryl Hollmann, M.B.,Ch.B., DA(SA)
University of Cape Town Department of Anaesthesia and Perioperative Medicine
Anesthesia and Perioperative medicine
D23
Cape Town Western Cape 7925
SOUTH AFRICA

RE: MS#: AA-D-17-01673 "A systematic review of outcomes associated with withholding or continuing angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) prior to noncardiac surgery."

Dear Dr. Hollmann:

Thank you for submitting your manuscript "A systematic review of outcomes associated with withholding or continuing angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) prior to noncardiac surgery." to Anesthesia & Analgesia for consideration. Your manuscript has been reviewed by our editorial board and outside experts. Based on their reviews and my own reading of the manuscript, your article is not acceptable for publication in Anesthesia & Analgesia in its present form, but I would be happy to receive a revised version. Please see my comments below and my Quantitative Evaluation Scores at the bottom:

Executive Section Editor Comments to the Author:

17 - 01673

from the Executive Section Editor:

Dear Dr. Caryl Hollmann—

Thank you for this important submission on the vexing issue of perioperative continuation of ACE-I (plus ARB's) and their association with the instability of post-induction vital signs. The meta-analysis validates the often-observed phenomenon of hypotension following induction of anesthesia when these drugs are continued, but unfortunately is unable to definitively determine if these blood pressure changes are associated with important OUTCOME variables such as MACE, mortality, or LOS. Nonetheless, there is a valuable message here, and the reviewers and I therefore have some suggestions for you.

Please implement the following key elements:

1) I agree with the suggestion to omit inclusion of case reports as it dilutes the impact and value of your analysis.
2) I also agree somewhat with Reviewer # 3 that the Discussion section can be consolidated a bit to improve the flow, clarity, and organization.
3) Provide additional insights using I2 as the measure of dispersion… I believe it is NOT a measure of absolute heterogeneity in metaanalyses. See keen insights from our expert statistician in this regard as well (immediately below).

Respectfully,
Richard C. Prielipp
Exec Section Editor
==========

Specific Statistical Review:
One concern is inclusion of nonrandomized trials, which is a serious weakness. It is also difficult to assess publication bias with only a few studies. Finally, especially since main results are negative, authors need to focus on the power of the made analysis to assess what they considered a priori to be clinically important effects.

1. P7L47-55 -- Nonrandomized studies in the manuscript. It would be much better for the authors to focus on randomized trials (check spelling – you have "trails" at least one location), even if that reduces the sample size for the analysis. Including the nonrandomized trials greatly weakens your made analyses.

Did the authors assess the treatment effects using only the clinical trials, as a sensitivity analysis? That would be helpful.

2. P4L13-17. This association is worded backwards – it would be easier to read if you started with the intervention.

3. P4L17-20. This could be more clear – tell the reader why you could not estimate a pooled effect for length of stay or CCF.

4. P4L27. Instead of "could not", which sounds a bit weighted, more straightforward to say "This made analysis did not demonstrate…".

5. P6L37-42. From the manuscript it appears you wanted to do more than describe the mortality and major morbidity for each group. It sounds like you are estimating and assessing the treatment effect or association between withholding/continuing and outcomes.

6. P9L46-51. Since the authors want to jump wise beyond the studies that are included in the made analysis, random effects models should be used for all analyses.

7. P9L51. Sample size justification. At the very end of statistical methods, authors need to justify the sample size of different analyses that were conducted. Did the authors have sufficient power to detect what they would have considered a priori to be clinically important associations or differences? This may differ depending on which outcome authors are assessing, and so should not be a single statement.

One suggestion, not a requirement, would be for the authors to conduct a trial sequential analysis which would project the total sample size needed to definitively address this research question. However, I think such an assessment should be done considering randomized trials alone. This would be an important addition to the manuscript if the authors are willing to undertake it.

8. Figures 2 and three. In these figures authors observed zero events for several of the studies, and were not able to estimate treatment effects for those studies. Please clarify in your statistical methods, perhaps repeating and results, whether or not the studies with zero events were included in your meta-analysis overall effect estimates. If there were included, please note any special statistical techniques that were needed to do so. Clarification that the studies were included, if that is the case, should be mentioned in the footnote for each of the figures.
The article at the following link gives good advice on the expected bias whether including or not including such studies. Their conclusion is that when the true effect is near zero, it is better to include them. Https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5013416/

9. Assessment of publication bias. Authors do not really have enough studies in any of the analyses to properly assess for evidence of location bias. Nevertheless, for the larger made analyses authors could construct a funnel plot at least observe whether there appears to be publication bias. In any

case, it should be stressed is a limitation that there was not enough data to assess this properly, and so the results might be biased by presence of publication bias.

10. Heterogeneity. In several places, authors state something like “there was no heterogeneity”. The I-squared statistic first of all is only an estimate of the amount of heterogeneity. Second, the fact that I-squared equals zero should be interpreted as no evidence of heterogeneity, not lack of heterogeneity. Please clarify throughout.

If you can address point-by-point my comments and those of the reviewers (see below), I will be happy to receive a revised version of the manuscript. However, I cannot promise that your revised version of the manuscript would achieve the priority necessary for publication in Anesthesia & Analgesia.

If we do not receive a revised manuscript from you within the 8 weeks, or a letter from you indicating your indication of sending a revised manuscript, I will assume that you have elected to decline to revise your manuscript.

If you choose to revise your manuscript, please submit your revision via Editorial Manager by logging in to your author account and clicking the link "Submissions Needing Revision." Be sure you have pasted your response to the reviewers into the appropriate box on the online submission site.

With all good wishes,
Richard C Prielipp, MD, MBA, FCCM
Executive Section Editor
Anesthesia & Analgesia

Jean-Francois Pittet, MD
Editor-in-Chief
Anesthesia & Analgesia

****

Executive Section Editor Quantitative Evaluation:

1. Novelty of the Topic: 5
2. Significance of Topic: 6
3. Approach to the Topic: 6
4. Interest of the Topic to the Specialty: 7
5. Impact of the Findings on the Specialty: 7

Scale:

Minor (1,2,3): Easily addressable weaknesses that do not substantially lessen the quality of the study/manuscript

Moderate (4,5,6): Weaknesses that somewhat lessen the quality of the study/manuscript

Major (7,8,9): Weaknesses that severely limit the quality of the study/manuscript

****

Reviewer Comments to the Author:

Reviewer 1:

Major Strengths: Addresses a current clinical dilemma, well-performed systematic review and meta-analysis.

Major Weaknesses: Unfortunately, the information from the study was inconclusive and did not solve the clinical dilemma.

Specific issues that need to be addressed by author(s):

This systematic review and meta-analysis assessed the effects of continuing versus discontinuing ACEI/ARB prior to surgery, which is a commonly faced clinical dilemma.

Specific Comments:

Page 6, line 2: Please include the recently published Canadian Cardiovascular Society guidelines [Duceppe E, et al. Canadian Cardiovascular Society guidelines on perioperative cardiac risk assessment and management for patients who undergo noncardiac surgery. Can J Cardiol 2017; 33: 17-32.], which recommends withholding ACEI/ARB starting 24 hours before noncardiac surgery in patients treated chronically with an ACEI/ARB (Strong Recommendation; Low-Quality Evidence). Obviously, there is bias as the authors (Duceppe et al) are basing the recommendations on the

analysis of the VISION study (Roshnav PAS, et al. Anesthesiology 2017) that has several flaws.

Page 10, line 49: the statement "five were randomized controlled trials…" is missing one reference (there are only 4 references quoted).

Page 16, lines 26-42: Please delete this paragraph as it discusses anecdotes and instills bias. There is no role of case reports in a meta-analysis of thousands of patients.

Reviewer 2:

Major Strengths: The topic is of current interest to practitioners of anesthesiology; a large number of adults and elderly are on antihypertensives including ACE-1/ARBs - it is still not clear in whom this therapy should be withheld for surgery and whether withholding or not-withholding has adverse outcomes;

Major Weaknesses: lack of standardization and a compilation of other studies with the hope of being able to combine them to increase the statistical validity of outcomes obtained.

Specific issues that need to be addressed by author(s): the authors did use standard statistical methodologies; however, it is preferable to let the readers know how they defined heterogeneity in the individual studies

Additional comments for author(s) (optional):personalized medicine is currently the name of the game; the authors should discuss and provide any information available from the studies reviewed if ethnicity and race could be identified in the individuals that did become hypotensive in the studies that reported the occurrence of hypotension in the patients who did not withhold their ACE-1/ARBs. this should be another item they should discuss especially since the authors are recommending a prospective well-planned study in the future to evaluate this very important practical issue. Some form of genetic analysis in those that do become hypotensive in future planned studies may help to provide additional information for planning their anesthetics during their preoperative visits.

Reviewer 3:

Thank you for the opportunity to review this interesting manuscript.
I applaud the authors for their efforts in conducting this rather complex analysis. I have some concerns that I wish to elaborate on.

1) The manuscript is written in a rather non-conventional way, especially if you look towards the end of the manuscript, there are subheadings such as strengths and weaknesses of this study, then strengths and weaknesses in relation to other studies??. I would recommend that this latter section be incorporated in the introduction justifying the need for this new metaanalysis.
2) Then there another whole section on "Limitations". Aren't limitations synonymous with weaknesses?
Recommend re-write of the introduction, and discussion section in an easy to follow, clear sequence manner to make it easy to follow, understand, and appreciate.
3) In the abstract "previous data failed… ", this is not true, please refer to your reference # 2, thus should be corrected to previous metaanalysis failed….
4) Congestive Cardiac Failure is not a commonly used term in the US, neither the abbreviation CCF, it is usually referred to as congestive heart failure (CHF)
5) Reference # 2 has appeared in publication and should be referred to in all tables and figures as it appeared in 2017 and not 2016 (ahead of print publication)
6) Is it possible that the authors would conduct sensitivity analysis including only studies with patients having major surgical procedures, and vascular, i.e. excluding studies like Twersky, and Schirmer.
7) Conclusions: this should be re-written in both the abstract and manuscript to reflect the aim of the study and the current findings. That (I'm paraphrasing here) continuation vs withholding had no association with the studied outcomes. We confirmed current observation of increased intraop hypotension with continuation. Randomized trials are still needed.
You were not set out to examine the other things that you make a statement about such as: whether intraoperative hypotension is associated with major postoperative morbidity. So it is adequate that you mentioned that in the discussion part.
The conclusion in the abstract is a bit better than at the end of the manuscript

****

First revision cover letter:

UNIVERSITY OF CAPE TOWN

Professorial Staff:

JLC Swanevelder MB ChB, MMed (Anes) (U Stell), FCA (SA), FRCA (Hon)
Head of Department
Email: justiaan.swanevelder@uct.ac.za
BM Biccard MBChB (UCT), FCA (SA), FFARCSI, MMed (UKZN), PhD
2nd Chair of Anaesthesia
Email: bruce.biccard@uct.ac.za
Administrative Officer: C Wyngaard, Email: cheryl.wyngaard@uct.ac.za

Department of Anaesthesia and Perioperative Medicine

Faculty of Health Science,
Anzio Road, Observatory
Western Cape, South Africa 7925

Richard C. Prielipp
Executive Section Editor
Anesthesia and Analgesia

Jean-Francois Pittet, MD
Editor-in-Chief
Anesthesia & Analgesia

Dear Dr Richard Prielipp

Revision: Manuscript: MS#: AA-D-17-01673 "A systematic review of outcomes associated with withholding or continuing angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) prior to noncardiac surgery."

Thank you for the opportunity to submit a revision of our paper for consideration for publication in Anesthesia and Analgesia.

We have itemised the queries with a written description of our changes. We have submitted a manuscript with tracked changes and a clean manuscript as requested.

Executive Section Editor's comments:

Query 1: Please implement the following key elements: I agree with the suggestion to omit inclusion of case reports as it dilutes the impact and value of your analysis.

Response 1: We did not include case reports or case-control studies in the current meta-analysis, however the text did not explicitly state this. In order to make this clearer, we have included the following line in the paragraph for eligibility criteria; "*Case reports and case control studies were excluded*".

Query 2: I also agree somewhat with Reviewer # 3 that the Discussion section can be consolidated a bit to improve the flow, clarity, and organization.

Response 2: We have reviewed and edited the discussion, as suggested by Reviewer #3. In addition, we have removed the subheadings, and added separate paragraphs for the limitations and the impact of ethnicity to the current meta-analysis, as requested.

Query 3: Provide additional insights using I2 as the measure of dispersion… I believe it is NOT a measure of absolute heterogeneity in meta-analyses. See keen insights from our expert statistician in this regard as well (immediately below).

Response 3: We have addressed this query, under our response for Statistical comments Query 13.

Statistical comments:

Query 1: One concern is inclusion of nonrandomized trials, which is a serious weakness. It is also difficult to assess publication bias with only a few studies. Finally, especially since main results are negative, authors need to focus on the power of the made analysis to assess what they considered a priori to be clinically important effects.

Response 1: We have added sensitivity analyses of randomized trials as supplementary data. These were conducted for intra-operative hypotension, and for the primary outcome of MACE. We included these sensitivity analyses as Supplementary Table 4.

We did not conduct any further sensitivity analyses of randomized trials, as; i) the outcome of mortality has no outcome events in the randomized trials, ii) the other outcomes were underpowered (even when including the larger sample of both nonrandomized and randomized trials in the meta-analyses), and iii) we could not perform a sensitivity analysis of randomized trials for postoperative hypotension as there are no randomized trials reporting this outcome. We have discussed this weakness as a limitation to our analysis which is addressed as part of the discussion.

We constructed two funnel plots for graphical representation of the effect of the potential for publication bias, and have included these as supplementary figures. As there are few studies, this remains a limitation in interpreting the potential for publication bias. This limitation is addressed in the discussion.

Query 2: P7L47-55 -- Nonrandomized studies in the manuscript. It would be much better for the authors to focus on randomized trials (check spelling – you have "trails" at least one location), even if that reduces the sample size for the analysis. Including the nonrandomized trials greatly weakens your made analyses.

Response 2: We have now addressed this concern as discussed in the response to Query 1 with a sensitivity analysis. The spelling of 'trials' is corrected throughout the manuscript.

Query 3: Did the authors assess the treatment effects using only the clinical trials, as a sensitivity analysis? That would be helpful.

Response 3: This is addressed above in the response to Query 1. The results of the sensitivity analyses are presented in supplementary table 4.

Query 4: P4L13-17. This association is worded backwards – it would be easier to read if you started with the intervention.

Response 4: This is corrected, and for clarity reference to only treatment effect of continuation of ACE-I/ARB referred to; *"An increased risk of intra-operative hypotension was associated with treatment continuation on the morning of surgery (odds ratio [OR] 0.63; 95% confidence interval [CI] 0.47-0.85 I^2=71%)."*

Query 5: P4L17-20. This could be more clear – tell the reader why you could not estimate a pooled effect for length of stay or CCF.

Response 5: We have attempted to make it clearer in the text. No pooled effect could be determined for CHF as there was only one study, and no reported outcome events. For LOS, two studies reported LOS, but both reported median duration of LOS, but one of these studies did not provide data for both groups, but rather a single LOS outcome for all patients, making a pooled effect inestimable.

Query 6: P4L27. Instead of "could not", which sounds a bit weighted, more straightforward to say "This made analysis did not demonstrate…".

Response 6: We agree that the line sounds weighted and have replaced the sentence now so it reads *"did not demonstrate".*

Query 7: P6L37-42. From the manuscript it appears you wanted to do more than describe the mortality and major morbidity for each group. It sounds like you are estimating and assessing the treatment effect or association between withholding/continuing and outcomes.

Response 7: We have now removed the term 'describe' and the objectives of the meta-analysis now read *"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 prior to noncardiac surgery."*

Query 8: P9L46-51. Since the authors want to jump wise beyond the studies that are included in the made analysis, random effects models should be used for all analyses.

Response 8: All analysis for outcomes assessed are changed to random effects models and explicitly stated in the methods section for statistical analysis.

Query 9: P9L51. Sample size justification. At the very end of statistical methods, authors need to justify the sample size of different analyses that were conducted. Did the authors have sufficient power to detect what they would have considered a priori to be clinically important associations or

differences? This may differ depending on which outcome authors are assessing, and so should not be a single statement.

Response 9: Based on the query 10 below, we have used the TSA to determine an adequate sample size for each outcome. Please see the response to query 10.This is incorporated into the statistical methods and results, and the results are represented in Supplementary table 5. All outcomes are underpowered to assess a treatment effect when considering only the included randomized trials. This is stated in the manuscript. However, the TSA analysis shows that withholding ACE/ARB therapy crosses the boundary favouring significantly less intra-operative hypotension.

Query 10: One suggestion, not a requirement, would be for the authors to conduct a trial sequential analysis which would project the total sample size needed to definitively address this research question. However, I think such an assessment should be done considering randomized trials alone. This would be an important addition to the manuscript if the authors are willing to undertake it.

Response 10: Thank you for this suggestion. We have now conducted a TSA using an O'Brien-Fleming α-spending analysis with a two-sided 5% boundary, and included a futility analysis. 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. The results of the required information size and crossing of 5% significance or futility boundaries are now shown in Supplementary Table 5.

Query 11: Figures 2 and three. In these figures authors observed zero events for several of the studies, and were not able to estimate treatment effects for those studies. Please clarify in your statistical methods, perhaps repeating and results, whether or not the studies with zero events were included in your meta-analysis overall effect estimates. If there were included, please note any special statistical techniques that were needed to do so. Clarification that the studies were included, if that is the case, should be mentioned in the footnote for each of the figures.
The article at the following link gives good advice on the expected bias whether including or not including such studies. Their conclusion is that when the true effect is near zero, it is better to include them. Https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5013416/

Response 11: Thank you for the above comment and for the reference to Cheng and colleagues, which we found helpful in addressing this query. The statistical programme RevMan unfortunately does not include both arm zero events (BA0E) into the estimation of treatment effect, thus studies in the meta-analysis reporting zero events were not included. Considering that MACE and mortality represent i) rare events; ii) the outcomes are underpowered with small sample sizes, and iii) both outcomes deal with harm, we therefore chose to exclude all zero events as the introduction of BOAE may introduce bias into possible estimated pooled effects. However, as a sensitivity analysis, we ran both meta-analyses on the TSA software, and using a continuity correction of 0.5 per cell, there was no difference in the outcome, with ORs and confidence intervals remaining the same. Footnotes for Figure 2 and 3 have been amended to state that these meta-analyses did not include zero events in both arms.

Query 12: Assessment of publication bias. Authors do not really have enough studies in any of the analyses to properly assess for evidence of location bias. Nevertheless, for the larger made analyses authors could construct a funnel plot at least observe whether there appears to be publication bias. In any case, it should be stressed is a limitation that there was not enough data to assess this properly, and so the results might be biased by presence of publication bias.

Response 12: Two funnel plots were created for the assessment for the potential of publication bias for the outcomes of MACE and intra-operative hypotension. Results are represented in Supplementary figures 2 and 3 respectively. As few studies were included we have stated this a limitation to the meta-analysis in the discussion, and that it does not exclude the potential for publication bias.

Query 13: Heterogeneity. In several places, authors state something like "there was no heterogeneity". The I-squared statistic first of all is only an estimate of the amount of heterogeneity. Second, the fact that I-squared equals zero should be interpreted as no evidence of heterogeneity, not lack of heterogeneity. Please clarify throughout.

Response 13: Thank you for this correction. We have made the corrections and if the I^2=0, the text reads; *"no evidence of heterogeneity was observed".*

Reviewer 1

Comments: Major Strengths: Addresses a current clinical dilemma, well-performed systematic review and meta-analysis. Major Weaknesses: Unfortunately, the information from the study was inconclusive and did not solve the clinical dilemma.

Response: Thank you for these comments and we agree with the reviewer.

Query 1: Specific issues that need to be addressed by author(s): This systematic review and meta-analysis assessed the effects of continuing versus discontinuing ACEI/ARB prior to surgery, which is a commonly faced clinical dilemma.

Specific Comments:

Query 1: Page 6, line 2: Please include the recently published Canadian Cardiovascular Society guidelines [Duceppe E, et al. Canadian Cardiovascular Society guidelines on perioperative cardiac risk assessment and management for patients who undergo noncardiac surgery. Can J Cardiol 2017; 33: 17-32.], which recommends withholding ACEI/ARB starting 24 hours before noncardiac surgery in patients treated chronically with an ACEI/ARB (Strong Recommendation; Low-Quality Evidence). Obviously, there is bias as the authors (Duceppe et al) are basing the recommendations on the analysis of the VISION study (Roshnav PAS, et al. Anesthesiology 2017) that has several flaws.

Response 1: Thank you for the above recommendation. The Canadian Cardiovascular Society guideline recommendation has been added into the introduction on Page 5 and compared to both the European Society of Cardiology/European Society of Anaesthesiologists (ESC/ESA) and American College of Cardiology/ American Heart Association (ACC/AHA) guidelines. We also note the limited evidence for these recommendations.

Query 2: Page 10, line 49: the statement "five were randomized controlled trials…" is missing one reference (there are only 4 references quoted).

Response 2: Thank you for the above. The fifth reference is added.

Query 3: Page 16, lines 26-42: Please delete this paragraph as it discusses anecdotes and instills bias. There is no role of case reports in a meta-analysis of thousands of patients.

Response 3: We agree that reference to case reports weakens the discussion and the afore mentioned paragraph has been deleted

Reviewer 2

Comments: Major Strengths: The topic is of current interest to practitioners of anesthesiology; a large number of adults and elderly are on antihypertensives including ACE-1/ARBs - it is still not clear in whom this therapy should be withheld for surgery and whether withholding or not-withholding has adverse outcomes;
Major Weaknesses: lack of standardization and a compilation of other studies with the hope of being able to combine them to increase the statistical validity of outcomes obtained.

Response: Thank you. We have stated in the limitations that there is insufficient randomized data, and hence we have included non-randomized studies in the meta-analysis which introduces further bias.

Query 1: Specific issues that need to be addressed by author(s): the authors did use standard statistical methodologies; however, it is preferable to let the readers know how they defined heterogeneity in the individual studies

Response 1: Thank you for the above. The definition of I^2 statistic test for heterogeneity is included under *Summary measures and statistical analysis* in order to provide further clarity and insight for the reader. The paragraph includes the following definition; *"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."*

Query 2: Additional comments for author(s) (optional): personalized medicine is currently the name of the game; the authors should discuss and provide any information available from the studies reviewed if ethnicity and race could be identified in the individuals that did become hypotensive in the studies that reported the occurrence of hypotension in the patients who did not withhold their ACE-1/ARBs. This should be another item they should discuss especially since the authors are recommending a prospective well-planned study in the future to evaluate this very important practical issue. Some form of genetic analysis in those that do become hypotensive in future planned

studies may help to provide additional information for planning their anesthetics during their preoperative visits.

Response 2: Thank you for this interesting suggestion. We have assessed all included papers again for data on race or ethnicity. Twersky et al were the only authors to include racial demographics in their published data, however study outcomes assessed the impact of ACE-I/ARB on pre-operative blood pressure measurements only with no data available for intra-operative hemodynamics. We have included a paragraph in the discussion addressing this issue and reiterated the need for possible genetic testing in the conclusion.

Reviewer 3

Comments: Thank you for the opportunity to review this interesting manuscript. I applaud the authors for their efforts in conducting this rather complex analysis.

Response: Thank you

Query 1: I have some concerns that I wish to elaborate on. The manuscript is written in a rather non-conventional way, especially if you look towards the end of the manuscript, there are subheadings such as strengths and weaknesses of this study, then strengths and weaknesses in relation to other studies??. I would recommend that this latter section be incorporated in the introduction justifying the need for this new metaanalysis.

Response 1: We have removed the subheadings and incorporated the *strengths and weaknesses in relation to other studies* into the introduction as suggested in order to validate the need for an updated meta-analysis.

Query 2: Then there another whole section on "Limitations". Aren't limitations synonymous with weaknesses?

Response 2: Thank you. We have now incorporated the ‘weaknesses’ and ‘limitations of meta-analysis’ into the same section of the discussion. We have also removed any subheadings which may have caused further confusion.

Query 3: Recommend re-write of the introduction, and discussion section in an easy to follow, clear sequence manner to make it easy to follow, understand, and appreciate.

Response 3: We have spent more time reviewing and altering the introduction and discussion in order to address these issues. We believe it is substantially improved following the necessary revisions from the editor and reviewers of this manuscript.

Query 4: In the abstract "previous data failed… ", this is not true, please refer to your reference # 2, thus should be corrected to previous metaanalysis failed….

Response 4: This has been corrected so that the sentence now reads *"previous meta-analysis failed".*

Query 5: Congestive Cardiac Failure is not a commonly used term in the US, neither the abbreviation CCF, it is usually referred to as congestive heart failure (CHF)

Response 5: Thank you for the above recommendation. All reference to Congestive Cardiac Failure in the text has been altered to Congestive Heart Failure (CHF)'

Query 6: Reference # 2 has appeared in publication and should be referred to in all tables and figures as it appeared in 2017 and not 2016 (ahead of print publication)

Response 6: We have addressed this issue and replaced all figures and tables citing the study to 2017.

Query 7: Is it possible that the authors would conduct sensitivity analysis including only studies with patients having major surgical procedures, and vascular, i.e. excluding studies like Twersky, and Schirmer.

Response 7: Two major surgical studies were identified – Coriat et al and Bertrand et al, of which both were randomized trails assessing outcomes in vascular surgical patients. We have included this now as a sensitivity analysis in the manuscript. In the results we now report; *"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 as the outcomes were either not assessed or no events reported. For the outcome of MACE, one trial could be included[4] with no treatment effect seen. For intra-operative hypotension pooled data revealed a significantly increased risk of intra-operative hypotension associated with treatment continuation (OR 0.07, 95% CI 0.02 -0.25, I2=0% P<0.0001)"

Query 8: Conclusions: this should be re-written in both the abstract and manuscript to reflect the aim of the study and the current findings. That (I'm paraphrasing here) continuation vs withholding had no association with the studied outcomes. We confirmed current observation of increased intraop hypotension with continuation. Randomized trials are still needed.

Response 8: Thank you for the above recommendation. We agree that more clarity is needed in the conclusion regarding results. We have rewritten the conclusions in both the abstract and discussion to allow for clearer interpretation of results.

Query 9: You were not set out to examine the other things that you make a statement about such as: whether intraoperative hypotension is associated with major postoperative morbidity. So it is adequate that you mentioned that in the discussion part.

Response 9: Thank you. We have removed this text from the conclusion of the abstract.

Query 10: The conclusion in the abstract is a bit better than at the end of the manuscript

Response 10: Thank you. We have modified the conclusion of the manuscript as recommend in Query 8.

Thank you for giving us the opportunity to revise and resubmit our paper. We believe the reviewers' comments have improved our manuscript. Thank you for your interest in our submission.

Regards

Signature Removed

Caryl Hollmann on behalf of all the authors

Editor Response 2:

Nov 20 2017 05:48PM

Caryl Hollmann, M.B.,Ch.B., DA(SA)
University of Cape Town Department of Anaesthesia and Perioperative Medicine
Anesthesia and Perioperative medicine
D23
Cape Town Western Cape 7925
SOUTH AFRICA

RE: MS#: AA-D-17-01673R1 "A systematic review of outcomes associated with withholding or continuing angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) prior to noncardiac surgery."

Dear Dr Hollmann:

Thank you for submitting your manuscript "A systematic review of outcomes associated with withholding or continuing angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) prior to noncardiac surgery." to Anesthesia & Analgesia for consideration. Your manuscript has been reviewed by our editorial board and outside experts. Based on their reviews and my own reading of your manuscript, I would be happy to accept your manuscript for publication in Anesthesia & Analgesia, if you can provide point-by-point responses to my comments and those of the reviewers. Please see my comments and the comments from the reviewers below.

Executive Section Editor Comments to the Author:

Dear Dr. Hollmann:

I appreciate your valuable manuscript revision,,,, it is an important submission. There are just a few (minor) edits to "clean up" a some things. I considered just making these edits myself, but upon reflection, I thought it would be best to let you make these changes yourself. In total, I suspect you can complete the entire revision process in 45 min or so. I look forward to seeing your final manuscript.

With gratitude,

Richard Prielipp, MD

ESE Patient Safety

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Specific Statistical Insights:

The manuscript is much improved. Please simply clarify the reporting of your results in the Abstract as given below. Currently, the results are not clear when reading the abstract alone, as many readers may do.

1. P4L7-18. As mentioned in initial review, the associations are worded backwards (starting with outcome instead of exposure/intervention), and thus awkward at best.

Please mention interventions first and make sure there is no confusion. E.g., in P4L12-17 authors say "An increased risk of intra-operative hypotension was associated with treatment continuation" then give an OR < 1, which implies a reduced odds of outcome.

Suggestion – list here exactly as you have done in Results P14L44-49 "An increased risk of intra-operative hypotension was associated with treatment continuation the morning of surgery (OR 0.63 95% CI 0.47;0.85)". This is clear and will remove confusion in Abstract.

2. P4L8-10. Please do the same here. The sentence does not make sense since you say:

"There was no difference in mortality (odds ratio [OR], 0.97; 95% confidence interval [CI], 0.62-1.52; I2=0%) or MACE (OR 1.12; 95% CI 0.82-1.52; I2=0%) associated with continued ACE-I/ARB therapy". It is not clear from your sentence what the odds ratio refers to – odds of continued versus withheld, or vice versa.

*** Instead of " no difference in mortality", talk about association with the outcome and say something like"odds ratio (95% CI) of YYY for withheld versus continuous was XXX (YY) for mortality and XXX (YY) for MACE…".

If we do not receive a revised manuscript from you within the 4 weeks, I will assume that you have elected to decline to revise your manuscript.

Please revise your paper as guided by the reviewers' suggestions and provide a point-by-point description of how you responded to their suggestions and concerns. Submit your revision via Editorial Manager by logging in to your author account and clicking the link "Submissions Needing Revision." Be sure you have pasted your response to the reviewers into the appropriate box on the online submission site.

With all good wishes,

Richard C Prielipp, MD, MBA, FCCM
Executive Section Editor
Anesthesia & Analgesia

Jean-Francois Pittet, MD
Editor-in-Chief
Anesthesia & Analgesia

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Executive Section Editor Quantitative Evaluation

1. Novelty of the Topic: 5
2. Significance of Topic: 6
3. Approach to the Topic: 6
4. Interest of the Topic to the Specialty: 7
5. Impact of the Findings on the Specialty: 7

Scale:
Minor (1,2,3): Easily addressable weaknesses that do not substantially lessen the quality of the study/manuscript
Moderate (4,5,6): Weaknesses that somewhat lessen the quality of the study/manuscript
Major (7,8,9): Weaknesses that severely limit the quality of the study/manuscript

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Reviewer Comments to the Author:

Reviewer 1:

Major Strengths: Provide new information that is clinically important

Specific issues that need to be addressed by author(s):
No further comments.

Reviewer 2:
Major Strengths: the manuscript has been much improved and clearly defines the need to do a prospective study evaluating this issue

Major Weaknesses: lack of adequate data available to come up with more meaningful and practitioner beneficial conclusions

Specific issues that need to be addressed by author(s): page 5 line 12 ----where it says both harm and benefit, please briefly describe what is the harm and what is the benefit here.

Additional comments for author(s) (optional):page 6 line 34 where it is increased in intra-operative hypotension .....it should be increased incidence of intra-operative hypotension; pate 7 line 10 waivered should be waived.page 17 line 15 briefly explain what is absolute and relative hypotension; The authors should also review the following recently published article in the BJA and add an element to the discussion from this study:
Cohort study of preoperative blood pressure and risk of 30-day mortality after elective non-cardiac surgery S. Venkatesan P. R. Myles H. J. Manning A. M. Mozid C. Andersson M. E. JørgensenJ. G. Hardman S. R. Moonesinghe P. Foex M. Mythen ... Show more
BJA: British Journal of Anaesthesia, Volume 119, Issue 1, 1 July 2017, Pages 65-77,

Reviewer 3:
No new comments.

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Second revision cover letter:

UNIVERSITY OF CAPE TOWN

Professorial Staff:

JLC Swanevelder MB ChB, MMed (Anes) (U Stell), FCA (SA), FRCA (Hon)
Head of Department
Email: justiaan.swanevelder@uct.ac.za
BM Biccard MBChB (UCT), FCA (SA), FFARCSI, MMed (UKZN), PhD
2nd Chair of Anaesthesia
Email: bruce.biccard@uct.ac.za
Administrative Officer: C Wyngaard, Email: cheryl.wyngaard@uct.ac.za

Department of Anaesthesia and Perioperative Medicine

Faculty of Health Science,
Anzio Road, Observatory
Western Cape, South Africa 7925

Richard C. Prielipp
Executive Section Editor
Anesthesia and Analgesia

Jean-Francois Pittet, MD
Editor-in-Chief
Anesthesia & Analgesia

Dear Dr Richard Prielipp

RE: MS#: AA-D-17-01673R1 "A systematic review of outcomes associated with withholding or continuing angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) prior to noncardiac surgery."

Thank you for the opportunity to submit a revision of our paper for consideration for publication in Anesthesia and Analgesia.

We have itemised the queries with a written description of our changes and have submitted a clean manuscript as requested.

Statistical comments:

Query 1: P4L7-1 As mentioned in initial review, the associations are worded backwards (starting with outcome instead of exposure/intervention), and thus awkward at best.
Please mention interventions first and make sure there is no confusion. E.g., in P4L12-17 authors say

"An increased risk of intra-operative hypotension was associated with treatment continuation" then give an OR < 1, which implies a reduced odds of outcome.

Suggestion – list here exactly as you have done in Results P14L44-49 "An increased risk of intra-operative hypotension was associated with treatment continuation the morning of surgery (OR 0.63 95% CI 0.47;0.85)". This is clear and will remove confusion in Abstract.

Response 1: Thank you for the above clarification. We have amended the abstract to now read *"Withholding ACE-I/ARB therapy was not associated with a significant 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%). Withholding therapy was however associated with significantly less intra-operative hypotension (OR 0.63 95% CI 0.47;0.85, I^2=71%).*

Query 2: P4L8-10. Please do the same here. The sentence does not make sense since you say: "There was no difference in mortality (odds ratio [OR], 0.97; 95% confidence interval [CI], 0.62-1.52; I2=0%) or MACE (OR 1.12; 95% CI 0.82-1.52; I2=0%) associated with continued ACE-I/ARB therapy". It is not clear from your sentence what the odds ratio refers to – odds of continued versus withheld, or vice versa.

*** Instead of " no difference in mortality", talk about association with the outcome and say something like "odds ratio (95% CI) of YYY for withheld versus continuous was XXX (YY) for mortality and XXX (YY) for MACE…".

Response 2: Thank you for the above comment. We have corrected this query, as stated in our response to query 1.

Reviewer 1:

Comments: Major Strengths: Provide new information that is clinically important

Specific issues that need to be addressed by author(s):

No further comments.

Reviewer 2:

Comments: Major Strengths: the manuscript has been much improved and clearly defines the need to do a prospective study evaluating this issue

Major Weaknesses: lack of adequate data available to come up with more meaningful and practitioner beneficial conclusions.

Query 1: page 5 line 12 ----where it says both harm and benefit, please briefly describe what is the harm and what is the benefit here.

Response 1: Thank you for the above comment. We have not amended the paragraph as after the sentence initially stating harm versus benefit, we describe these two outcomes in the following two sentences; "*Intra-operative hypotension secondary to continuation of ACE-I and ARB therapy in the perioperative period may be associated with major perioperative morbidity (harm) and has led some clinicians to withhold therapy. Conversely, continuation of ACE-I/ARBs in the perioperative period may also be associated with improved outcomes, where preoperative ACE-I have been associated with improved outcomes (benefit) in vascular surgical patients who have sustained a perioperative myocardial infarction (MI).*'

Query 2: Additional comments for author(s) (optional): page 6 line 34 where it is increased in intra-operative hypotension .....it should be increased incidence of intra-operative hypotension.

Response 2: The afore mentioned sentence has been amended and now reads; *"despite a clear demonstration of increased incidence of intra-operative hypotension".*

Query 3: page 7 line 10 waivered should be waived.

Response 3: Thank you for the above comment. We have replaced the word 'waivered' with *'waived'*.

Query 4: page 17 line 15 briefly explain what is absolute and relative hypotension.

Response 4: We have clarified this text, so that it is clear that it is relative risk increase, and absolute risk increase with the following text; "*Concerning intra-operative 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."

Query 5: The authors should also review the following recently published article in the BJA and add an element to the discussion from this study: Cohort study of preoperative blood pressure and risk of 30-day mortality after elective non-cardiac surgery S. Venkatesan P. R. Myles H. J. Manning A. M. Mozid C. Andersson M. E. JørgensenJ. G. Hardman S. R. Moonesinghe P. Foex M. Mythen ... BJA: British Journal of Anaesthesia, Volume 119, Issue 1, 1 July 2017, Pages 65-77.

Response 5: Thank you for the above comment. We have included a sentence referencing the above article in the discussion part of the manuscript. The sentence reads; *"Furthermore preoperative hypotension itself has recently been linked to the increased incidence of postoperative mortality,54 and thus the impact of continuing regular ACE-I/ARB therapy in the light of preoperative hypotension unknown"*

Reviewer 3: No new comments.

Response: Thank you

Thank you for giving us the opportunity to revise and resubmit our paper, and for your interest in our submission.

Regards

Signature Removed

Caryl Hollmann on behalf of all the authors