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REVIEW ARTICLE/BRIEF REVIEW

Morbidity and mortality in patients managed with high compared with low blood pressure targets during on-pump cardiac surgery: a systematic review and meta-analysis of randomized controlled trials

Morbidité et mortalité des patients pris en charge avec des cibles élevées ou basses de pression artérielle pendant la chirurgie cardiaque sous circulation extracorporelle : une revue systématique et une méta-analyse d'études randomisées contrôlées

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Abstract

Purpose *Many believe that blood pressure management during cardiac surgery is associated with postoperative outcomes. We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to determine the impact of high compared with low intraoperative blood pressure targets on postoperative morbidity and mortality in adults undergoing cardiac surgery on cardiopulmonary bypass (CPB). Our primary objective was to inform the design of a future large RCT.*

Source *We searched MEDLINE, EMBASE, Web of Science, CINAHL, and CENTRAL for RCTs comparing high with low intraoperative blood pressure targets in adult patients undergoing any cardiac surgical procedure on CPB. We screened reference lists, grey literature, and conference proceedings.*

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This article was updated to correct Hessam Kashani's name.

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Principal findings *We included eight RCTs (N =1,116 participants); all examined the effect of blood pressure management only during the CPB. Trial definitions of high compared with low blood pressure varied and, in some, there was a discrepancy between the target and achieved mean arterial pressure. We observed no difference in delirium, cognitive decline, stroke, acute kidney injury, or mortality between high and low blood pressure targets (very-low to low quality evidence). Higher blood pressure targets may have increased the risk of requiring a blood transfusion (three trials; n = 456 participants; relative risk, 1.4; 95% confidence interval, 1.1 to 1.9; P = 0.01; moderate quality evidence) but this finding was based on a small number of trials.*

Conclusion *Individual trial definitions of high and low blood pressure targets varied, limiting inferences. The effect of high (compared with low) blood pressure targets on other morbidity and mortality after cardiac surgery remains unclear because of limitations with the body of existing evidence. Research to determine the optimal management of blood pressure during cardiac surgery is required.*

Study registration *PROSPERO (CRD42020177376); registered: 5 July 2020.*

Résumé

Objectif *Pour beaucoup, la prise en charge de la pression artérielle pendant la chirurgie cardiaque serait associée aux issues postopératoires. Nous avons réalisé une revue systématique et une méta-analyse d'études randomisées contrôlées (ERC) afin de déterminer l'impact de cibles peropératoires de pression artérielle élevées par rapport à des cibles basses sur la morbidité et la mortalité postopératoires d'adultes bénéficiant d'une chirurgie cardiaque sous circulation extracorporelle (CEC). Notre objectif principal était d'orienter la conception d'une future ERC d'envergure.*

Sources *Nous avons analysé les bases de données MEDLINE, EMBASE, Web of Science, CINAHL et CENTRAL afin d'en tirer les ERC comparant des cibles de pression artérielle peropératoire élevées à des cibles basses chez des patients adultes bénéficiant d'une intervention chirurgicale cardiaque sous CEC. Nous avons passé au crible les listes de références, la littérature grise et les travaux de congrès.*

Constatations principales *Nous avons inclus huit ERC (N = 1116 participants); toutes les études ont examiné l'effet de la prise en charge de la pression artérielle uniquement pendant la CEC. Les définitions d'une pression artérielle élevée ou basse variaient d'une étude à l'autre et, dans certains cas, un écart a été noté entre la pression artérielle cible et la pression artérielle moyenne atteinte. Nous n'avons observé aucune différence dans les taux de delirium, de déclin cognitif, d'accident vasculaire cérébral, d'insuffisance rénale aiguë ou de mortalité entre les cibles de pression artérielle élevée et basse (données probantes de qualité très faible à faible). Des cibles de pression artérielle plus élevées pourraient avoir augmenté le risque de transfusion sanguine (trois études; n = 456 participants; risque relatif, 1,4; intervalle de confiance à 95 %, 1,1 à 1,9; P = 0,01; données probantes de qualité modérée), mais ce résultat se fondait sur un petit nombre d'études.*

Conclusion *Les définitions individuelles des cibles d'hypertension et d'hypotension artérielle variaient, ce qui a limité les inférences. L'effet de cibles de pression artérielle élevée (par rapport à une pression artérielle basse) sur d'autres mesures de la morbidité et de la mortalité après une chirurgie cardiaque demeure incertain en raison des limites de l'ensemble des données probantes existantes. Des recherches visant à déterminer la prise en charge optimale de la pression artérielle pendant la chirurgie cardiaque sont nécessaires.*

Enregistrement de l'étude *PROSPERO (CRD42020177376); enregistrée le 5 juillet 2020.*

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Keywords Blood pressure targets · Cardiopulmonary bypass · Cardiac surgery · Morbidity and mortality

Blood pressure during cardiac surgery is a key parameter that is controlled by anesthesiologists before and after cardiopulmonary bypass (CPB) and facilitated by perfusionists during CPB. Clinicians manage intraoperative blood pressure using vasopressors, inotropes, vasodilators, anesthetic agents, pump flow changes during CPB, and intravascular volume administration. Generally, clinicians believe that optimal management of blood pressure during cardiac surgery is important because of an assumed relationship with postoperative morbidity and mortality. Nevertheless, available evidence is limited, so what constitutes "optimal" blood pressure management during cardiac surgery remains poorly defined. As a result, the blood pressure maintained during cardiac surgery is largely based on institutional preference,[1] often with higher (or lower) targets chosen for patients with certain comorbidities. The use of low, high, and personalized blood pressure targets has been described.

Many clinicians believe that a lower mean arterial pressure (MAP) in the range of 40–60 mmHg is associated with end-organ hypoperfusion and resultant ischemia; therefore, higher targets ($\geq$ 70 mmHg) are preferable. This belief has been inconsistently supported by observational studies and several small randomized controlled trials (RCTs) in cardiac surgery that have suggested a relationship between low MAP and an increased risk of adverse outcomes.[2–5] In contrast, other clinicians target this lower blood pressure range (e.g., MAP 40–60 mmHg) because they believe that higher targets may be associated with their own harms, which is supported by limited observational and RCT data.[6,7] A third group support a personalized approach to blood pressure management based on the concept of autoregulation (principally cerebral), where constant blood flow to an organ is maintained across a range of perfusion pressures. Because the blood pressure range within which end-organ blood flow is kept constant may be influenced by individuals' baseline blood pressure, pre-existing hypertension, and the presence of obstructive vascular disease, this approach establishes intraoperative blood pressure targets based on the preoperative assessment of baseline blood pressure[8] or cerebral autoregulation thresholds.[9]

Considering the uncertainty as to the optimal approach, we conducted a systematic review and meta-analysis of RCTs to assess the impact of high compared with low blood pressure targets during cardiac surgery on CPB on postoperative morbidity and mortality. Our objective was to inform the design of future RCTs evaluating the use of intraoperative blood pressure management as an intervention.

Methods

We registered the protocol for this systematic review with PROSPERO International Prospective Register of Systematic Reviews (CRD42020177376). Our review was conducted according to the guidelines recommended by the Cochrane Handbook[10] and is reported according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines (see Electronic Supplementary Material [ESM], eAppendix 1: PRISMA checklist).[11]

Trial eligibility criteria

We included RCTs comparing high with low intraoperative blood pressure targets in adult patients undergoing cardiac surgery on CPB; within-patient crossover and quasi-randomized studies were excluded. We examined the postoperative outcomes of delirium, cognitive decline, stroke, myocardial infarction (MI), acute kidney injury, blood transfusion, intensive care unit (ICU) length of stay (LOS), hospital LOS, all-cause mortality, and quality of life. We accepted outcomes as defined by the trial.

Identification of trials

Our search strategy was designed and conducted with the support of a health sciences librarian (J.Y.). We searched MEDLINE, EMBASE, Web of Science, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Cochrane Register of Controlled Trials (CENTRAL) from inception to 7 May 2021, to identify potentially relevant publications (see ESM eAppendix 2 for detailed search terms). We reviewed reference lists of included trials, abstracts from major conferences from the preceding five years (American Society of Anesthesiologists, Society of Cardiovascular Anesthesiologists, European Association of Cardiothoracic Anesthesiologists, and European Society of Cardiology), and searched clinical trials registries (ClinicalTrials.gov, International Standard Randomised Controlled Trial Number Register, Australian New Zealand Clinical Trials Registry, and World Health Organization International Clinical Trials Registry Platform) to identify relevant publications. When potentially relevant clinical trials registry entries without

associated publications were identified, we contacted investigators to determine the status of the trial and whether preliminary data were available.

Selection of trials

Five reviewers (C.M., Y.Q., T.A., E.B.C., J.S.) screened titles and abstracts for eligibility using *Covidence*, an online platform for systematic review management (https://www.covidence.org; Covidence, Melbourne, VIC, Australia).[12] We retrieved full texts of included trials and reviewed each full text to determine whether it met inclusion criteria. When relevant, we identified the primary reason for exclusion. We performed all steps independently and in duplicate; disagreements between reviewers were resolved by discussion. If the discussion failed to resolve disagreement, a third reviewer was consulted to make a final decision.

Data extraction

We developed and piloted a standardized data extraction form. Four reviewers (C.M., Y.Q., T.A., H.K.) independently extracted data about the trial intervention and outcomes; a third reviewer (M.K., E.B.C., or J.S.) checked for incongruency and resolved conflicts. Along with general trial information, we extracted trial characteristics (e.g., trial design, data collection process, follow-up period), participant and intervention characteristics (e.g., age and sex distribution of participant groups, procedure types, mean duration of CPB), and outcomes reported, including how the outcome was defined. We contacted authors to obtain relevant unreported data. We attempted contact twice, after which we considered the data missing.

Assessment of risk of bias

Six reviewers (C.M., Y.Q., T.A., H.K., M.K., J.S.) independently and in duplicate assessed the risk of bias of included trials using the Cochrane risk of bias tool.[13] We assessed the following domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases. We considered trials to have a "high risk of bias" if they had a high risk of bias in a single domain or unclear risk of bias in two or more domains. Any incongruencies in risk of bias assessment were resolved by discussion.

Data analysis

We conducted analyses using Review Manager 5.3 software (Cochrane Collaboration, London, UK).[14] We used a random effects model to pool results and summarize evidence. When trials reported outcomes at multiple timepoints, we meta-analyzed the outcome assessment reported closest to hospital discharge only unless otherwise specified. We present point estimates as relative risks (RRs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes, with 95% confidence intervals (CI) and corresponding *P* values. When continuous outcomes were reported as median and interquartile range [IQR], we used validated methods to convert to mean and standard deviation (SD) for the purposes of calculating a pooled effect estimate.[15] We constructed forest plots to describe available evidence according to the method described by DerSimonian and Laird.[16] For the outcome of blood transfusion incidence, we made a post hoc adjustment using the Hartung–Knapp method, a correction that can be applied to random effects meta-analysis to minimize type I error when the number of included studies is small.[17] We assessed the heterogeneity of data for each outcome using I^2 statistics with the thresholds recommended by Cochrane for interpretation.[18]

Subgroup analyses

We a priori planned to undertake subgroup analyses to explain statistical heterogeneity and to assess subgroup effects. Our planned subgroup analyses included the following: high risk of bias compared with low risk of bias trials, older ($\geq$ 75 yr) compared with younger patients, patients with vascular risk factors compared with those without, type of surgery, and timing of follow-up. If sufficient trials were identified, we planned to compare trials where MAP targets were applied during the entire intraoperative period with studies only targeting MAP during CPB.

Publication bias

We planned to use a funnel plot or the Egger test to assess for publication bias if more than ten trials were identified.

Assessment of quality of evidence

We assessed the quality of the evidence for each outcome using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach,[19] which considers within-trial risk of bias, consistency (or heterogeneity) of the data, directness of the evidence, precision of effect estimates, and the presence of possible reporting bias.

Results

Literature search

We identified 6,370 records and, after removal of duplicates, screened the titles and abstracts of 4,467 studies. Following screening of titles and abstracts, 59 studies were included for full text review. Of these, we excluded 51 studies—19 were duplicates (conference abstracts or substudies of already included trials); four were clinical trial entries (contact with investigators confirmed that two studies were incomplete, one had been stopped before data had been collected, and one had generated a publication that was included); three were the wrong population (one animal study and two studies in nonsurgical heart failure patients);[6,20,21] 13 were not RCTs; and 12 used the wrong intervention. Three of the 12 RCTs using the "wrong intervention" reported the effects of an intraoperative blood pressure management strategy on patient outcomes but were excluded because the intervention arms could not be categorized as "high" compared with "low" (see ESM eAppendix 3: Blood pressure RCTs using a different intervention strategy). We included eight RCTs (N = 1,116 participants);[4,5,22–24] two of these RCTs reported outcomes in additional substudy publications (see ESM eAppendix 4: List of sub-study publications).[6,25] The study flow diagram is presented in Fig. 1.

Characteristics of included trials

Table 1 summarizes the characteristics of included trials. Most patients underwent elective coronary artery bypass grafting (CABG); some trials included urgent and emergent cases as well as more complex cardiac procedures. The MAP targets used across trials are shown in Fig. 2. Individual trial definitions of high and low targets were 40–70 mmHg in low arms and 70–100

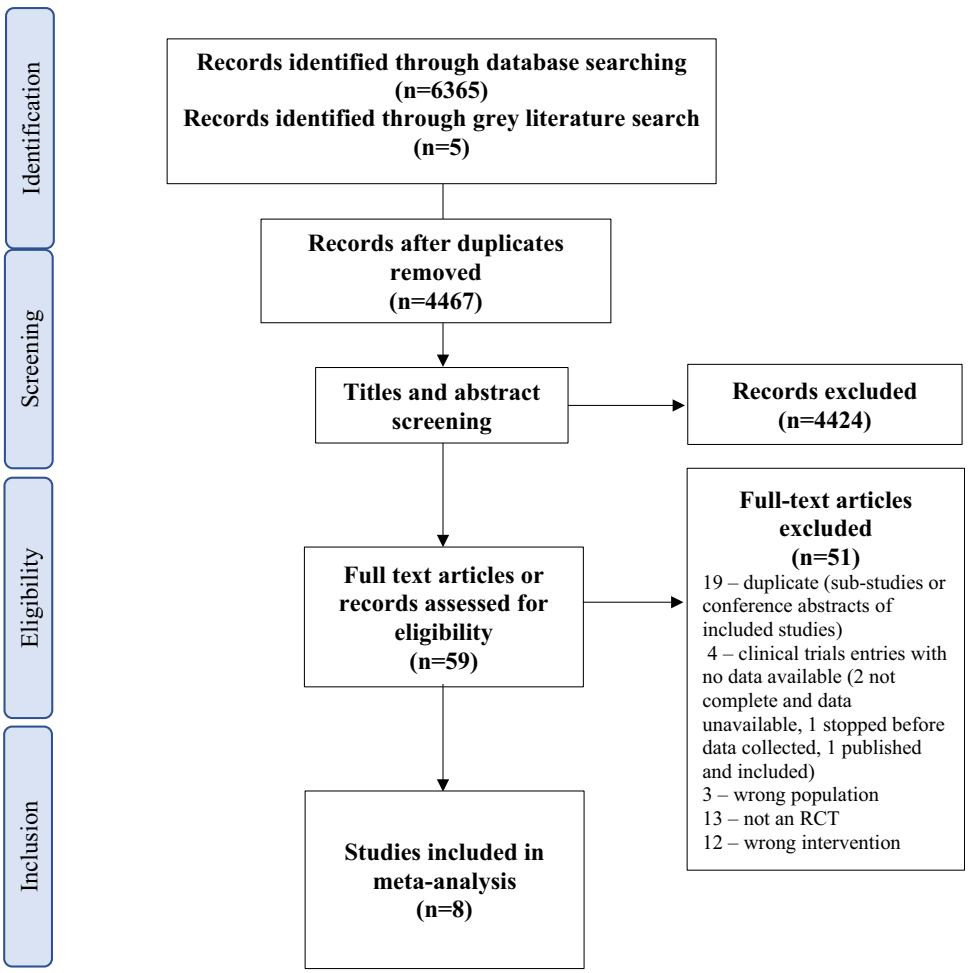

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

Table 1 Characteristics of included studies

Study (language)	Total *N*; *n* low MAP/ *n* high MAP	Patients	Intervention; low MAP target/high MAP target	Achieved MAP "low" arm, mean (SD)	Achieved MAP "high" arm, mean (SD)	Achieved MAP "other" arm, mean (SD)	Outcomes evaluated	Follow-up period
Azau 2014 (English)[22]	292; 147/145	Adults > 60 years with risk factors for AKI undergoing elective CABG, valvular surgery or ascending aorta using normothermic CPB	Low compared with high target applied during CPB, goal MAP 70–90 in both groups before and after CPB; 50–60 mmHg/75–85 mmHg	60 (6) mmHg	79 (6) mmHg	n/a	AKI Perioperative MI Incidence transfusion Units transfused Hospital LOS All-cause mortality	6 months
Bagheri 2012 (Persian)[23]	108; 54/54	Adults undergoing CABG	Low compared with high target applied during CPB, no target before and after CPB; 50–70 mmHg/70–90 mmHg	Not reported	Not reported	n/a	Cognitive decline ICU LOS Hospital LOS	In hospital
Gold 1995 (English)[5]	248; 124/124	Adults undergoing elective CABG on CPB and able to complete neurocognitive testing and follow–up	Low compared with high target applied during CPB, no target before and after CPB; 50–60 mmHg/80-100 mmHg	51.8 (5.2) mmHg	69.5 (7.1) mmHg	n/a	Cognitive decline Stroke MI Units transfused Hospital LOS ICU LOS All-cause mortality QOL	6 months
Kandler 2019 (English)[24]	90; 45/45	Adults >70 years with normal renal function undergoing combined CABG and valve surgery	Low compared with high target applied during CPB, no target before and after CPB; <60 mmHg/>60 mmHg	47 (5) mmHg	61 (4) mmHg	n/a	AKI Stroke All-cause mortality	6 months
Siepe 2011 (English)[4]	92; 44/48	Adults undergoing elective or urgent CABG on CPB	Low compared with high target applied during CPB, no target before and after CPB; 60–70 mmHg/80–90 mmHg	64.7 (8.2) mmHg	84.3 (11.2) mmHg	n/a	Delirium Cognitive decline AKI MI Incidence transfusion Units transfused ICU LOS Hospital LOS	30 days

Table 1 continued

Study (language)	Total *N*; *n* low MAP/ *n* high MAP	Patients	Intervention; low MAP target/high MAP target	Achieved MAP "low" arm, mean (SD)	Achieved MAP "high" arm, mean (SD)	Achieved MAP "other" arm, mean (SD)	Outcomes evaluated	Follow-up period
Sirvinskas 2012 (English)[20]	122; low MAP 36/moderate MAP 50/high MAP 36	Adults >70 years with normal renal function undergoing first–time elective CABG	Compared the effect of three different MAP targets (low, medium, high) during CPB; no target before and after CPB; <60 mmHg/60–70 mmHg/>70 mmHg	54.4 (2.9) mmHg	75.1 (4.3) mmHg	65.0 (3.1) mmHg	Neurologic disorders AKI Incidence transfusion ICU LOS Hospital LOS	In hospital
Urzua 1992 (English)[21]	21; 7/14	Adults 50–70 years old with normal renal function undergoing elective CABG on CPB	Low compared with high target applied during CPB, no target before and after CPB; no target/ >70 mmHg	57.7 (8.2) mmHg	71.1 (3.1) mmHg	n/a	AKI	One week
Vedel 2018 (English)[6]	197; 98/99	Adults >18 yr with no history of neurologic disease undergoing elective or urgent CABG on CPB or left-sided valvular surgery	Low compared with high target applied during CPB, no target before and after CPB; 40–50 mmHg/70–80 mmHg	44.7 (4.7) mmHg	66.8 (4.9) mmHg	n/a	Delirium Cognitive decline Stroke MI ICU LOS Hospital LOS All-cause mortality	30 days

AKI = acute kidney injury; CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; ICU = intensive care unit; LOS = length of stay; MAP = mean arterial pressure; MI = myocardial infarction; QOL = quality of life

mmHg in high arms; the pooled mean (SD) high and low achieved MAPs were 70 (9) and 54 (9) respectively, not including one trial that did not report the achieved blood pressure.[23] Two trials compared a high MAP target to a "usual care" arm without a formally stated target.[21,24] Trial definitions of high compared with low blood pressure overlapped significantly and, in some trials, there was a discrepancy between the target MAP and the actual MAP achieved. Sirvinskas *et al.*[20] divided patients into three blood pressure ranges (low, middle, and high pressure); for the purposes of meta-analysis, we included outcomes reported for the high and low target arms and excluded the "middle" group.

Data collection

The data extracted for each trial, as well as details regarding how it was handled, are described in ESM eAppendix 5. The corresponding author for one trial provided unpublished mean with SD values for ICU and hospital LOS, which had originally been reported as median with IQR.[6]

Risk of bias

The risk of bias of each included trial is illustrated in Fig. 3, and detailed assessment rationale are available in ESM eAppendix 6. Two trials had a low risk of bias[5,22] and six had a high risk of bias.[4,6,20,21,23,24] Four high risk of bias trials were at high risk of reporting or attrition bias.[6,20,21,23] Two high risk of bias trials were at high risk of selection bias.[21,24] Three high risk of bias trials had high risk of performance and detection bias.[4,6,23]

Assessment of quality of evidence

The GRADE assessment is presented in ESM eAppendix 7; the overall quality of evidence for each outcome is specified below. In general, most outcomes were rated down because of the high risk of bias of included trials,

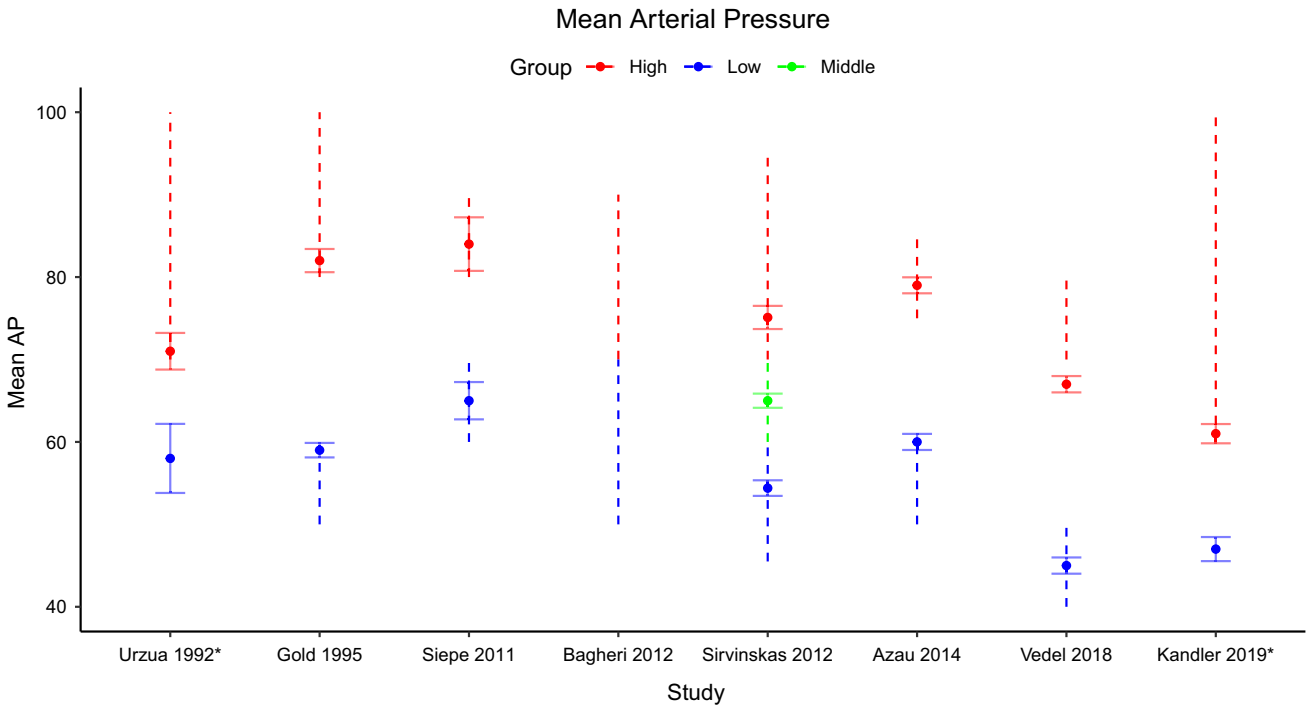

Fig. 2 Target and achieved mean arterial pressure (MAP) by intervention arm within each trial. Point with solid vertical line represents achieved mean and standard deviation blood pressure. Hatched vertical line represents target blood pressure range. High, low, and middle range MAP targets are represented in red, blue, and green respectively. *Trials with no specified low blood pressure range.

high statistical heterogeneity, and a confidence interval that included both significant benefit and significant harm.

Outcomes

Table 2 presents the pooled effect estimate for each outcome; associated forest plots can be found in ESM eAppendix 8. Due to the small number of trials and limited data reported for each outcome, we were unable to conduct subgroup analyses or assess for publication bias.

Neurocognitive outcomes

We found no difference in the incidence of delirium (two trials; n = 289 participants; RR, 0.5; 95% CI, 0.03 to 8.6; P = 0.61; very low quality evidence),[4,6] cognitive decline (two trials; n = 394 participants; RR, 1.2; 95% CI, 0.7 to 2.1; P = 0.46; very low quality evidence),[5,6] or stroke (three trials; n = 527 participants; RR, 1.0; 95% CI, 0.2 to 4.9; P = 0.95; very low quality evidence)[5,6,24] when high compared with low intraoperative blood pressure targets were used. Four trials could not be meta-analyzed because of the way in which outcomes were reported. Azau *et al.* reported no difference between low and high blood pressure target arms in the incidence of "neurologic complications of surgery," which was a composite that included stroke, seizure, and transient mental confusion or agitation.[22] Sirvinskas *et al*. reported no difference between low, middle, and high blood pressure arms in the incidence of postoperative "neurologic disorders," an outcome that was not defined.[20] Bagheri *et al.* reported no difference between low and high target groups in mean postoperative cognitive test scores.[23] Siepe *et al*. reported a greater decline in postoperative Mini Mental Status Exam in the low compared with the high blood pressure target arm (mean [SD] 3.9 [6.1] *vs* 1.1 [1.9]; P = 0.012).[4]

Myocardial infarction

Myocardial infarction was reported in three trials (n = 734 participants), with an overall event rate of 2.0% (15/734).[5,6,22] There was no difference in MI (RR, 0.9; 95% CI, 0.3 to 3.2; P = 0.89; low quality evidence) when high compared with low intraoperative blood pressure targets were used.

Acute kidney injury

The number of patients that required postoperative hemodialysis was reported by five trials (n = 740

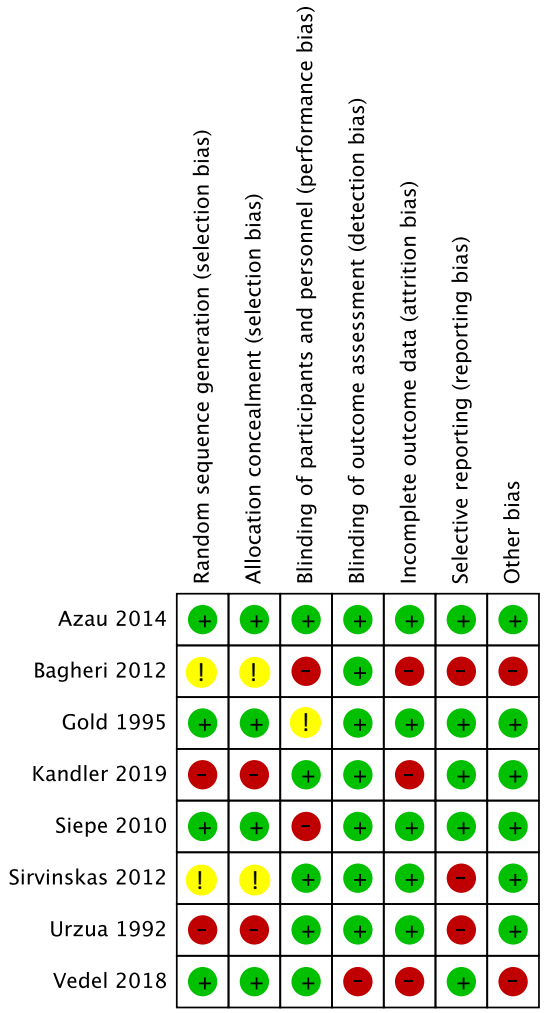

Fig. 3 Cochrane risk of bias assessment for each included trial. Red circles depict a domain with a high risk of bias, green circles depict a domain with a low risk of bias, and yellow circles depict a domain with an unclear risk of bias.

participants), with no significant difference between high and low MAP target (RR, 1.0; 95% CI, 0.5 to 2.3; $P = 0.98$; low quality evidence).[4,6,20,22,24] The number of patients meeting RIFLE "risk" criteria was reported by four trials ($n = 600$ participants); there was no significant difference when high compared with low intraoperative blood pressure targets were used (RR, 1.3; 95% CI, 0.9 to 1.8; $P = 0.25$; very-low quality evidence).[6,21,22,24]

Bleeding/transfusion

Three trials reported the incidence of transfusion ($n = 456$ participants);[4,20,22] one reported this as the number of patients who received transfusion of red blood cells[20] and two reported the number of patients who received blood products.[4,22] Using random effects meta-analysis, patients managed using a high target blood pressure were more likely to be transfused than those in low blood pressure arms (RR, 1.4; 95% CI, 1.1 to 1.9; $P < 0.01$; moderate quality evidence). We were surprised at this finding and, post hoc, applied a Hartung–Knapp adjustment, a correction that can be applied to random effects meta-analysis to minimize type I error when the number of included studies is small.[17] Doing so resulted in a wider CI that no longer achieved statistical significance (RR, 1.4; 95% CI, 0.8 to 2.5; $P = 0.10$). There was no difference in the mean number of units transfused when high compared with low intraoperative blood pressure targets were used (three trials; $n = 632$ participants; MD, 0.1 units; 95% CI, -0.1 to 0.3; $P = 0.35$; high quality evidence).[4,5,22]

Length of stay

Intensive care unit LOS was reported by four trials ($n = 609$ participants).[4–6,20] While most trials separated ICU LOS from all other levels of care, Siepe *et al*. reported time spent in ICU and "intermediate care" as a single measure. When meta-analyzed, there was no difference in ICU LOS between high and low blood pressure groups (MD, 0.2 days; 95% CI, -0.4 to 0.8; $P = 0.55$; very-low quality evidence). Hospital LOS was 1.1 days longer when high compared with low intraoperative blood pressure targets were used (five trials; $n = 901$ participants; MD, 1.1 days; 95% CI, 0.3 to 1.8; $P < 0.01$; low quality evidence).[4–6,20,22] Nevertheless, the quality of evidence for this outcome was rated down for indirectness, as the results of one trial[22] had to be converted from median [IQR] to mean (SD), which likely resulted in a falsely narrow confidence interval for the results of both that individual trial and the point estimate for the pooled effect.

Mortality

Mortality was reported by four trials ($n = 671$ participants) with a pooled event rate of 5.1% at six months (34/671).[4–6,24] The use of high compared with low intraoperative blood pressure targets did not result in a difference in mortality, whether in hospital (RR, 1.1; 95% CI, 0.4 to 3.3; $P = 0.84$; very low quality evidence), at 30 days after surgery (RR, 1.6; 95% CI, 0.6 to 4.4; $P = 0.33$; low quality evidence) or six months after surgery (RR, 0.8; 95% CI, 0.4 to 1.6; $P = 0.55$; moderate quality evidence).

Quality of life

Quality of life was reported by one trial ($n = 248$ participants). Gold *et al*. used the SF-36 to assess quality of life at baseline and six months after surgery. They reported that most patients improved in all seven domains

Table 2 Summary of pooled effect estimates for high compared with low intraoperative blood pressure targets on postoperative morbidity and mortality

Outcome (number of studies)	High MAP target, *n*/total *N*	Low MAP target, *n*/total *N*	Relative risk	95% CI	*P* value	I^2 (%)
Dichotomous variables						
Hospital mortality (4)	8/311	6/316	1.1	0.4 to 3.3	0.84	0
30-day mortality (4)	12/334	6/337	1.6	0.6 to 4.36	0.33	0
6-month mortality (3)	15/310	19/309	0.8	0.4 to 1.6	0.55	0
Myocardial infarction (3)	7/367	8/367	0.9	0.3 to 3.2	0.89	18
Delirium (2)	10/142	13/147	0.5	0.03 to 8.6	0.61	75
Cognitive decline (2)	39/190	35/204	1.2	0.7 to 2.1	0.46	35
Stroke (3)	11/261	13/266	1.0	0.2 to 4.9	0.95	65
Hemodialysis (5)	11/368	11/372	1.0	0.5 to 2.3	0.98	0
RIFLE "risk" criteria (4)	120/297	98/303	1.3	0.9 to 1.8	0.25	41
Number transfused (3)	85/227	60/229	1.4	1.1 to 1.9	0.004	0

Outcome (number of studies)	High MAP target, mean (SD)	Low MAP target, mean (SD)	Weighted mean difference	95% CI	*P* value	I^2 (%)
Continuous variables						
ICU LOS in days (4)	2.4 (4.7)	2.6 (5.3)	0.2	-0.4 to 0.8	0.55	29
Hospital LOS in days (4)	10.7 (7.8)	11.1 (9.4)	1.1	0.3 to 1.8	0.006	13
PRBCs transfused/patient (3)	2.1 (2.7)	1.9 (2.9)	0.1	-0.1 to 0.3	0.35	0

CI = confidence interval; ICU = intensive care unit; MAP = mean arterial pressure; LOS = length of stay; PRBC = packed red blood cell; RIFLE = Risk, Injury, Failure, Loss, and End-stage Kidney classification

with no difference between high and low blood pressure arms in quality of life or decline in physical function at six months after surgery as measured by the SF-36.[5]

Discussion

Eight RCTs enrolled 1,116 adult patients undergoing cardiac surgery on CPB and assessed the effect of high compared with low intraoperative blood pressure targets on postoperative morbidity and mortality. Based on low–moderate quality evidence, high compared with low intraoperative blood pressure targets did not result in a demonstrable difference in delirium, cognitive decline, stroke, MI, acute kidney injury, ICU LOS, hospital LOS, or all-cause mortality, despite the positive results in some of the individual trials included in this meta-analysis. Higher blood pressure targets were associated with a 40% increase in the risk of transfusion (moderate quality evidence) using random effects meta-analysis. Nevertheless, when we undertook a post hoc analysis using a more conservative statistical method, this finding was no longer statistically significant. Hospital LOS was 1.1 days longer when high compared with low intraoperative blood pressure targets were used. Nevertheless, because the results of one trial[22] had to be converted from median [IQR] to mean (SD), we had limited confidence in this finding.

Several observational studies have examined the impact of intraoperative blood pressure throughout the entire surgical period on postoperative outcomes of cardiac surgery. Reich *et al*. conducted a retrospective study of 2,149 patients undergoing CABG and identified a 30% increase in the odds of in-hospital mortality in patients with increased time during CPB with a MAP below 50 mmHg.[26] Aronson *et al.* conducted a retrospective study of 7,808 patients undergoing cardiac surgery, and found that every minute during surgery above or below a systolic blood pressure of 105–130 mmHg was associated with a 3% increase in the odds of 30-day mortality (odds ratio [OR], 1.03 per minute; 95% CI, 1.02 to 1.39; $P < 0.0001$). Sun *et al*. found that a sustained MAP of less than 64 mmHg during CPB was associated with postoperative stroke. Every ten minutes that MAP was between 55 and 64 mmHg was associated with a 13% increase in the odds of stroke (adjusted OR [aOR], 1.13; 95% CI, 1.05 to 1.21) and every ten minutes that MAP was less than 55 mmHg was associated with a 16% increase in the odds of stroke (aOR, 1.16; 95% CI, 1.08 to 1.23). While these studies had relatively large sample sizes, all were derived from single centres, which limits the generalizability of their findings. Furthermore, no RCTs have gone on to evaluate whether implementing strategies to avoid the extremes of blood pressure associated with risk in these observational studies decreases postoperative morbidity and mortality.

Other work examining the relationship between intraoperative MAP and postoperative outcomes has examined the effect of individualized blood pressure targets on postoperative morbidity and mortality. In a single-centre RCT of 412 patients undergoing CABG, Charlson *et al.* compared the use of a "high" MAP (80 mmHg) target with the use of a custom MAP based on patients' baseline blood pressure and found no difference in mortality, deterioration in quality of life, and major neurologic, cardiac, and cognitive complications. Using target based proprietary hardware and software that calculated the individualized lower limit of cerebral autoregulation,[9] Brown *et al.* conducted a nested substudy[27] of a larger trial of individualized blood pressure management,[28] and found that the incidence of postoperative delirium was 37.9% when an individualized blood pressure target was used, compared with an incidence of 52.7% among patients who received usual care (OR, 0.55; 95% CI, 0.31 to 0.97; $P = 0.04$).[27] Nevertheless, there was no difference between these two groups in the primary composite neurologic outcome of clinical stroke, new ischemic lesions on postoperative diffusion-weighted magnetic resonance imaging, or cognitive decline from baseline to four to six weeks after surgery in either the Brown substudy[27] or its parent trial conducted by Hogue *et al.*[28] Furthermore, the technique used to determine the lower limit of cerebral autoregulation is specialized and requires access to technology that is not widely available, which limits its applicability in routine clinical practice.

The effect of blood pressure management on morbidity and mortality has been studied in settings other than cardiac surgery, with varying results. A recent systematic review of observational studies including 130,862 patients undergoing noncardiac surgery examined the relationship between intraoperative hypotension (using variable definitions of what constituted hypotension) and postoperative morbidity and mortality.[29] The authors found that intraoperative hypotension was associated with an increased risk of morbidity (OR, 2.1; 95% CI, 1.6 to 2.8) and mortality (OR, 1.9; 95% CI, 1.3 to 2.8).[29] In contrast, in the ICU setting, an individual patient data meta-analysis of 894 patients with septic shock found no difference in the odds of 28-day mortality when higher compared with lower MAP targets were used (OR, 1.2; 95% CI, 0.9 to 1.5).[30] Nevertheless, when patients in the higher MAP groups had been on vasopressors for more than six hours prior to randomization, they had a higher risk of death (OR, 3.0; 95% CI,1.3 to 6.7).[30] Based on this finding, the authors hypothesized that the administration of elevated doses of vasopressors to maintain blood pressure at higher target levels may be harmful when used for prolonged periods.[30]

With considerable uncertainty as to what constitutes the optimal blood pressure during cardiac surgery, professional bodies have issued conflicting recommendations for blood pressure management. In their consensus statement concerning the management of intraoperative blood pressure, the Perioperative Quality Initiative—an international organization aiming to improve patient care by developing consensus statements related to perioperative medicine—recommended that intraoperative systolic blood pressure be maintained below 140 mmHg and stated that injury was a function of arterial pressure severity and duration.[31] No recommendation was made with respect to a lower limit of blood pressure. In contrast, guidelines from the European Association of Cardiothoracic Anesthesiologists/European Association of Cardiothoracic Surgeons on the management of CPB recommend that MAP during CPB be maintained between the broad range of 50–80 mmHg; no recommendation was made for blood pressure management before and after CPB.[32]

Our systematic review is limited by the available evidence. Our search strategy and inclusion criteria identified eight small, single-centre RCTs that were eligible for inclusion. Across RCTs, the definition of what constitutes a "high" compared with a "low" target varied, such that "low" and "high" targets overlapped across trials (Fig. 2). In addition, there was often a discrepancy between the target and achieved blood pressure. For example, the "low" blood pressure range of 60–70 mmHg targeted by Siepe *et al.*[4] overlapped with the "high" value of > 60 mmHg targeted by Kandler *et al.*,[24] as well as the achieved "high" blood pressure mean (SD) of 66.8 (4.9) mmHg observed by Vedel *et al.* (despite a "high" blood pressure target range of 70–80 mmHg).[6] This limits our ability to make inferences about the relative effects of these two approaches. Ideally, rather than dichotomizing blood pressure targets as "high" and "low," we would undertake an individual patient meta-analysis, which would allow us to characterize the relationship between blood pressure (characterized continuously) and postoperative morbidity and mortality. This would prevent the loss of power that occurs because of dichotomization. Unfortunately, even given access to patient-level data for each included trial, the small number of trials and patients would be unlikely to provide adequate power to do so. Furthermore, because included RCTs only considered blood pressure during the CPB period, blood pressure management before or after CPB may have diminished the observed impact of "high" compared with "low" blood pressure targets on postoperative morbidity and mortality. Finally, in conducting our meta-analysis, we did not adjust for multiple comparisons. Nevertheless, only one of our results was statistically significant using a

threshold $P = 0.05$; we have limited confidence in this result (for hospital LOS) because it involved the conversion of median [IQR] to mean (SD). Thus, adjusting for multiple comparisons would not have changed our interpretation of our findings. The results of our systematic review highlight the gaps in the existing literature and provide the basis for future work examining the relationship between intraoperative blood pressure and major morbidity and mortality after cardiac surgery.

Conclusions

The effect of high compared with low blood pressure targets on morbidity and mortality after cardiac surgery remains unclear because of limitations in existing evidence. Research to determine the optimal management of blood pressure during cardiac surgery is required.

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