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High versus low blood pressure targets for cardiac surgery while on cardiopulmonary bypass (Review)

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[Intervention Review]

High versus low blood pressure targets for cardiac surgery while on cardiopulmonary bypass

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ABSTRACT

Background

Cardiac surgery is performed worldwide. Most types of cardiac surgery are performed using cardiopulmonary bypass (CPB). Cardiac surgery performed with CPB is associated with morbidities. CPB needs an extracorporeal circulation that replaces the heart and lungs, and performs circulation, ventilation, and oxygenation of the blood. The lower limit of mean blood pressure to maintain blood flow to vital organs increases in people with chronic hypertension. Because people undergoing cardiac surgery commonly have chronic hypertension, we hypothesised that maintaining a relatively high blood pressure improves desirable outcomes among the people undergoing cardiac surgery with CPB.

Objectives

To evaluate the benefits and harms of higher versus lower blood pressure targets during cardiac surgery with CPB.

Search methods

We used standard, extensive Cochrane search methods. The latest search of databases was November 2021 and trials registries in January 2020.

Selection criteria

We included randomised controlled trials (RCTs) comparing a higher blood pressure target (mean arterial pressure 65 mmHg or greater) with a lower blood pressure target (mean arterial pressure less than 65 mmHg) in adults undergoing cardiac surgery with CPB.

Data collection and analysis

We used standard Cochrane methods. Primary outcomes were 1. acute kidney injury, 2. cognitive deterioration, and 3. all-cause mortality. Secondary outcomes were 4. quality of life, 5. acute ischaemic stroke, 6. haemorrhagic stroke, 7. length of hospital stay, 8. renal replacement therapy, 9. delirium, 10. perioperative transfusion of blood products, and 11. perioperative myocardial infarction. We used GRADE to assess certainty of evidence.

Main results

We included three RCTs with 737 people compared a higher blood pressure target with a lower blood pressure target during cardiac surgery with CPB. A high blood pressure target may result in little to no difference in acute kidney injury (risk ratio (RR) 1.30, 95% confidence interval (CI) 0.81 to 2.08; I^2 = 72%; 2 studies, 487 participants; low-certainty evidence), cognitive deterioration (RR 0.82, 95% CI 0.45 to 1.50; I^2 = 0%; 2 studies, 389 participants; low-certainty evidence), and all-cause mortality (RR 1.33, 95% CI 0.30 to 5.90; I^2 = 49%; 3 studies, 737 participants; low-certainty evidence). No study reported haemorrhagic stroke. Although a high blood pressure target may increase the length of hospital stay slightly, we found no differences between a higher and a lower blood pressure target for the other secondary outcomes.

We also identified one ongoing RCT which is comparing a higher versus a lower blood pressure target among the people who undergo cardiac surgery with CPB.

Authors' conclusions

A high blood pressure target may result in little to no difference in patient outcomes including acute kidney injury and mortality. Given the wide CIs, further studies are needed to confirm the efficacy of a higher blood pressure target among those who undergo cardiac surgery with CPB.

PLAIN LANGUAGE SUMMARY

Blood pressure targets for people undergoing heart surgery

Review question

What effect does a high blood pressure target compared with a low blood pressure target have in people undergoing heart surgery while on cardiopulmonary bypass (CPB).

Key messages

A high blood pressure target compared with a lower target may result in little to no difference in kidney injury, cognition (ability to learn and understand) damage, or survival.

A high blood pressure target may increase the length of hospital stay slightly.

What is heart surgery?

Heart surgery is a common type of surgery throughout the world. Most types of heart surgery are performed with CPB. CPB is a medical device that replaces the work of the heart and lungs by pumping the blood, and taking oxygen into and removing carbon dioxide from the blood. People undergoing heart surgery usually have high blood pressure (called hypertension). People with hypertension need a higher blood pressure to keep the blood flow to important organs such as the brain and kidneys. However, the evidence about the best blood pressure targets to use during heart surgery is scarce.

What did we want to find out?

We wanted to assess the effects of a higher blood pressure target compared with a lower blood pressure target on the kidneys, brain, quality of life, and complications occurring while in hospital.

What did we do?

We searched medical databases for clinical trials comparing high versus low blood pressure targets during heart surgery while on CPB.

What did we find?

We found three studies including 737 people undergoing heart surgery. The duration of the studies varied from two to three years. The average age of included participants ranged between 65.8 and 76 years and about 72% were men.

There was little to no difference between a high and low blood pressure target in injury to the kidneys, cognition damage, or deaths. Although a high blood pressure target may increase the length of hospital stay slightly, there may be little to no differences in quality of life or complications during hospitalisation.

What are the limitations of the evidence

Our confidence in the evidence for kidney injury and death was very limited as the studies were small, did not provide data about everything that we were interested in, and included different types of people. We are also less confident in the evidence for cognition damage as the studies were small and did not provide data about everything that we were interested in.

How up to date is this evidence?

The evidence is current to November 2021.

SUMMARY OF FINDINGS

Summary of findings 1. High versus low blood pressure target for cardiac surgery with cardiopulmonary bypass

High versus low blood pressure target for cardiac surgery with cardiopulmonary bypass

Patient or population: adults undergoing cardiac surgery with cardiopulmonary bypass
Setting: hospital
Experimental: high blood pressure target with mean arterial pressure ≥ 65 mmHg
Comparison: low blood pressure target with mean arterial pressure < 65 mmHg

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with low blood pressure target	Risk with high blood pressure target				
Acute kidney injury Follow-up: until discharge from the surgical department or 6 months after the surgery	**Study population**		**RR 1.30** (0.81 to 2.08)	487 (2 RCTs)	⊕⊖⊖⊖ **Very low**[a]	—
	107 per 1000	139 per 1000 (86 to 222)				
Cognitive deterioration Follow-up: 90 days to 6 months	**Study population**		**RR 0.82** (0.45 to 1.50)	389 (2 RCTs)	⊕⊕⊖⊖ **Low**[b]	Definition of cognitive deterioration of each study was: Vedel 2018: change from baseline neuropsychological test performance; ISPOCD test (Moller 1998) 90 days after surgery. Gold 1995: deterioration on ≥ 3 cognitive tests at 6 months after surgery defined as a cognitive complication. For each test, assessment was based on within-patient change in test performance from preoperative baseline. Since we could not obtain the study protocol, details of each test were unclear. Minimally important difference of cognitive deterioration was defined as a minimal difference in frequency of cognitive deterioration required to have a clinical significance.
	104 per 1000	89 per 1000 (48 to 162)				

All-cause mortality Follow-up: 30 days to 6 months	**Study population**		**RR 1.33** (0.30 to 5.90)	737 (3 RCTs)	⊕⊖⊖⊖ **Very low**[c]	—
	22 per 1000	29 per 1000 (7 to 128)				
Quality of life Follow-up: 6 months	**Study population**		**RR 0.78** (0.30 to 2.01)	218 (1 RCT)	⊕⊖⊖⊖ **Very low**[d]	Since Gold 1995 counted quality of life as a dichotomous outcome defined as a decline of > 5 points on the Physical Component Summary score of the SF-36 (Stewart 1989), we used this definition in this review.
	83 per 1000	64 per 1000 (24 to 161)				
Acute ischaemic stroke Follow-up: 30 days to 6 months	**Study population**		**RR 1.29** (0.07 to 23.63)	426 (2 RCTs)	⊕⊖⊖⊖ **Very low**[e]	—
	46 per 1000	43 per 1000 (18 to 100)				
Length of hospital stay Follow-up: 6 months	The mean length of stay in the low blood pressure target group was 12 days	**MD 1.25 days longer** (0.78 longer to 1.73 longer)	—	540 (2 RCTs)	⊕⊖⊖⊖ **Very low**[f]	—
Perioperative transfusion of blood products Follow-up: not reported	The mean perioperative transfusion of blood products was 2.0 units.	**MD 0.1 units higher** (0.13 lower to 0.34 higher)	—	540 (2 RCTs)	⊕⊖⊖⊖ **Very low**[g]	—

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **ISPOCD:** International Study of Post-Operative Cognitive Dysfunction; **MD:** mean difference; **OIS:** optimal information size; **RCT:** randomised controlled trial; **RR:** risk ratio; **SF-36:** 36-item Short Form.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for imprecision because the OIS of 33,954 was over 10 times larger than the number of participants; one level for indirectness because the definitions used in the included studies were inconsistent with each other, causing quite different occurrences; one level for risk of bias since Azau 2014 was not of overall low risk of bias; and one level for inconsistency with large heterogeneity (I^2 = 72%).

[b]Downgraded one level for risk of bias because the number of follow-ups was not balanced in one study; and one level for imprecision because the OIS of 910 was not met.

[c]Downgraded one level for risk of bias because the two studies were not at overall low risk of bias; one level for inconsistency with large heterogeneity I^2 = 49%; and one level for imprecision because the OIS of 5948 was not met.

[d]Downgraded one level for risk of bias because the study was not at overall low risk of bias; and two levels for imprecision because the sample size was small and the CIs around the RR included 1.0.

[e]Downgraded one level for risk of bias because the number of follow-ups was not balanced in one study; one level for imprecision because the OIS of 4670 was not met; one level because the CI spanned potential benefit, no benefit, and possible harm; and one level for inconsistency for large heterogeneity (I^2 = 82%).

[f]Downgraded one level for risk of bias because it was unclear whether physicians decided the date of discharge could know the allocation of the patients in one study; one level for imprecision because the OIS (1540 or 4906 depending on standard deviation used) was not met; and one level for inconsistency with large heterogeneity (I^2 = 76%).

[g]Downgraded one level for risk of bias because the study was not at overall low risk of bias; one level for performance bias because the allocation of the participants could affect the strategy of transfusion; and one level for imprecision because the CI spanned potential benefit, no benefit, and possible harm. The OIS was met (174 or 230 depending on standard deviation used).

BACKGROUND

Description of the condition

Cardiac surgery is performed worldwide. The annual number of cardiac surgeries was over 200,000 in North America in 2016, over 40,000 in Japan in 2015, over 20,000 in China in 2013, over 100,000 in Europe in 2008, and over 35,000 in Brazil in 2005 (D'Agostino 2018; Gurfinkel 2007; Head 2013; Masuda 2018; Rao 2016). The costs associated with the procedure are enormous. In the USA, for example, the mean cost per person for a cardiac surgery between 2005 and 2008 was US dollars (USD) 40,000; the total cost was more than USD 20 billion, which accounted for 1% to 2% of total national healthcare costs (Kilic 2014). Most types of cardiac surgery are commonly performed using cardiopulmonary bypass (CPB) (D'Agostino 2018; Hillis 2011; Masuda 2018). CPB is an extracorporeal circulation that replaces the heart and lungs, includes circulation of blood, oxygenation, and ventilation by draining venous blood from the body, oxygenating the blood and sending the oxygenated blood back to the body so that other end organs remain adequately oxygenated and perfused. The CPB circuit consists of pumps, cannulae, reservoir, oxygenator, heat exchanger, and arterial line filter. The right atrium or both superior and inferior vena cavae are cannulated to drain blood through the venous line of the CPB circuit into a venous reservoir. The arterial pump moves blood from the venous reservoir to the oxygenator through a heat exchanger and finally to an arterial line filter. The blood is then returned to the body via an arterial cannula located in the ascending aorta or other major arteries. During CPB, the ascending aorta is usually cross-clamped and cardioplegia solution is administered to allow surgeons to operate safely on a heart without beating in a bloodless field. Modern CPB machines also have systems for monitoring circuit pressure, temperature, oxygen saturation, haemoglobin, blood gases and electrolytes, as well as safety features, such as air detectors (Wahba 2020).

Cardiac surgery performed with CPB is associated with morbidities. For example, cardiac surgery-associated acute kidney injury (CSA-AKI) is one of the major complications of cardiac surgery. Acute kidney injury (AKI) is an abrupt kidney dysfunction, defined as a relative increase of serum creatinine level within seven days or oliguria (KDIGO 2012). CSA-AKI occurs in 20% to 40% of people after cardiac surgery and is the second most common cause of AKI among critically ill people (Englberger 2011; Machado 2014; Mao 2013). CSA-AKI is associated with worse mortality even at 10 years after the surgery (Hobson 2009). About 1% to 5% of people with CSA-AKI received renal replacement therapy (Conlon 1999). Another important complication of cardiac surgery with CPB is perioperative delirium. Delirium after cardiac surgery is common and is associated with mortality and long-term cognitive decline (Rudolph 2010; Saczynski 2012).

Effective strategies backed by robust evidence to prevent or treat the CSA-AKI are lacking. Studies evaluating statins, remote ischaemic preconditioning, and fenoldopam have found no benefits for the kidneys (Bove 2014; Lewicki 2015; Menting 2017). One single-centre trial showed that an AKI care bundle guideline reduced the incidence of severe AKI among the people undergoing cardiac surgery. However, because this was a phase II trial, we could not draw any definitive conclusion from this result (Meersch 2017). There is no proven effective strategy to prevent or treat delirium among people undergoing cardiac surgery, either. Therefore, finding a treatment strategy to improve the desirable outcomes of cardiac surgery remains a challenge.

Description of the intervention

Blood pressure is an important determinant for blood supply to vital organs. The concept of autoregulation is important when considering perfusion to the brain and kidney (Palmer 2002; Strandgaard 1973). Autoregulation maintains a constant blood flow to organs, even if the blood pressure varies within a specific range. Because it is well known that the lower limit of autoregulation blood pressure shifts in people with chronic hypertension, maintaining a relatively high blood pressure may be beneficial for this population. One randomised controlled trial (RCT) evaluating a higher versus lower blood pressure target in septic shock showed that a higher blood pressure target did not result in survival benefit, but was associated with higher incidence of atrial fibrillation and a requirement for higher doses of noradrenaline (Asfar 2014). However, the prespecified subgroup analysis of the RCT showed that a higher blood pressure target led to less renal replacement therapy among the people with chronic hypertension. In addition, one animal experiment showed that the lower limit of renal autoregulation can be higher than that of cerebral autoregulation (Rhee 2012), which might suggest that a high blood pressure target has different effects on renal and cerebral outcomes.

Several RCTs have evaluated different blood pressure targets during non-cardiac surgery, but they did not reach a clinically meaningful result (Carrick 2016; Williams-Russo 1999). One guideline on perioperative care in non-cardiac surgery suggested individualising care in people with associated conditions and comorbidities (Fleisher 2014). One RCT showed that individualised blood pressure management, close to the preoperative value, led to less organ dysfunction compared to standard management (Futier 2017).

Among the people undergoing cardiac surgery, the optimal blood pressure target is controversial. Several observational studies have suggested an association between blood pressure abnormality and adverse outcomes. Hypotension during cardiac surgery can lead to decreased organ perfusion and is associated with organ dysfunction and mortality after the surgery (Ono 2013; Ono 2014). On the contrary, excessive hypertension is also associated with postoperative delirium (Hori 2014), or may result in excess haemorrhage.

How the intervention might work

A higher blood pressure target might be beneficial for organ perfusion given that most people who undergo a cardiac surgery have hypertension (Gillinov 2016; Landoni 2019; Mazer 2017). However, maintaining a higher blood pressure target might require an increased level of fluid intake as well as higher doses of vasoactive agents (drugs that increase blood pressure by increasing vascular resistance, e.g. noradrenaline), which may lead to adverse outcomes (Asfar 2014).

Why it is important to do this review

Several Cochrane Reviews have compared a higher versus a lower blood pressure target in chronic management amongst various populations (Arguedas 2013; Garrison 2017; Saiz 2018). An international guideline for AKI stated that the optimal blood pressure target may vary according to the characteristics of

people, such as comorbidities or premorbid blood pressure (KDIGO 2012). However, the question of how one determines the optimal blood pressure target in the acute settings, especially for people undergoing cardiac surgery with CPB, remains unanswered. Consequently, this review is our attempt to determine the optimal blood pressure target for cardiac surgery requiring CPB.

OBJECTIVES

To evaluate the benefits and harms of higher versus lower blood pressure targets during cardiac surgery with CPB.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs irrespective of their publication type, publication status, publication date, or language. We included all individual RCTs and only those cluster-RCTs that reported the intracluster correlation coefficient (ICC) because the ICC is necessary for an approximately correct analysis of cluster-RCTs by reducing the size of a cluster-RCT to the effective sample size (Rao 1992).

We excluded cross-over studies because it is unlikely that the participants in this review underwent the same surgery twice. We excluded quasi-randomised studies for which the applied randomisation methods are inadequate and susceptible to selection bias.

Types of participants

We included adults (aged 18 years or older) undergoing cardiac surgery with CPB. For this review, we defined cardiac surgery as coronary artery bypass graft (CABG) or heart valve surgery. We also included isolated aortic surgery because we believe such procedural differences hardly affect blood pressure management, although we planned to exclude isolated aortic surgery in the protocol (Kotani 2019). We excluded adults undergoing surgical procedures for congenital heart diseases or cardiac tumours because these surgical procedures are quite different from a coronary or a valve surgery and these conditions are rare.

We defined CPB as all CPB irrespective of how it was performed in terms of site of cannulation, non-pulsatile or pulsatile flow, body temperature, or with or without cardioplegic arrest.

Types of interventions

- Experimental intervention: high blood pressure target (defined as mean arterial pressure (MAP) 65 mmHg or greater during CPB).
- Comparator: low blood pressure target (defined as MAP less than 65 mmHg during CPB).

Although there is currently a lack of consensus on the optimum blood pressure target in cardiac surgery, we used the threshold of MAP based on the evidence in other populations: four large cohort studies in non-cardiac surgery showed that intraoperative MAP less than 65 mmHg or less than 60 mmHg was associated with mortality or morbidities (Mascha 2015; Salmasi 2017; Sun 2015; van Waes 2016). In addition, the latest clinical guidelines for sepsis and AKI recommends maintaining MAP at 65 mmHg or greater (KDIGO 2012; Rhodes 2017). We defined experimental intervention and comparator by blood pressure targets during CPB. We allowed any blood pressure targets intraoperatively without CPB because most studies on blood pressure targets in cardiac surgery have investigated blood pressure during CPB (Gottesman 2007; Haase 2012; Hori 2014; Kanji 2010; Ono 2013; Ono 2014; Reich 1999; Sickeler 2014). We performed a sensitivity analysis that excluded studies defining blood pressure targets without CPB.

We regarded any co-interventions that were not part of the randomised treatment as equally delivered in the intervention and comparator groups. We assessed the risk of bias of co-interventions.

Types of outcome measures

The reporting of outcomes was not an inclusion criterion in the review.

Primary outcomes

We referred to a core outcome set for adult cardiac surgery trials to identify our outcome measures of interest (Benstoem 2017).

- **AKI** within seven days after the surgery. AKI was defined as an abrupt kidney dysfunction within seven days after the surgery. If a study used the Risk, Injury, Failure, Loss and End-stage kidney disease (RIFLE) criteria (Bellomo 2004), AKI was defined as 'R' or worse within seven days after the surgery. If a study used the Acute Kidney Injury Network (AKIN) (Mehta 2007), or Kidney Disease Improving Global Outcomes (KDIGO) criteria (KDIGO 2012), AKI was defined as stage I or worse of each criterion within seven days after the surgery. If a study did not use RIFLE, AKIN, or KDIGO criteria, AKI was defined by trial authors within seven days after the surgery. We defined the minimally important difference for AKI as a 20% decrease in relative risk (Azau 2014).
- **Cognitive deterioration** was defined as a decrease in cognition in any validated assessment scale, such as the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph 1998), from three to six months after the surgery (Annane 2018; Pandharipande 2013). If a study reported cognitive deterioration between three and six months after the surgery more than once, we included only the last timing as the outcome because a longer-term cognitive deterioration has a more negative impact. We defined the minimally important difference for cognitive deterioration as a 50% decrease in relative risk (Cheng 2019).
- **All-cause mortality** during the longest study period. We defined the minimally important difference for mortality as 1% in absolute risk (Landoni 2019).

Secondary outcomes

- **Quality of life** was defined as physical functioning and mental health measured on any validated scale, such as the 36-item Short Form (SF-36) Survey, during the longest study period. We defined quality of life as a dichotomous outcome and the minimally important difference for quality of life as a decline of more than 5 points on the Physical Component Summary score in the SF-36 (Busija 2008).
- **Acute ischaemic stroke** during hospitalisation, defined by trial authors. We defined the minimally important difference for acute ischaemic stroke as a 35% decrease in relative risk (Mack 2017).

- **Haemorrhagic stroke** during hospitalisation, defined by trial authors. We defined the minimally important difference for haemorrhagic stroke as a 10% decrease in relative risk (Li 2013).
- **Length of hospital stay** during the longest study period. We defined the minimally important difference for length of stay in hospital as two days between the two groups (Gillinov 2016).
- **Renal replacement therapy** during hospitalisation, defined by trial authors. We did not restrict modality of renal replacement therapy, such as intermittent or continuous; haemofiltration, haemodialysis, or haemodiafiltration. We defined the minimally important difference for renal replacement therapy as a 50% decrease in relative risk (Bove 2014).
- **Delirium** at any time during hospitalisation. Delirium was diagnosed with the Confusion Assessment Method (CAM; Inouye 1990), Confusion Assessment Method for Intensive Care Unit (CAM-ICU; Ely 2001), Intensive Care Delirium Screening Checklist (ICDSC; Bergeron 2001), International Classification of Diseases the 11th Revision (ICD-11; WHO 2018), or Diagnostic and Statistical Manual of Mental Disorders, the Fifth Edition (DSM-V; APA 2013). We allowed all the previous versions of these criteria. We included only the earliest timing as the outcome when a study reported delirium during hospitalisation more than once. We defined the minimally important difference for delirium as a 50% decrease in relative risk (Subramaniam 2019).
- **Perioperative transfusion of blood products** at any time from the cardiac surgery to hospital discharge. We defined the minimally important difference for the perioperative transfusion of blood products as two units between the two groups (Zhang 2018). We defined a unit of blood product as the minimal unit of packed red blood cells, which is equivalent to nearly 300 mL (Carson 2016).
- **Perioperative myocardial infarction** during hospitalisation, defined by trial authors. We defined the minimally important difference for perioperative myocardial infarction as a 50% decrease in relative risk (Briguori 2009).

Reporting one or more of the outcomes listed here in the trial was not an inclusion criterion in this review. Where a published article did not appear to report one of these outcomes, we accessed the trial protocol and contacted the trial authors to ascertain whether the outcomes were measured but not reported. We included relevant trials that measured these outcomes but did not report the data at all, or not reported them in a usable format, in the review as part of the narrative.

Search methods for identification of studies

Electronic searches

We identified RCTs through systematic searches of the following bibliographic databases on 28 November 2021:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (Issue 11, 2021);
- Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE (Ovid, 1946 to 24 November 2021);
- Embase (Ovid, 1980 to 2021 week 46);
- Web of Science Core Collection (Clarivate Analytics, 1900 to 28 November 2021).

We adapted the preliminary search strategy for MEDLINE (Ovid), as illustrated in Appendix 1, for use in the other databases. We applied the Cochrane sensitivity- and precision-maximising RCT filter to MEDLINE (Ovid) and adaptations of it to the other databases (Lefebvre 2011), with the exception of CENTRAL.

We also conducted a search of ClinicalTrials.gov (www.clinicaltrials.gov) on 20 July 2021 and the World Health Organization International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch) for ongoing or unpublished trials on 21 July 2021.

We searched all databases from their inception, and imposed no restriction on language of publication or publication status. We did not perform a separate search for adverse events but we considered adverse events described in included studies.

Searching other resources

We checked the reference lists of all included studies and any identified relevant systematic reviews for additional references to trials. We also examined any relevant retraction statements and errata for included studies.

Data collection and analysis

Selection of studies

We used the Cochrane's Screen4Me workflow to help assess the search results. Screen4Me comprises three components: known assessments – a service that matches records in the search results to records that have already been screened in Cochrane Crowd and been labelled as an RCT or as not an RCT; the RCT classifier – a machine learning model that distinguishes RCTs from non-RCTs, and if appropriate, Cochrane Crowd – Cochrane's citizen science platform where the crowd help to identify and describe health evidence.

More information about Screen4Me and the evaluations that have been done are available on the Screen4Me webpage on the Cochrane Information Specialist's portal (community.cochrane.org/organizational-info/resources/resources-groups/information-specialists-portal). In addition, more detailed information regarding evaluations of the Screen4Me components can be found in Marshall 2018, McDonald 2017, Noel-Storr 2018, and Thomas 2017.

Following Screen4Me, three review authors (YKo, SF, TY) independently screened the titles and abstracts of all the potential studies identified and coded them as 'to retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. If there were any disagreements, a fourth review author arbitrated (JK or JI or JSK or YKa). We retrieved the full-text study reports/publications and three review authors (YKo and SF and TY) independently screened the full-text, identified studies for inclusion, and recorded the reasons for exclusion of the ineligible studies. We resolved any disagreements through discussion or, if required, we consulted a fourth review author (JK or JI or JSWK or YKa). We identified and excluded duplicates and collated multiple reports of the same study so that each study rather than each report was the unit of analysis in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Liberati 2009), and we provided our reasons for excluding studies in the Characteristics of excluded studies table.

Data extraction and management

We used a prestandardised data collection form to extract study characteristics and outcome data. We piloted this data extraction sheet on at least one included study before using it on the remaining studies. Two review authors (SF and TY) performed data extraction and collected the following study characteristics.

- Methods: total duration of study, details of any 'run-in' period, number of study centres and location, study setting, and date of study.
- Participants: number randomised, number lost to follow-up/ withdrawn, number analysed, mean age, gender, inclusion criteria, and exclusion criteria.
- Interventions: experimental intervention, comparison, concomitant medications, and excluded medications.
- Outcomes: specified and collected primary and secondary outcomes, and their reported time points.
- Notes: funding source for trial, and notable conflict of interests among trial authors.

Two review authors (SF and TY) independently extracted outcome data from the included studies. We resolved disagreements by consensus or by involving a third review author (YKo or JK or JI or JSWK or YKa). One review author (YKo) input data into Review Manager 2020.

Assessment of risk of bias in included studies

Two review authors (SF and TY) independently assessed risk of bias for each study using the Cochrane RoB 1 tool for assessing risk of bias, as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion or by involving a third review author (JK or JI or JSWK or YKa). We assessed risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessor.
- Incomplete outcome data.
- Selective outcome reporting.
- Other biases.

We assessed and categorised each potential source of bias as 'low risk', 'high risk', or 'unclear risk', and provided a quote from the study report together with a justification for our judgement in the risk of bias table. We summarised the risk of bias judgements across different studies for each of the domains listed. Where information on risk of bias was related to unpublished data or to correspondence with trial authors, we noted this in the risk of bias table.

When considering treatment effects, we considered the risk of bias for the studies that contributed to that outcome.

Measures of treatment effect

We analysed dichotomous variables, that is, variable in two mutually exclusive categories (AKI, delirium, all-cause mortality, acute ischaemic stroke, renal replacement therapy, haemorrhagic stroke, and perioperative myocardial infarction) as risk ratios (RRs) with 95% confidence intervals (CIs). For continuous outcomes (length of stay in hospital, perioperative transfusion of blood products), we presented mean differences (MDs) with 95% CIs. We planned to pool quality of life as a continuous variable and present MDs with 95% CIs when studies used the same scale or standardised mean differences with 95% CIs when studies used different scales. However, since Gold 1995 was the only study to report quality of life and they reported it as a dichotomous outcome, we counted quality of life as a dichotomous variable.

Unit of analysis issues

When analysing multiple-armed trials, we combined all relevant experimental intervention groups of the study into a single group and all relevant control groups into a single control group. If we could not classify one of the arms into either of the experimental or comparator intervention, we excluded it from the analysis.

When incorporating the result of cluster-RCTs with ICCs with that of individual RCTs, we obtained the effective sample size of cluster-RCTs using the design effect calculated from the number of clusters and ICC. After reducing cluster-RCTs to the effective sample size, we combined the result of both individual and cluster-RCTs in a meta-analysis.

Dealing with missing data

We contacted investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study was identified as abstract only). Where possible, we used the Review Manager 5 calculator to calculate missing standard deviations (SDs) using other data from the trial (Review Manager 2020), such as CIs. When sample sizes were large and the distribution of the outcome was similar to the normal distribution, we regarded the width of the interquartile range as 1.35 SDs. Where this was not possible, and the missing data were thought to introduce serious bias, we explored the impact of including such studies in the overall assessment of results using a sensitivity analysis. We analysed on an intention-to-treat basis for all outcomes whenever possible.

Assessment of heterogeneity

We inspected forest plots visually to consider the direction and magnitude of effects and the degree of overlap between CIs. We used the I^2 statistic to measure heterogeneity among the trials in each analysis, but acknowledged that there is substantial uncertainty in the value of the I^2 statistic when there is a small number of studies; we also considered the P value from the Chi^2 test, for which a value less than 0.1 defined statistical significance (Higgins 2002).

We followed the recommendations for heterogeneity threshold of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: may represent considerable heterogeneity.

If we identified substantial and considerable heterogeneity, we reported it and explored possible causes by prespecified subgroup analysis.

Assessment of reporting biases

To assess reporting biases, we used funnel plots and assessed its asymmetry by visual inspection. If 10 or more studies were included in the meta-analysis, we performed Egger's test to assess the small-study effects (Egger 1997).

Data synthesis

We undertook meta-analyses only where this was meaningful, that is, if the treatments, participants, and the underlying clinical question were similar enough for pooling to make sense.

As we expected heterogeneity in the blood pressure target of experimental and comparator interventions across included studies, we used a random-effects model (DerSimonian 1986).

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses for all outcomes.

- Preoperative chronic hypertension: participants with preoperative chronic hypertension versus participants without preoperative chronic hypertension. Trial authors defined preoperative chronic hypertension.
- Age: participants aged 65 years or older versus participants aged less than 65 years.
- Gender: men versus women.
- Type of cardiac surgery: CABG alone, valve surgery alone, or CABG plus valve surgery.

We planned to use the formal test for subgroup differences in Review Manager 2020 and based our interpretation on this.

Sensitivity analysis

We planned to carry out the following sensitivity analyses, to test whether key methodological factors or decisions had affected the effect size.

- Only including studies with overall low risk of bias. We classified the outcome result as overall low risk of bias if we classified the bias for random sequence generation, allocation concealment, incomplete outcome data, and selective reporting as low risk.
- Only including studies evaluating AKI within seven days after the surgery using the RIFLE (Bellomo 2004), AKIN (Mehta 2007), or KDIGO (KDIGO 2012) classifications.
- We replaced any kidney dysfunction defined by trial authors within 90 days after the surgery or during the hospitalisation with AKI to explore for any effect of outcome definition on effect size.
- Excluding studies that define target blood pressure not on CPB.
- Where we were unable to obtain missing numerical outcome data, and the missing data were thought to introduce serious bias, we explored the impact of including such studies in the overall assessment of results by a sensitivity analysis. To assess the effect of the missing data for dichotomous outcomes, we performed the following sensitivity analyses and reported the results from both scenarios in the review.
  - Best-case scenario: we assumed that all individuals lost to follow-up in the experimental group survived, did not have AKI, cognitive deterioration, acute ischaemic stroke, haemorrhagic stroke, renal replacement therapy, delirium, or perioperative myocardial infarction; and all those with missing outcomes in the control group did not survive, had AKI, cognitive deterioration, acute ischaemic stroke, haemorrhagic stroke, renal replacement therapy, delirium, or perioperative myocardial infarction.
  - Worst-case scenario: we assumed that all individuals lost to follow-up in the experimental group did not survive, had AKI, cognitive deterioration, acute ischaemic stroke, haemorrhagic stroke, renal replacement therapy, delirium, or perioperative myocardial infarction; and all those with missing outcomes in the control group survived, did not have AKI, cognitive deterioration, acute ischaemic stroke, haemorrhagic stroke, renal replacement therapy, delirium, or perioperative myocardial infarction.
- To assess the effect of missing SDs for continuous outcomes, we performed a sensitivity analysis where we excluded studies that were imputed.
- We performed a sensitivity analysis excluding studies that included participants undergoing isolated aortic surgery to investigate whether the procedural difference could affect the effect size.
- We performed sensitivity analyses excluding studies published before 2000 because the practice and outcomes of cardiac surgery have evolved significantly over time.
- Cognitive deterioration was defined as a relative decrease of cognitive score from the baseline. This definition does not consider learning effects caused by repeated examination of the same test. In contrast, neuropsychological tests such as the International Study of Postoperative Cognitive Dysfunction (ISPOCD) (Moller 1998) subtract the mean learning effect from the postoperative changes from the baseline, which can provide more appropriate criteria. Thus, we conducted a sensitivity analysis for cognitive deterioration, including only studies that considered learning effects caused by multiple testings.

We limited the first sensitivity analysis to the primary outcomes (AKI, cognitive deterioration, and all-cause mortality) and the second and third sensitivity analysis to AKI. We planned to conduct the fourth to seventh sensitivity analyses for all the outcomes. However, we could not perform the following sensitivity analyses.

- Only including studies evaluating AKI within seven days after the surgery using the RIFLE (Bellomo 2004), AKIN (Mehta 2007), or KDIGO (KDIGO 2012) because there was no such study using the AKI criteria.
- Replacing any kidney dysfunction with AKI as no study reported kidney dysfunction.
- Excluding studies that defined target blood pressure not on CPB because there was no study defining target blood pressure not on CPB.
- The best-case and worst-case scenarios for AKI, all-cause mortality, and delirium because there were no missing outcome data in the included studies.
- Excluding studies that were imputed for missing SDs of perioperative because there was no such study.
- Excluding studies that included participants undergoing isolated aortic surgery for cognitive deterioration, quality of life, acute ischaemic stroke, delirium because only Gold 1995 included participants with isolated aortic surgery.

- Excluding studies published before 2000 for AKI, renal replacement therapy, delirium, because there was no study reporting such outcomes and for quality of life because Gold 1995 was the only study reporting quality of life.

Summary of findings and assessment of the certainty of the evidence

We created Summary of findings 1 using the following outcomes (AKI, cognitive deterioration, all-cause mortality, quality of life, acute ischaemic stroke, length of stay in hospital, and perioperative transfusion of blood products). We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence as it related to the studies that contributed data to the meta-analyses for the prespecified outcomes. We used methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro GDT software (GRADEpro GDT).

Two review authors (SF and TY) independently assessed certainty of the evidence, with disagreements resolved by discussion or by involving a third review author (YKo or JK or JI or JSWK or YKa). We justified all decisions to downgrade the certainty of the evidence using footnotes, and we made comments to aid the readers' understanding of the review where necessary.

As planned in the protocol, we extracted study data, formatted our comparisons in data tables, and prepared a summary of findings table before writing the results and conclusions of our review.

For the purposes of assessing imprecision in dichotomous outcomes, the optimal information size (OIS) was determined to provide 80% power to detect a minimally important difference in each outcome on the basis of the outcome occurrence in the low blood pressure target group with a two-sided P value of less than 0.05 indicating statistical significance. For continuous outcomes, the OIS was determined to provide 80% power to detect a minimally important difference in each outcome on the basis of the SD of the outcome in the low blood pressure target group with a two-sided P value of less than 0.05 indicating statistical significance.

RESULTS

Description of studies

See Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; and Characteristics of ongoing studies tables.

Results of the search

Our study selection process is illustrated in Figure 1. The comprehensive literature search identified a total of 13,867 results. After deduplication, we screened 8806 titles and abstracts. We used Cochrane's Screen4Me workflow to help identify potential reports of randomised trials. The results of the assessment process with the Screen4Me assessment process can be seen in Figure 2.

Figure 1. Study flow diagram.

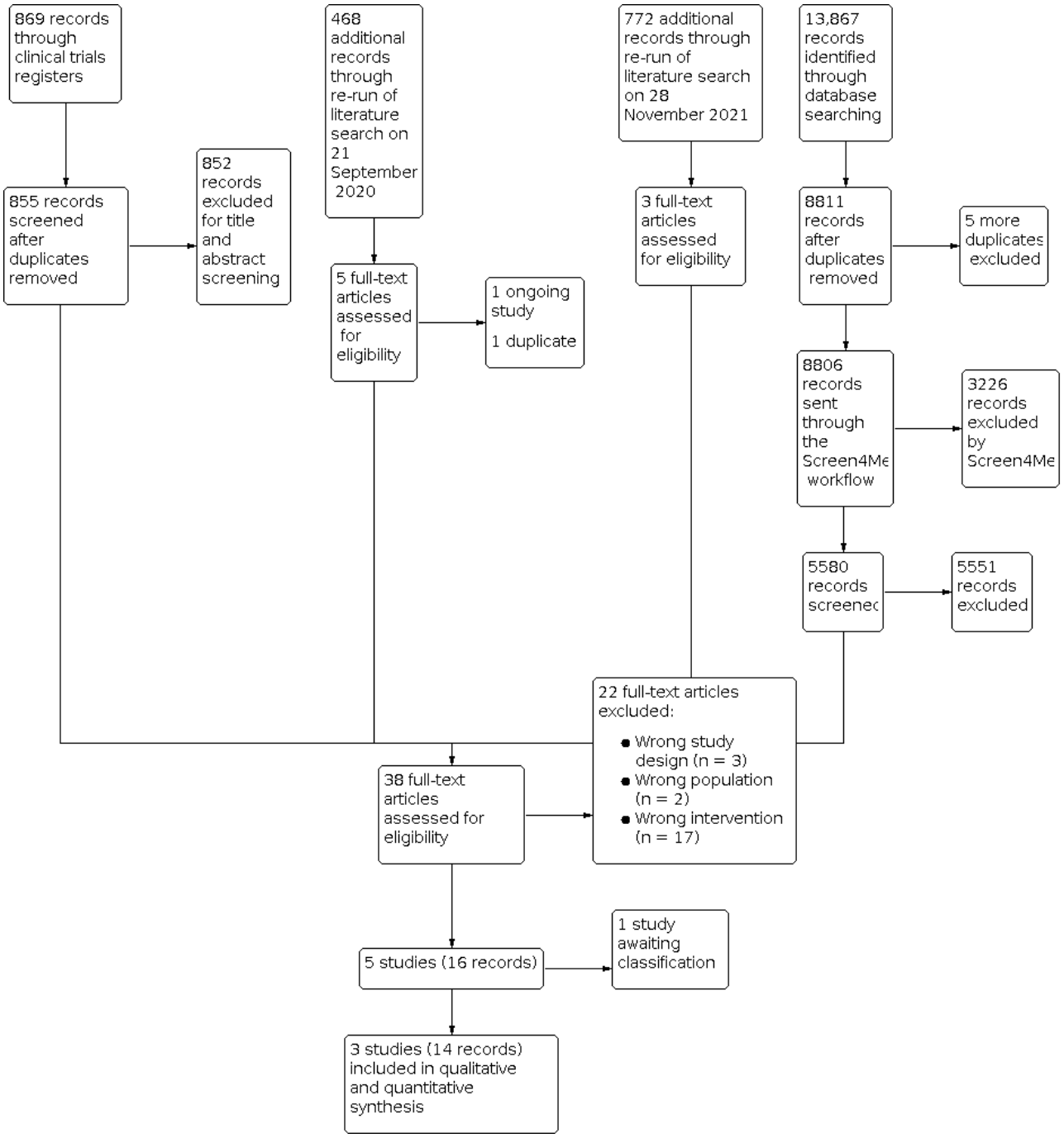
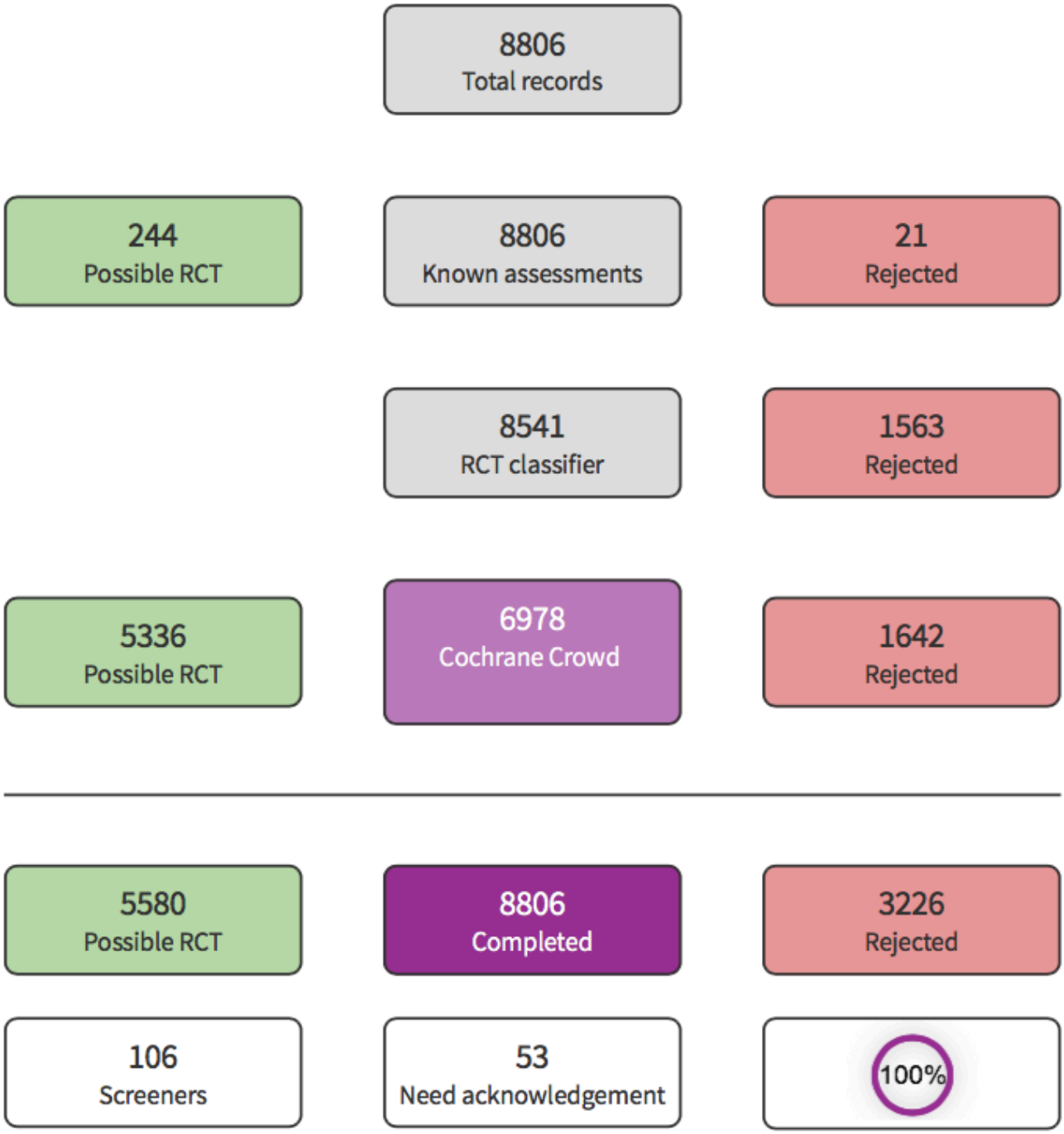


Figure 2. Screen4Me summary diagram.



A total of 5580 records remained after the assessment process with Screen4Me. We excluded 5551 irrelevant records from which 29 study reports remained for full-text review. After excluding 21 full texts (Characteristics of excluded studies table), we identified one study awaiting assessment and we contacted the corresponding author for further details in order to determine its eligibility but we received no response (Characteristics of studies awaiting classification table). Therefore, we eventually included three studies (Azau 2014; Gold 1995; Vedel 2018).

Considering the time lapse since the first literature search was run, we conducted updated literature searches on 21 September 2020 and 28 November 2021 and screened an additional 468 and 772 records, respectively. For the second literature search, we excluded 463 irrelevant records. One was identified as an ongoing study (Characteristics of ongoing studies table). We eventually included three articles from this updated search, for which all were publications of a single study (Vedel 2018). For the third literature search, we excluded 769 records. Among the remaining three records, one was excluded for wrong intervention (Damén 2021), while the other two records were publications of a single study (Vedel 2018).

Overall we included three studies, excluded 22 studies, one study is awaiting classification, and one study is ongoing.

Included studies

See Characteristics of included studies table.

In total, we included three RCTs (Azau 2014; Gold 1995; Vedel 2018). All were single-centre, open-label, parallel-group trials. The sample size and the inclusion period for each study were: 300 people between January 2008 and June 2010 for Azau 2014, 251 people between October 1991 and February 1994 for Gold 1995, and 197 people between July 2014 and January 2016 for Vedel 2018. The mean age of the included participants ranged from 65.8 to 76 years. Of the 745 study participants, 72.1% (537/745) were men. Azau 2014 included people undergoing elective cardiac surgery, including CABG, valvular surgery, or reconstructive surgery of the ascending aorta under normothermic CPB with known risk factors for AKI. Gold 1995 included people receiving elective CABG. Vedel 2018 included people undergoing elective or subacute CABG or left heart valve surgery, or both. The MAP targets for intervention versus comparison in Azau 2014 were 75 mmHg to 85 mmHg versus 50 mmHg to 60 mmHg, in Gold 1995 were 80 mmHg to 100 mmHg versus 50 mmHg to 60 mmHg, and in Vedel 2018 were 70 mmHg to 80 mmHg versus 40 mmHg to 50 mmHg. Azau 2014 was supported by a grant from the "Programme Hospitalier pour la Recherche Clinique" (PHRC Inter-Régional, 2007) from the French Health Ministry. Gold 1995 received grant HL44719 from the National Institutes of Health, National Heart, Lung, and Blood Institute. Vedel 2018 received grants from the Danish Heart Foundation (14-R97-A5179-22868 and 15-R99-A6034-22905) and the Research Foundations at Rigshospitalet (E-22329-01), University of Copenhagen, Denmark.

Excluded studies

We excluded 22 full texts and summarised the reasons for exclusion in Characteristics of excluded studies table.

Studies awaiting classification

We contacted the corresponding author of one study for further details to determine its eligibility but we received no response (von Knobelsdorff 1996).

Ongoing studies

One study is ongoing (ChiCTR2000028941).

Risk of bias in included studies

We summarised the results of our assessment of risk of bias for included studies in Figure 3 and Figure 4.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

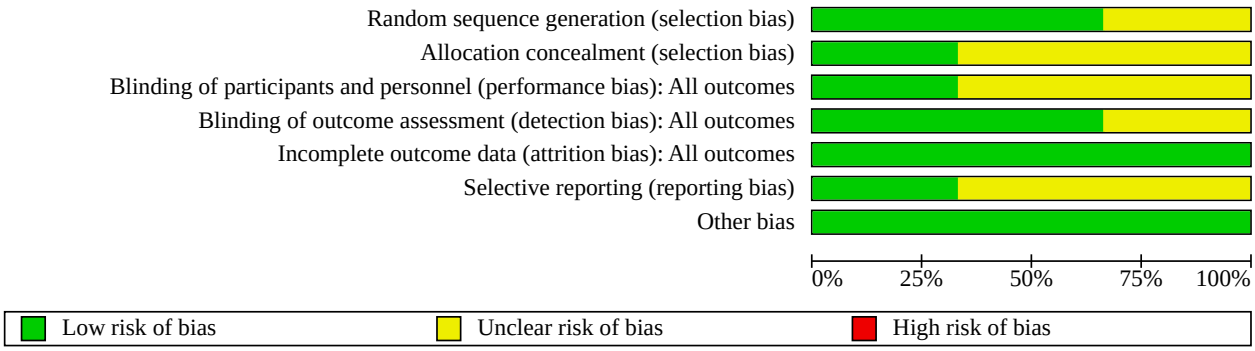
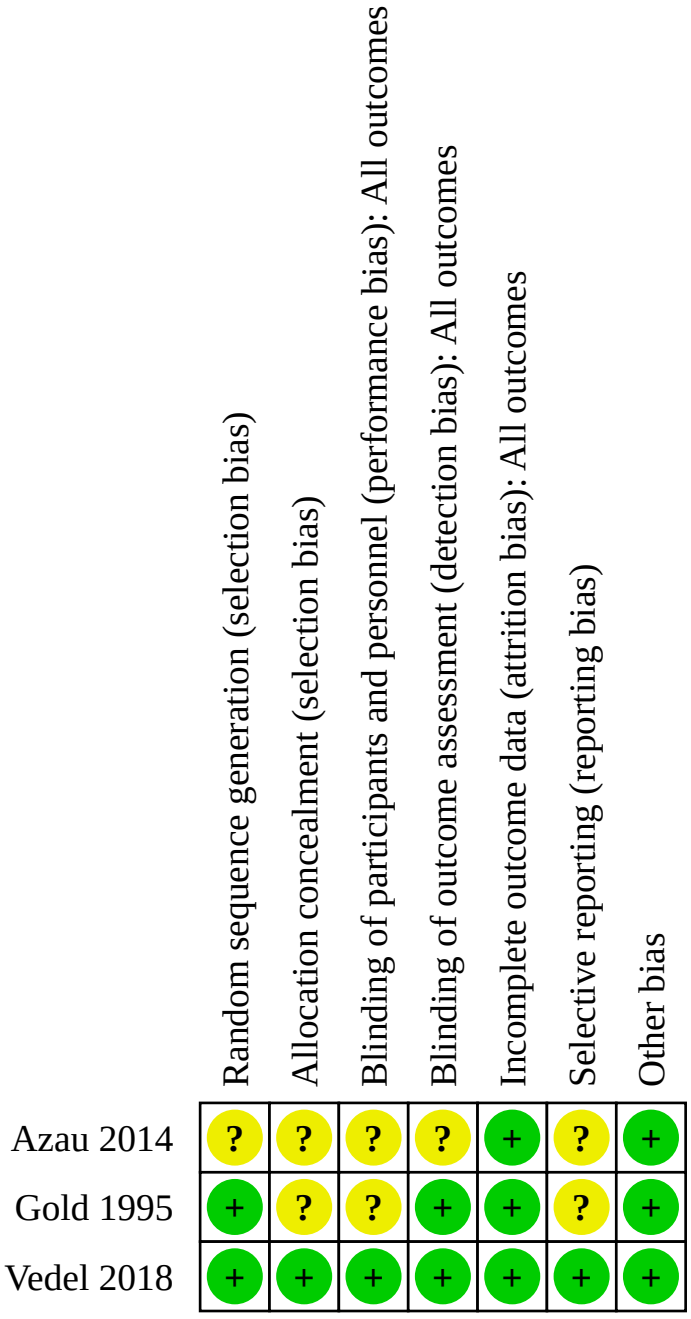


Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All three included studies were RCTs. Two studies described the details of the randomisation processes. We considered the random sequence generation of both studies at low risk of bias (Gold 1995; Vedel 2018). Azau 2014 did not report the randomisation processes, so the random sequence generation of this study was unclear.

Allocation concealment was unclear in Azau 2014 and Gold 1995 because the details of the allocation process were not described in the manuscript and a protocol was not available. Allocation

concealment was at low risk of bias in Vedel 2018, where the allocation sequence was computer-generated with a varying block size of four to eight.

Blinding

Performance bias in Azau 2014 was unclear because study personnel was not blinded. Detection bias was unclear in Azau 2014 because the definition and assessor for several outcomes were unclear. Performance bias was unclear in Gold 1995. Because not all treatment strategies were predetermined, some of the outcomes could be affected by treatment allocation. For example, some physicians could use more blood products to a patient in a higher blood pressure target arm. In Vedel 2018, the protocol reported that participants and healthcare providers were blinded from the group allocation. Detection bias was at low risk of bias in both studies because the outcome assessors were blinded to the intraoperative management (Gold 1995; Vedel 2018).

Incomplete outcome data

Attrition bias was low in all three studies. They reported complete outcome data for all-cause mortality. Although Vedel 2018 reported a difference in follow-up of cognitive deterioration between high and low blood pressure target groups, we considered that the missing outcome data did not lead to a significant bias because the missingness in the outcome was unrelated to its true value in each intervention group.

Selective reporting

Reporting bias was unclear in Azau 2014 and Gold 1995 because the protocols were not available. Vedel 2018 reported all outcome data.

Other potential sources of bias

There was no other identified bias in all three studies.

Effects of interventions

See: **Summary of findings 1** High versus low blood pressure target for cardiac surgery with cardiopulmonary bypass

See Summary of findings 1.

Primary outcomes

Acute kidney injury

The evidence is very uncertain about the effect of a high blood pressure target on AKI, but the wide CIs were consistent with possible benefit and possible harm (RR 1.30, 95% CI 0.81 to 2.08; I^2 = 72%; 2 studies, 487 participants; very low-certainty evidence; Analysis 1.1).

Cognitive deterioration

A high blood pressure target may result in little to no difference in cognitive deterioration, but the wide CIs were consistent with possible benefit and possible harm (RR 0.82, 95% CI 0.45 to 1.50; I^2 = 0%; 2 studies, 389 participants; low-certainty evidence; Analysis 1.2).

All-cause mortality

The evidence is very uncertain about the effect of a high blood pressure target on all-cause mortality, but the wide CIs were consistent with possible benefit and possible harm (RR 1.33, 95% CI 0.30 to 5.90; I^2 = 49%; 3 studies, 737 participants; very low-certainty evidence; Analysis 1.3). However, the worst absolute effect of the high blood pressure target compared with the low blood pressure target was 106 more deaths per 1000 participants, which could be judged as appreciable harm.

Secondary outcomes

Quality of life

The evidence is very uncertain about the effect of a high blood pressure target on quality of life, but the wide CIs were consistent with possible benefit and possible harm (RR 0.78, 95% CI 0.30 to 2.01; 1 study, 218 participants; very low-certainty evidence; Analysis 1.5).

Acute ischaemic stroke

The evidence is very uncertain about the effect of a high blood pressure target on acute ischaemic stroke (RR 1.29, 95% CI 0.07 to 23.73; I^2 = 82%; 2 studies, 437 participants; very low-certainty evidence; Analysis 1.6).

Haemorrhagic stroke

None of the three studies reported the number of haemorrhagic strokes.

Length of hospital stay

Vedel 2018 reported the length of stay in intensive care unit (ICU) and cardiac surgery ward separately. In addition, the length of ICU stay was reported in hours (mean 21 hours in high and low blood pressure groups) while the length of stay in cardiac surgery ward was reported in days (mean six days in both groups). However, it was unclear whether the length of stay in cardiac surgery ward included that in the ICU or not. Therefore, we excluded Vedel 2018 from this analysis.

The evidence is very uncertain about the effect of a high blood pressure target on length of hospital stay (MD 1.25 days, 95% CI 0.78 days to 1.73 days; I^2 = 76%; 2 studies, 540 participants; very low-certainty evidence; Analysis 1.7).

Renal replacement therapy

A high blood pressure target may result in little to no difference in renal replacement therapy but the wide CIs were consistent with possible benefit and possible harm (RR 1.33, 95% CI 0.47 to 3.77; I^2 = 0%; 2 studies, 486 participants; Analysis 1.8).

Delirium

A high blood pressure target may result in little to no difference in delirium but the wide CIs were consistent with possible benefit and possible harm (RR 1.44, 95% CI 0.57 to 3.64; 1 study, 197 participants; Analysis 1.9). Since there were no missing data for delirium, we did not perform sensitivity analyses using best-case scenario or worst-case scenario.

Perioperative transfusion of blood products

The evidence is very uncertain about the effect of a high blood pressure target on perioperative transfusion of blood products (MD 0.10 units, 95% CI –0.13 to 0.34; I^2 = 0%; 2 studies, 540 participants; very low-certainty evidence; Analysis 1.10).

Perioperative myocardial infarction

To diagnose perioperative myocardial infarction, the protocol of Vedel 2018 stated that they used European Society of Cardiology (ESC) classification. Although we contacted the author to request which version of ESC classification they used, we received no reply. Gold 1995 used the agreement of two cardiologists. Since we could not obtain the protocol of Azau 2014, it is uncertain how they diagnosed perioperative myocardial infarction.

A high blood pressure target may result in little to no difference in perioperative myocardial infarction but the wide CIs were consistent with possible benefit and possible harm (RR 0.91, 95% CI 0.26 to 3.16; I^2 = 18%; 3 studies, 734 participants; Analysis 1.11).

Sensitivity analysis

Sensitivity analyses for all the outcomes were consistent with their primary analyses except for AKI (Table 1). When studies at high risk of bias and those including participants undergoing isolated aortic surgery were excluded, the results appeared to be inconsistent with the primary analysis for the AKI outcome. However, given the sparsity of data, these results should be interpreted with caution.

DISCUSSION

Summary of main results

This systematic review identified three prospective RCTs evaluating adults undergoing cardiac surgery with CPB who were randomised to a high (MAP 65 mmHg or greater) or a low (MAP less than 65 mmHg) blood pressure target. We found that the evidence is very uncertain about the effect of a high blood pressure target on AKI and all-cause mortality compared with a low blood pressure target and that a high blood pressure target may result in little to no difference in cognitive deterioration. Due to the low to very low certainty of the evidence and wide CIs, the effects of interventions were unclear in the primary and secondary outcomes reported. No studies reported haemorrhagic stroke. The sensitivity analyses excluding the study enroling participants undergoing isolated aortic surgery showed similar results with the main analysis. Based on the published data, we were unable to conduct any predetermined subgroup analyses.

Overall completeness and applicability of evidence

There are several limitations to the evidence identified in this systematic review. The number of studies that met the inclusion criteria for the review was low and all the included studies were conducted in a single-centre setting, which may limit the external validity of the results. The number of participants included in the meta-analysis was lower than the OIS for most outcomes. Not all the outcomes predefined in our protocol for the review were included in all the trials and some were not reported in any included trial (Kotani 2019). Since we used the MAP of 65 mmHg as the cut-off value between high and low blood pressure targets, we excluded several studies that used different definitions of high and low blood pressure targets.

Quality of the evidence

See Summary of findings 1.

Although we found that two included studies reported AKI, the two studies used different definitions. Vedel 2018 reported the proportion of people with doubling of serum creatinine from the baseline. We considered this as AKI in this study because such a definition is consistent with stage 2 AKI according to the creatinine criteria given in the latest AKI classification (KDIGO 2012). Azau 2014 reported a 30% rise in serum creatinine as a surrogate for AKI, which is consistent with stage 1 AKI. These differences in the definitions of AKI between the studies could lead to indirectness of the outcome, which might be illustrated in the different incidence between the studies (2% to 9% in Vedel 2018 and 17% in Azau 2014). Therefore, we downgraded the certainty of the evidence of AKI for indirectness. In addition, due to serious concern about imprecision, risk of bias, and inconsistency, we concluded that the certainty of evidence for AKI was very low.

The evidence for cognitive deterioration was downgraded to low certainty due to imprecision from small sample size and study limitations.

The evidence for all-cause mortality was downgraded to very low certainty. There was serious concern about imprecision in the small sample size, and the wide CIs suggested potential harm that was not neglectable. There was also serious concern about inconsistency and risk of bias.

The evidence of certainty was very low for the secondary outcomes, mainly due to study limitations, inconsistency, imprecision from the small sample size, and wide CIs, including the possibility of benefit and harm. Therefore, our review could not evaluate the effect of a high blood pressure target on these outcomes. No study reported haemorrhagic stroke.

Potential biases in the review process

Due to the relatively small sample size of the included studies, this review did not reach the OIS in most outcomes. Since most of the participants in the included studies were men, the included studies under-represented women in their study populations. Because of the nature of the intervention, the attending physicians were not blinded to the allocation of the participants to the study groups. However, it was unlikely that a lack of blinding had an impact on primary outcomes of AKI, cognitive deterioration, and all-cause mortality because the assessors of the primary outcomes were blinded to treatment allocation.

Agreements and disagreements with other studies or reviews

In this review, we investigated the benefits and harms of a high blood pressure target in comparison to a low blood pressure target during cardiac surgery with CPB. The result of our review found no beneficial effect of a high blood pressure target (MAP 65 mmHg or greater) during CPB. Our review was consistent with one narrative review on blood pressure management in perioperative care (Meng 2018), which stated that maintaining a higher blood pressure target, compared with a lower one, during CPB has no detrimental effect in people undergoing cardiac surgery based on the results of previous RCTs (Azau 2014; Charlson 2007; Gold 1995; Siepe 2011; Vedel 2018). Our review was also consistent with one guideline on CPB, which stated that the MAP of 50 mmHg to 80 mmHg is acceptable (Wahba 2020).

We found that the evidence is very uncertain about the effect of a high blood pressure target on AKI and that a high blood pressure target may result in little to no difference in renal replacement

therapy. One review article on cardiac surgery-associated AKI suggested that although clinicians seek to avoid low MAP during cardiac surgery on the basis of the conventional physiological assumption, there is a lack of evidence obtained from RCTs to support this clinicians' attitude (Wang 2017). The small number of participants included in our review led to a wide CIs. Thus, we are uncertain about the benefits or harms of a higher blood pressure target in terms of AKI.

We found that the evidence is very uncertain about the effect of a high blood pressure target on all-cause mortality. Another RCT enroling people undergoing elective or urgent CABG found no deaths among the population (Siepe 2011). Since the mortality rate is low in elective cardiac surgery (Landoni 2019; Subramaniam 2019; Turan 2020), it would be difficult to find a significant difference in mortality between groups. Thus, we are uncertain about the benefits or harms of a higher blood pressure target in terms of mortality.

We found that a high blood pressure target may result in little to no difference in cognitive deterioration and delirium. In contrast, Siepe 2011 tested a hypothesis that keeping MAP of 80 mmHg to 90 mmHg compared with 60 mmHg to 70 mmHg during CPB would decrease early cognitive dysfunction and delirium after coronary bypass surgery. Siepe 2011 included people undergoing elective or urgent CABG and reported that cognitive deterioration was significantly less in the higher blood pressure target and that significantly fewer people in the higher blood pressure target developed postoperative delirium. However, there are two major limitations of Siepe 2011. One is the small sample size (92 people) and the other is that Siepe 2011 used the Mini-Mental Status Examination as a cognitive outcome. Therefore, we are uncertain about the effect of a higher blood pressure target on cognitive deterioration and delirium. In addition, the evidence is very uncertain about the effect of a high blood pressure target on acute ischaemic stroke. None of the included studies in our review reported haemorrhagic stroke. Thus, we are uncertain about the benefits or harms of a higher blood pressure target in terms of neural outcomes.

Our review excluded two studies (Charlson 2007; Siepe 2011) due to a wrong intervention that were included in an existing review article (Meng 2018). Although the definition of a higher or lower blood pressure is still under investigation, it was essential to define the cut-off value between high and low blood pressure targets for this review. We chose the cut-off value of 65 mmHg because this value was adopted in sepsis and AKI guidelines (KDIGO 2012; Rhodes 2017). In addition, observational studies have suggested the association of hypotension during and after CPB with end-organ dysfunction and mortality among people undergoing cardiac surgery with CPB. One large cohort study (6523 participants) showed that MAP less than 65 mmHg after CPB was associated with AKI and renal replacement therapy (Ngu 2020). One cohort study enroling 7457 people showed that MAP less than 65 mmHg during CPB was associated with stroke (Sun 2018). Another cohort study (6627 participants) showed the association between MAP less than 65 mmHg after CPB and mortality in people at intermediate risk of mortality (Ristovic 2020). These findings support that MAP 65 mmHg is appropriate for the cut-off value of high and low blood pressure targets during cardiac surgery and warrant future trials to investigate the optimal blood pressure targets to reduce mortality or morbidities in the population. In contrast, one existing review article examining blood pressure targets in a perioperative setting did not set specific cut-off values for blood pressure targets for literature search (Meng 2018). As a result, we excluded the two studies (Charlson 2007; Siepe 2011) that were included in the Meng 2018 review. Since the definition of a higher or lower blood pressure is still under investigation, we chose the cut-off value of 65 mmHg because this value was adopted in a sepsis and AKI guideline (KDIGO 2012; Rhodes 2017).

Different patterns of CPB flow among studies might influence the effect of a high blood pressure target. All the included studies prespecified the flow rate during CPB. Vedel 2018 set 2.4 L/minute/m^2 in normothermia. Azau 2014 set CPB flow at 2.4 L/minute/m^2 in normothermia and further adjusted to maintain venous oxygen saturation above 70%. Gold 1995 used 1.6 L/minute/m^2 during cooling and 2.4 L/minute/m^2 during warming. A high blood pressure target showed a negative effect on several outcomes (mortality, acute ischaemic stroke, length of hospital stay, perioperative myocardial infarction) in Vedel 2018 and Azau 2014, while Gold 1995 revealed that a high blood pressure target was beneficial in these outcomes. This discrepancy can be explained by different CPB flows. During adequate CPB flow, a high blood pressure target can require more vasopressors or fluids, leading to adverse effects of these drugs, such as increased tissue oxygen demand. During low CPB flow, a high blood pressure can help to restore organ perfusion, reducing adverse outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

The findings of our review showed that a higher blood pressure target may make little or no difference to any outcomes including acute kidney injury (AKI), cognitive deterioration, or mortality among people undergoing cardiac surgery with cardiopulmonary bypass (CPB).

Implications for research

The small number of participants included in our review and the very low quality of evidence indicate that future research is highly likely to change the estimated effect. Further research is needed to evaluate the effect of a higher blood pressure, to investigate the best cut-off value for higher or lower mean arterial pressure (MAP) considering preoperative blood pressure in the CPB as well as post-CPB periods among people undergoing cardiac surgery with CPB.

Conducting these studies will help to clarify the definition and effects of a higher blood pressure target for cardiac surgery with CPB.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Azau 2014

Study characteristics	
Methods	Study design: randomised, open-label controlled clinical trial
	Study duration: 30 months between January 2008 and June 2010
	'Run-in' period: none
	Number of study centres and location: 1 in France
Participants	Total number of study participants: 300

Azau 2014 *(Continued)*

	Number of randomised participants: 300 Number lost to follow-up: 0 Number withdrawn: 8 Number analysed: 292 Mean age: 76 years Gender: 200 men Inclusion criteria: elective cardiac surgery, including CABG, valvular surgery or reconstructive surgery of the ascending aorta performed under normothermic CPB in people with known risk factors for AKI. These risk factors were serum creatinine clearance 30–60 mL/minute/1.73 m^2 or 2 factors among the following: aged > 60 years, diabetes mellitus, and diffuse atherosclerosis. Exclusion criteria: infusion of a radiocontrast agent 1 week before surgery or treatment with a nephrotoxic agent 3 weeks before surgery; chemotherapy within last 3 months; liver cirrhosis; heart failure (left ventricular ejection fraction < 30%); renal artery stenosis; pulmonary hypertension (systolic pulmonary pressure > 60 mmHg); endocarditis; surgery requiring hypothermic CPB. Patients who eventually had a major perioperative complication (shock, emergent reoperation) identified as AKI cause disclosed a major perioperative complication (shock, emergent reoperation)
Interventions	Experimental: maintaining MAP during CPB at 75–85 mmHg by infusing noradrenaline Comparison: maintaining MAP during CPB at 50–60 mmHg. Vasopressors were administered when MAP < 50 mmHg. Concomitant treatment: following anaesthesia induction, a systematic 12 mL/kg saline infusion load was administered in all participants. CPB was performed with a roller pump. Before and after CPB, and in both groups, the MAP endpoint was 70–90 mmHg, with venous oxygen saturation > 70% until the end of surgery. CPB flow was set at 2.4 L/minute/m^2 and further adjusted to maintain SvO_2 > 70%.
Outcomes	Primary endpoint: 30% rise in serum creatinine was the primary endpoint and surrogate for AKI. Renal function assessed at day 28 and 6 months after surgery. There were additional surrogate endpoints for AKI: RIFLE "risk" category (50% rise in serum creatinine or glomerular filtration rate decrease > 25%, urine output < 0.5 mL/kg/hour × 6 hours); RIFLE 'injury' category (100% rise in serum creatinine or glomerular filtration rate decrease > 50%, urine output < 0.5 mL/kg/hour × 12 hours); > 50% postoperative rise of serum creatinine; and need for haemodialysis. Neurological complications of surgery (stroke, seizure, transient mental confusion/agitation) were also recorded. Death date was identified either by medical records received from doctors who cared for the patients after discharge from hospital or, in the absence of such records, the authors asked the national registry of deaths.
Notes	Supported by a grant from the "Programme Hospitalier pour la Recherche Clinique" (PHRC Inter-Régional, 2007) from the French Health Ministry.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not provided.
Allocation concealment (selection bias)	Unclear risk	Although this study used opaque sealed envelopes, their random sequence generation was unclear.

Azau 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	In the methods section, the authors reported that participants were blinded but study personnel were not.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The definitions and assessors for several outcomes, i.e. cognitive deterioration, acute ischaemic stroke, haemorrhagic stroke, delirium, and perioperative myocardial infarction, were unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up 2.7% (8/300).
Selective reporting (reporting bias)	Unclear risk	Study protocol not available.
Other bias	Low risk	Review authors believed the study free of other sources of bias.

Gold 1995

Study characteristics	
Methods	Study design: randomised, open-label controlled clinical trial Study duration: 30 months between October 1991 and February 1994 'Run-in' period: none Number of study centre and location: 1 in the US
Participants	Total number of study participants: 251 Number of randomised participants: 248 Number lost to follow-up: 0 Number withdrawn: 0 Number analysed: 248 Mean age: 65.8 years Gender: 160 men Inclusion criteria: people undergoing primary elective multivessel CABG for left main or multivessel coronary artery disease Exclusion criteria: inability to complete the neuropsychological tests (blindness, deafness, language difficulties), participation in other studies, and inability to return for follow-up.
Interventions	Experimental: maintaining MAP during CPB at 80–100 mm Hg Comparison: maintaining MAP during CPB at 50–60 mm Hg Concomitant medications: CPB flow by body surface area and temperature were held constant, and vasoactive drugs were used to maintain MAP in the desired range. Anaesthesia was induced with thiopental (1–2 mg/kg), fentanyl (25 µg/kg), and pancuronium, and was maintained with a fentanyl bolus (1–5 µg/kg, to a total of 50–70 µg/kg), midazolam, or isoflurane (pre-CPB and post-CPB periods only). After sternotomy and pericardial incision, heparin was administered to maintain an activated clotting time > 480 seconds. After cannulation of the aorta and right atrium, non-pulsatile CPB was instituted. Flow

Gold 1995 *(Continued)*

	rates were set at 1.6 L/minute/m^2 during cooling and 2.4 L/minute/m^2 during warming. If the MAP increased above the target level and was unresponsive to fentanyl or midazolam, sodium nitroprusside infusion was administered. If the MAP fell below the target level, phenylephrine was used. If necessary, noradrenaline or metaraminol was added. Intraoperative ischaemia was managed by an identical algorithm in both groups. Excluded medications: none
Outcomes	Mortality, cardiac morbidity, neurological morbidity, deterioration in cognitive status, and deterioration in quality of life reported at 6 months. Cardiac complications were myocardial infarction, pulmonary oedema, adult respiratory distress syndrome, low flow state/cardiogenic shock, and cardiopulmonary arrest. Definite stroke was the principal neurological complication determined by the neurologist. Stroke included the new onset of a localised and persistent neurological deficit (e.g. paresis, plegia, aphasia, hemianopsia, cortical blindness). Deterioration on ≥ 3 cognitive tests was defined as a cognitive complication. For each test, the assessment was based on within-patient change in test performance from preoperative baseline. Changes from preoperative to postoperative function that would be considered clinically important were determined a priori by a panel of experts. Deterioration in quality of life was defined as a decline of > 5 points on the Physical Component Summary score of the SF-36.
Notes	Funding source: grant HL44719 from the National Institutes of Health, National Heart, Lung, and Blood Institute.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation based on a table of random numbers.
Allocation concealment (selection bias)	Unclear risk	Information not provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information not provided.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study cardiologist and neurologist, blinded to the intraoperative management, performed standardised examinations at 1, 2, and 7 days, and 6 months after the operation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up among the randomised participants.
Selective reporting (reporting bias)	Unclear risk	Information not provided.
Other bias	Low risk	Review authors believed the study to be free of other sources of bias.

Vedel 2018

Study characteristics	
Methods	Study design: randomised, open-label controlled clinical trial Study duration: 19 months between July 2014 and January 2016 'Run-in' period: none Number of study centre and location: 1 in Denmark
Participants	Total number of study participants: 197 Number of randomised participants: 197 Number lost to follow-up: 0 Number withdrawn: 3 Number analysed: 197 Mean age: 67.2 years Gender: 177 men Inclusion criteria: aged ≥ 18 years and in need of elective or subacute CABG or left heart valve surgery (or both) using CPB Exclusion criteria: history of stroke or intracranial bleeding, history of reversible ischaemic deficits (duration of symptoms 24–72 hours), history of transient ischaemic attacks (duration of symptoms < 24 hours), diagnosis of neurodegenerative disorders such as Alzheimer's disease and multiple sclerosis, or contraindications to magnetic resonance imaging
Interventions	Experimental: maintaining MAP at 70–80 mmHg during CPB Comparison: maintaining MAP at 40–50 mmHg during CPB Concomitant medications: an intended fixed, equal, and non-pulsatile blood flow of 2.4 L/minute/m^2 body surface area plus 10–20% was applied in both groups, and assigned MAP levels were targeted with intermittent intravenous doses of phenylephrine to a total maximum dose of 2.0 mg followed by continuous intravenous infusion of noradrenaline up to 0.4 µg/kg/minute. Concomitant treatment interventions were at the treating clinicians' discretion. According to departmental guidelines, CPB was performed with arterial oxygen saturation > 96% (and partial pressure of oxygen in the arterial blood > 13.0 kPa), normocapnia (partial pressure of carbon dioxide in the arterial blood 4.5–6.0 kPa), normothermia (body temperature > 36.5 °C), α-stat pH management, and transfusion of packed red blood cells if haematocrit was < 24% (or at higher haematocrit levels in case of lactic acidosis or low mixed venous saturation). Excluded medications: no vasodilatory drugs were accepted in the low-target group, and MAP levels above the low-target window were accepted.
Outcomes	Primary outcome: total volume of new ischaemic lesions (sum in millimetres cubed), expressed as the difference between DWI conducted preoperatively and again between days 3 and 6. Secondary outcomes: total number of new ischaemic cerebral lesions, POCD, new focal neurological deficits, both evaluated as a change from baseline neuropsychological and neurological test performance to the result at 1 week, at discharge from the hospital, or at healthcare relocation from the cardiac surgery ward to a local hospital, whichever came first. Cognitive function was re-evaluated at 2–4 months postoperatively. Used the International Study of Postoperative Cognitive Dysfunction test battery, 14–16 which was developed for people with an intact cognitive capability. Also conducted a Mini-Mental State Examination to screen for potential signs of dementia. If a participant had a baseline Mini-Mental State Examination score ≤ 24, there was no further cognitive testing.

Vedel 2018 *(Continued)*

Notes	Dr Vedel received grants from the Danish Heart Foundation (14-R97- A5179-22868 and 15-R99-A6034-22905) and the Research Foundations at Rigshospitalet (E-22329-01), University of Copenhagen, Denmark.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised web-based randomisation was performed with a computer-generated allocation sequence with varying block size of 4–8.
Allocation concealment (selection bias)	Low risk	Centralised web-based randomisation was performed with a computer-generated allocation sequence with varying block size of 4–8.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients were blinded from the group allocation. Healthcare providers in the intensive care unit and ward were unaware of the assigned MAP strategy unless they specifically consulted the handwritten anaesthesia report and guessed to which group the participant was allocated based on the continuous registration of MAP data. Throughout the trial, the study authors stressed that the staff involved in the experimental setup in the operating room at no point disclosed group allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	According to the protocol, assessors of the primary and selected secondary endpoints (DWI scans and POCD) were blinded to treatment allocation. Furthermore, blood samples were labelled with a unique participant number, and personnel carrying out blood sample analysis did not know the group allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up 3.0% (6/197).
Selective reporting (reporting bias)	Low risk	All outcome data but MRS described in the protocol (Vedel 2016 – see under Vedel 2018) were reported.
Other bias	Low risk	Review authors believed the study free of other sources of bias.

AKI: acute kidney injury; CABG: coronary artery bypass graft; CPB: cardiopulmonary bypass; DWI: diffusion-weighted imaging; MAP: mean arterial pressure; MRS: magnetic resonance spectroscopy; POCD: postoperative cognitive dysfunction; SF-36: 36-item Short Form.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aghadavoudi Jolfaei 2012	Wrong intervention
Aronson 2011	Wrong study design
Bagheri 2012	Wrong intervention
Bertolissi 1996	Wrong intervention
Brown 2019	Wrong population
Charlson 2007	Wrong intervention

Study	Reason for exclusion
CTRI/2018/01/011487	Wrong intervention
Damén 2021	Wrong intervention
Ge 2018	Wrong study design
Getsios 2013	Wrong intervention
Goepfert 2013	Wrong intervention
Hamada 2004	Wrong intervention
IRCT2015112916151N4	Wrong population
Kapoor 2008	Wrong intervention
Kapoor 2016	Wrong intervention
Mölström 2017	Wrong intervention
NCT01408420	Wrong intervention
NCT04005105	Wrong intervention
Paulson 2019	Wrong study design
Siepe 2011	Wrong intervention
Sirvinskas 2008	Wrong intervention
Urzua 1992	Wrong intervention

Characteristics of studies awaiting classification *[ordered by study ID]*

von Knobelsdorff 1996

Methods	Randomised, parallel group trial
Participants	ASA III patients undergoing CABG
Interventions	Experimental: mean arterial pressure > 70 mmHg during rewarming of cardiopulmonary bypass. Comparator: mean arterial pressure 55–65 mmHg during rewarming of cardiopulmonary bypass.
Outcomes	Jugular bulb oxygen saturation
Notes	No response to email requests for the full-text article.

ASA: American Society of Anesthesiologists; CABG: coronary artery bypass graft.

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR2000028941	
Study name	Target blood pressure management during cardiopulmonary bypass improves postoperative lactic acid levels: a randomised controlled clinical study
Methods	Design: single-centre parallel-group double-blind randomised controlled trial
Participants	Inclusion criteria: selective heart valve surgery; aged > 18 years; New York Heart Association class II–III; ejection fraction > 50%; blood lactate level < 1.6 mmol/L; alanine transferase < 50 U/L; brain natriuretic peptide < 100 pg/mL; stay overnight in intensive care unit after surgery Exclusion criteria: secondary aortic occlusion during operation; emergency surgery again within 24 hours after the operation.
Interventions	Experimental: mean arterial pressure 70–80 mmHg with noradrenaline Control: mean arterial pressure 50–60 mmHg with or without vasoactive drugs
Outcomes	Primary outcome: postoperative blood lactate value
Starting date	Date of approved by ethic committee: 31 October 2019
Contact information	Miao Qing Tel: +86 15026635802 E-mail: miaoqmz@163.com Affiliation: Department of Anesthesiology, Shanghai Chest Hospital, Shanghai Jiaotong University, Shanghai, China
Notes	Prospective registration Status: recruiting

DATA AND ANALYSES

Comparison 1. High versus low blood pressure target

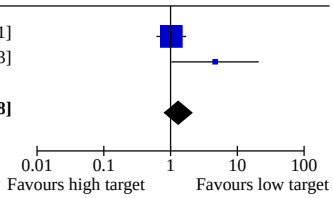
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Acute kidney injury	2	487	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.81, 2.08]
1.2 Cognitive deterioration	2	389	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.45, 1.50]
1.3 All-cause mortality	3	737	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.30, 5.90]
1.5 Quality of life	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.6 Acute ischaemic stroke	2	426	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.07, 23.63]
1.7 Length of hospital stay	2	540	Mean Difference (IV, Fixed, 95% CI)	1.25 [0.78, 1.73]
1.8 Renal replacement therapy	2	486	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.47, 3.77]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.9 Delirium	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.10 Perioperative transfusion of blood products	2	540	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.13, 0.34]
1.11 Perioperative myocardial infarction	3	734	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.26, 3.16]

Analysis 1.1. Comparison 1: High versus low blood pressure target, Outcome 1: Acute kidney injury

Study or Subgroup	High blood pressure target Events	Total	Low blood pressure target Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Azau 2014	25	147	24	145	92.5%	1.03 [0.62 , 1.71]
Vedel 2018	9	96	2	99	7.5%	4.64 [1.03 , 20.93]
Total (95% CI)		**243**		**244**	**100.0%**	**1.30 [0.81 , 2.08]**
Total events:	34		26			

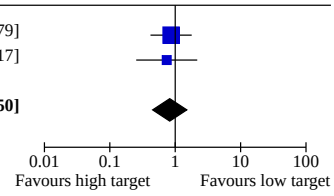
Heterogeneity: Chi² = 3.56, df = 1 (P = 0.06); I² = 72%
Test for overall effect: Z = 1.09 (P = 0.28)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: High versus low blood pressure target, Outcome 2: Cognitive deterioration

Study or Subgroup	High blood pressure target Events	Total	Low blood pressure target Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Gold 1995	12	112	14	113	68.7%	0.86 [0.42 , 1.79]
Vedel 2018	5	75	8	89	31.3%	0.74 [0.25 , 2.17]
Total (95% CI)		**187**		**202**	**100.0%**	**0.82 [0.45 , 1.50]**
Total events:	17		22			

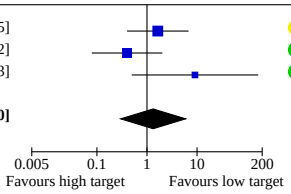
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.63 (P = 0.53)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: High versus low blood pressure target, Outcome 3: All-cause mortality

Study or Subgroup	High blood pressure target Events	Total	Low blood pressure target Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Azau 2014	5	147	3	145	42.8%	1.64 [0.40 , 6.75]
Gold 1995	2	124	5	124	38.1%	0.40 [0.08 , 2.02]
Vedel 2018	4	98	0	99	19.1%	9.09 [0.50 , 166.63]
Total (95% CI)		**369**		**368**	**100.0%**	**1.33 [0.30 , 5.90]**
Total events:	11		8			

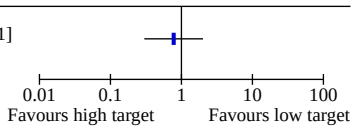
Heterogeneity: Tau² = 0.83; Chi² = 3.89, df = 2 (P = 0.14); I² = 49%
Test for overall effect: Z = 0.37 (P = 0.71)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.5. Comparison 1: High versus low blood pressure target, Outcome 5: Quality of life

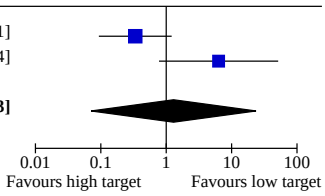
Study or Subgroup	High blood pressure target Events	Total	Low blood pressure target Events	Total	Risk Ratio M-H, Fixed, 95% CI
Gold 1995	7	109	9	109	0.78 [0.30 , 2.01]



Analysis 1.6. Comparison 1: High versus low blood pressure target, Outcome 6: Acute ischaemic stroke

Study or Subgroup	High blood pressure target Events	Total	Low blood pressure target Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Gold 1995	3	118	9	119	54.1%	0.34 [0.09 , 1.21]
Vedel 2018	6	92	1	97	45.9%	6.33 [0.78 , 51.54]
Total (95% CI)		**210**		**216**	**100.0%**	**1.29 [0.07 , 23.63]**
Total events:	9		10			

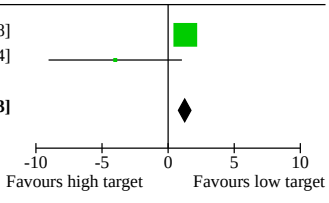
Heterogeneity: Tau² = 3.63; Chi² = 5.62, df = 1 (P = 0.02); I² = 82%
Test for overall effect: Z = 0.17 (P = 0.86)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: High versus low blood pressure target, Outcome 7: Length of hospital stay

Study or Subgroup	High blood pressure target Mean	SD	Total	Low blood pressure target Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Azau 2014	9.5	2.4	147	8.2	1.7	145	99.1%	1.30 [0.82 , 1.78]
Gold 1995	13	14	124	17	25	124	0.9%	-4.00 [-9.04 , 1.04]
Total (95% CI)			**271**			**269**	**100.0%**	**1.25 [0.78 , 1.73]**

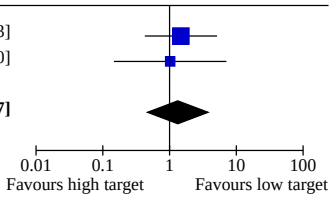
Heterogeneity: Chi² = 4.21, df = 1 (P = 0.04); I² = 76%
Test for overall effect: Z = 5.18 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: High versus low blood pressure target, Outcome 8: Renal replacement therapy

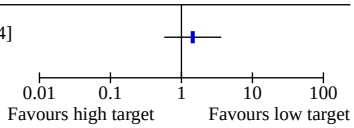
Study or Subgroup	High blood pressure target Events	Total	Low blood pressure target Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Azau 2014	6	147	4	145	67.0%	1.48 [0.43 , 5.13]
Vedel 2018	2	96	2	98	33.0%	1.02 [0.15 , 7.10]
Total (95% CI)		**243**		**243**	**100.0%**	**1.33 [0.47 , 3.77]**
Total events:	8		6			

Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.53 (P = 0.59)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: High versus low blood pressure target, Outcome 9: Delirium

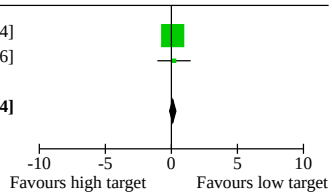
Study or Subgroup	High blood pressure target Events	Total	Low blood pressure target Events	Total	Risk Ratio M-H, Fixed, 95% CI
Vedel 2018	10	98	7	99	1.44 [0.57 , 3.64]



Analysis 1.10. Comparison 1: High versus low blood pressure target, Outcome 10: Perioperative transfusion of blood products

Study or Subgroup	High blood pressure target Mean	SD	Total	Low blood pressure target Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Azau 2014	0.6	1.1	147	0.5	1	145	96.5%	0.10 [-0.14 , 0.34]
Gold 1995	4	4.7	124	3.8	5.4	124	3.5%	0.20 [-1.06 , 1.46]
Total (95% CI)			**271**			**269**	**100.0%**	**0.10 [-0.13 , 0.34]**

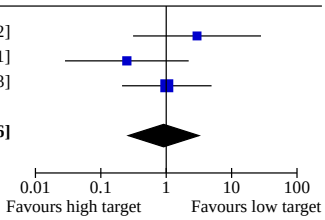
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 0.86 (P = 0.39)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: High versus low blood pressure target, Outcome 11: Perioperative myocardial infarction

Study or Subgroup	High blood pressure target Events	Total	Low blood pressure target Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Azau 2014	3	147	1	145	26.1%	2.96 [0.31 , 28.12]
Gold 1995	1	124	4	124	27.6%	0.25 [0.03 , 2.21]
Vedel 2018	3	96	3	98	46.3%	1.02 [0.21 , 4.93]
Total (95% CI)		**367**		**367**	**100.0%**	**0.91 [0.26 , 3.16]**
Total events:	7		8			

Heterogeneity: Tau² = 0.22; Chi² = 2.43, df = 2 (P = 0.30); I² = 18%
Test for overall effect: Z = 0.14 (P = 0.89)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Sensitivity analyses

Outcome	Studies with overall low risk of bias	Best-case scenario	Worst-case scenario	Exclusion of studies with SD imputed	Exclusion of studies including participants undergoing isolated aortic surgery	Exclusion of studies published before 2000	Including only studies that considered learning effects caused by multiple testings
Acute kidney injury	RR 4.64 (95% CI 1.03 to 20.93)	—	—	—	RR 4.64 (95% CI 1.03 to 20.93)	—	—
Cognitive deterioration	RR 0.74 (95% CI 0.25 to 2.37)	RR 0.41 (95% CI 0.24 to 0.69)	RR 2.39 (95% CI 1.18 to 4.86)	—	—	RR 0.74 (95% CI 0.25 to 2.17)	RR 0.74 (95% CI 0.25 to 2.17)
All-cause mortality	RR 9.09 (95% CI 0.50 to 166.63)	—	—	—	RR 1.52 (95% CI 0.07 to 34.75)	RR 0.62 (95% CI 0.16 to 2.34)	—
Acute ischaemic stroke	—	RR 0.81 (95% CI 0.14 to 4.74)	RR 1.85 (95% CI 0.05 to 72.46)	—	—	RR 6.33 (95% CI 0.78 to 51.54)	—
Length of hospital stay, day	—	—	—	MD −4.00 (95% CI −9.04 to 1.04)	MD −4.00 (95% CI −9.04 to 1.04)	MD 1.30 (95% CI 0.82 to 1.78)	—
Renal replacement therapy	—	RR 1.32 (95% CI 0.46 to 3.75)	RR 1.79 (95% CI 0.67 to 4.80)	—	RR 1.02 (95% CI 0.15 to 7.10)	—	—
Perioperative transfusion of blood products, unit	—	—	—	—	MD 0.20 (95% CI −1.06 to 1.46)	MD 0.10 (95% CI −0.14 to 0.34)	—
Perioperative myocardial infarction	—	RR 0.79 (95% CI 0.24 to 2.63)	RR 1.17 (95% CI 0.32 to 4.26)	—	RR 0.62 (95% CI 0.16 to 2.34)	RR 1.45 (95% CI 0.40 to 5.27)	—

CI: confidence interval; MD: mean difference; RR: risk ratio; SD: standard deviation.

APPENDICES

Appendix 1. Search strategies

CENTRAL

#1 MeSH descriptor: [Blood Pressure] explode all trees

#2 (blood pressure or bloodpressure)

#3 MeSH descriptor: [Hypertension] explode all trees

#4 hypertens*

#5 ((target* or strict* or goal* or tight* or intensive* or below or control or lowering) NEAR/3 (systolic or diastolic or bp or dbp or sbp or antihypertensive* or anti hypertensive*))

#6 ((bp or blood pressure) NEAR/2 lowering)

#7 #1 or #2 or #3 or #4 or #5 or #6

#8 MeSH descriptor: [Cardiac Surgical Procedures] explode all trees

#9 ((heart or cardiac or aortic or mitral or pulmonary or tricuspid or valv*) NEAR/4 (surg* or replace* or repair* or reconstruc* or operat*))

#10 MeSH descriptor: [Coronary Artery Bypass] explode all trees

#11 ((coronary or heart or cardio* or cardiac* or valve) NEAR/5 (surg* or graft* or bypass or plasty or replacement))

#12 CABG

#13 #8 or #9 or #10 or #11 or #12

#14 MeSH descriptor: [Cardiopulmonary Bypass] this term only

#15 ((coronary or heart or cardio* or cardiac* or valve) NEAR/5 (surg* or graft* or bypass or plasty or replacement))

#16 CPB

#17 #14 or #15 or #16

#18 #13 and #17

#19 #7 and #18

MEDLINE Ovid

1 exp blood pressure/

2 (blood pressure or bloodpressure).tw.

3 exp hypertension/

4 hypertens*.tw.

5 ((target* or strict* or goal* or tight* or intensive* or below or control or lowering) adj3 (systolic or diastolic or bp or dbp or sbp or antihypertensive* or anti hypertensive*)).tw.

6 ((bp or blood pressure) adj2 lowering).tw.

7 1 or 2 or 3 or 4 or 5 or 6

8 exp Cardiac surgical procedures/

9 ((heart or cardiac or aortic or mitral or pulmonary or tricuspid or valv*) adj4 (surg* or replace* or repair* or reconstruc* or operat*)).tw.

10 exp Coronary Artery Bypass/

11 ((coronary or heart or cardio* or cardiac* or valve) adj5 (surg* or graft* or bypass or plasty or replacement)).tw.

12 CABG.tw.

13 8 or 9 or 10 or 11 or 12

14 Cardiopulmonary Bypass/

15 ((coronary or heart or cardio* or cardiac* or valve) adj5 (surg* or graft* or bypass or plasty or replacement)).tw.

16 CPB.tw.

17 14 or 15 or 16

18 13 and 17

19 7 and 18

20 randomized controlled trial.pt.

21 controlled clinical trial.pt.

22 randomized.ab.

23 placebo.ab.

24 clinical trials as topic.sh.

25 randomly.ab.

26 trial.ti.

27 20 or 21 or 22 or 23 or 24 or 25 or 26

28 exp animals/ not humans.sh.

29 27 not 28

30 19 and 29

Embase Ovid

1 exp blood pressure/

2 (blood pressure or bloodpressure).tw.

3 exp hypertension/

4 hypertens*.tw.

5 ((target* or strict* or goal* or tight* or intensive* or below or control or lowering) adj3 (systolic or diastolic or bp or dbp or sbp or antihypertensive* or anti hypertensive*)).tw.

6 ((bp or blood pressure) adj2 lowering).tw.

7 1 or 2 or 3 or 4 or 5 or 6

8 exp heart surgery/

9 ((heart or cardiac or aortic or mitral or pulmonary or tricuspid or valv*) adj4 (surg* or replace* or repair* or reconstruc* or operat*)).tw.

10 exp coronary artery bypass graft/

11 ((coronary or heart or cardio* or cardiac* or valve) adj5 (surg* or graft* or bypass or plasty or replacement)).tw.

12 CABG.tw.

13 8 or 9 or 10 or 11 or 12

14 cardiopulmonary bypass/

15 ((coronary or heart or cardio* or cardiac* or valve) adj5 (surg* or graft* or bypass or plasty or replacement)).tw.

16 CPB.tw.

17 14 or 15 or 16

18 13 and 17

19 7 and 18

20 random$.tw.

21 factorial$.tw.

22 crossover$.tw.

23 cross over$.tw.

24 cross-over$.tw.

25 placebo$.tw.

26 (doubl$ adj blind$).tw.

27 (singl$ adj blind$).tw.

28 assign$.tw.

29 allocat$.tw.

30 volunteer$.tw.

31 crossover procedure/

32 double blind procedure/

33 randomized controlled trial/

34 single blind procedure/

35 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34

36 (animal/ or nonhuman/) not human/

37 35 not 36

38 19 and 37

39 limit 38 to embase

Web of Science

16 #15 AND #14

15 TS=(random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*)

14 #13 AND #5

13 #12 AND #9

12 #11 OR #10

11 TS=CPB

10 TS=((coronary or heart or cardio* or cardiac* or valve) NEAR/5 (surg* or graft* or bypass or plasty or replacement))

9 #8 OR #7 OR #6

8 TS=CABG

7 TS=((coronary or heart or cardio* or cardiac* or valve) NEAR/5 (surg* or graft* or bypass or plasty or replacement))

6 TS=((heart or cardiac or aortic or mitral or pulmonary or tricuspid or valv*) NEAR/4 (surg* or replace* or repair* or reconstruc* or operat*))

5 #4 OR #3 OR #2 OR #1

4 TS= ((bp or "blood pressure") NEAR/2 lowering)

3 TS=((target* or strict* or goal* or tight* or intensive* or below or control or lowering) NEAR/3 (systolic or diastolic or bp or dbp or sbp or antihypertensive* or "anti hypertensive*"))

2 TS=hypertens*

1 TS=(blood pressure or bloodpressure)

ClinicalTrials.gov

Condition or disease: cardiac surgery

Study type: Interventional Studies (Clinical Trials)

Other terms: cardiopulmonary bypass

WHO ICTRP

"cardiac surgery" AND "cardiopulmonary bypass"

HISTORY

Protocol first published: Issue 11, 2019

CONTRIBUTIONS OF AUTHORS

YKo: conception of the review, design of the review, search and selection of studies for inclusion in the review, assessment of the risk of bias in the included studies, analysis of data, assessment of certainty of evidence, interpretation of data, writing of the review, and approval of the final version of the manuscript. Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

YKa: design of the review, search and selection of studies for inclusion in the review, assessment of the risk of bias in the included studies, analysis of data, assessment of certainty of evidence, interpretation of data, writing of the review, and approval of the final version of the manuscript. Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

JI: conception of the review, design of the review, search and selection of studies for inclusion in the review, interpretation of data, writing of the review, and approval of the final version of the manuscript. Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

SF: conception of the review, design of the review, search and selection of studies for inclusion in the review, collection of data for the review, assessment of the risk of bias in the included studies, interpretation of data, writing of the review, and approval of the final version of the manuscript. Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

TY: conception of the review, design of the review, search and selection of studies for inclusion in the review, collection of data for the review, assessment of the risk of bias in the included studies, interpretation of data, writing of the review, and approval of the final version of the manuscript. Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

JK: conception of the review, design of the review, search and selection of studies for inclusion in the review, interpretation of data, writing of the review, and approval of the final version of the manuscript. Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

JSWK: design of the review, co-ordination of the review, writing of the review, and approval of the final version of the manuscript. Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DECLARATIONS OF INTEREST

YKo: none.

YKa: none.

JI: none.

SF: none.

TY: none.

JK: none.

JSWK: none.

SOURCES OF SUPPORT

Internal sources

- New Source of support, Other

  None

External sources

- NIHR, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes from the protocol (Kotani 2019).

In the protocol, we excluded isolated aortic surgery because the surgical procedure itself can affect peripheral organ perfusion differently from CABG or heart valve surgery. However, we included isolated aortic surgery because we believe such a procedural difference hardly affects blood pressure management. Besides, we added a sensitivity analysis excluding studies including participants undergoing isolated aortic surgery to investigate the procedural difference can affect the effect size.

Since Gold 1995 was the only study to report quality of life and they reported quality of life as a dichotomous outcome, we also counted quality of life as a dichotomous variable.

Since the amount of intraoperative haemorrhage is easily influenced by multiple factors such as intraoperative blood salvage and cardioplegic solution, we removed the outcome and added perioperative transfusion of blood products. Since we did not replace the outcome of the amount of intraoperative haemorrhage with perioperative transfusion of blood products in the summary of findings table in the protocol, we revised the outcome.

We defined the measurement period to the outcome of perioperative transfusion of blood products as at any time from the cardiac surgery to hospital discharge.

We added the sensitivity analysis excluding studies published before 2000 because the practice and outcomes of cardiac surgery have evolved significantly over time.

We conducted a sensitivity analysis for cognitive deterioration, including only studies which considered learning effects caused by multiple testings for the following reason. Cognitive deterioration was defined as a relative decrease of cognitive score from the baseline, which does not consider learning effects caused by repeated examination of the same test. In contrast, neuropsychological tests such as the International Study of Postoperative Cognitive Dysfunction (ISPOCD; Moller 1998) subtract the mean learning effect from the postoperative changes from the baseline, which can provide more appropriate criteria.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Kidney Injury [epidemiology]; *Cardiac Surgical Procedures [adverse effects]; *Cardiopulmonary Bypass [adverse effects]; Hemorrhagic Stroke; Hypertension; Hypotension; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans