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REVIEW

Effect of Cardioplegia for Myocardial Protection in Pediatric Cardiac Surgery: A Network Meta-Analysis

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ABSTRACT

Cardioplegia has been widely used to reduce myocardial injury during pediatric cardiac surgery; however, which cardioplegia solution has the best protective effect has not been established. Thus, we compared the myocardial protective effects of different cardioplegia solutions used in pediatric cardiac surgery. Seven databases were searched to identify the relevant randomized controlled trials. A network meta-analysis with a Bayesian framework was conducted. The outcomes included the following biochemical and clinical outcomes: serum concentrations of the creatine kinase-myocardial band at 6 h postoperatively; cardiac troponin I (cTnI) at 4, 12, and 24 h postoperatively; spontaneous beating after declamping; postoperative arrhythmias; inotropic support percentage and duration; mechanical ventilation hours; intensive care unit stay in days; hospital stay in days; and mortality. The group treated with cold crystalloid cardioplegia (cCCP) was chosen as the control group. The 22 studies involved 1529 patients. Six types of cardioplegia solutions were described in these studies, including cold blood cardioplegia, cCCP, del Nido, histidine-tryptophan-ketoglutarate (HTK), terminal warm blood cardioplegia, and warm blood cardioplegia (wBCP). The serum concentrations of the 24-h cTnI with wBCP (MD = −2.52, 95% CI: −4.74 to −0.27) was significantly lower than cCCP. The serum concentrations of the 24-h cTnI with HTK (MD = 4.91, 95% CI: 2.84–7.24) was significantly higher than cCCP. There was no significant difference in other biochemical and clinical outcomes when compared to cCCP. In conclusion, wBCP may have a superior myocardial protective effect with lower 24-h cTnI levels postoperatively and similar clinical outcomes after pediatric cardiac surgery.

KEYWORDS

Cardioplegia; pediatric cardiac surgery; cardiac troponin I; meta-analysis

1 Introduction

Approximately 100 congenital heart surgeries are performed by each pediatric cardiac surgeon in North America every year [1], and 40,000 children undergo congenital heart surgical procedures in the United States each year [2]. It is important to protect the myocardium during open heart surgery because cardiopulmonary bypass can cause myocardial ischemia and reperfusion injury, leading to impaired cardiac function. During cardiopulmonary bypass surgery, there are several methods of myocardial protection, including cardioplegia solution, hypothermia, and local cooling [3]. The most studied method, however, is the application of cardioplegia.

Cardioplegia is a chemical cardiac arrest solution that is administered to intentionally and temporarily arrest the heart. Cardioplegia decreases the myocardial metabolic demand. Cardioplegia is divided into two main categories (crystalloid- or blood-based solutions). Cold crystalloid cardioplegia (cCCP) has been the cornerstone of cardiac surgical practice since the 1950s. Cold blood cardioplegia (cBCP) was introduced in the 1970s due to the increased oxygen-carrying capacity, maintenance of oncotic pressure, and scavenging of free radicals [4]. Since the introduction of cBCP, several modified types of cardioplegia have been used in clinical applications, including del Nido (DN) and histidine-tryptophan-ketoglutarate (HTK) solutions. Although there are numerous studies comparing the effects of two or three cardioplegia solutions, there is no consensus on a cardioplegia solution that affords optimal myocardial protection. Therefore, we conducted this network meta-analysis (NMA) to systematically evaluate the myocardial protective effects of various cardioplegia solutions currently used in pediatric cardiac surgery.

2 Material and Methods

We followed a reporting guideline (Preferred Reporting Items for Systematic Reviews and Meta-Analyses for NMA) to conduct this study [5]. The review protocol (number: CRD42020215431) was registered in the PROSPERO database. Using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, we assessed the certainty of evidence derived from the network meta-analysis results. GRADE provides a system for rating the quality of NMAs, and evaluates the quality of evidence at 4 levels (high, moderate, low, and very low).

2.1 Search Strategy

Two examiners (KZ and XZ) independently searched for the significant studies in databases, including PubMed, MEDLINE, Web of Science, EMBASE, Scopus, ClinicalTrials.gov, and the Cochrane library on 20 January 2021. The search words were ‘cardioplegia,’ ‘pediatric,’ and ‘randomized controlled trials (RCTs).’ The details of the search strategy are shown in Tab. S1. At the same time, we read the references cited in the studies to further locate the literature which met the criteria.

2.2 Data Extraction

Reviewers (KZ and XZ) were assigned to screen the titles and abstracts for eligibility. The third reviewer (DL) resolved any disagreement between the reviewers. Original studies were eligible if the following criteria were met: (I) RCTs of cardiac surgery; (II) full text with language restrictions; and (III) literature on assessment of the effect of myocardial protection using different cardioplegia solutions in pediatric cardiac surgery. Original studies were ineligible for the following reasons: (I) reviews, observational studies, case-control studies, abstracts, letters, or case reports; (II) patients other than children; (III) cardioplegia with adjuncts, such as nicardipine or esmolol, or leukocyte-depleted cardioplegia studies; and (IV) laboratory animal studies. If there were several publications from the same study, the study with the most cases and relevant information was included.

For eligible studies, the first author (year of publication), region, median age of participants, gender, cardioplegia type and number of participants in each group, temperature, delivery method, aortic cross-clamp time, cardiopulmonary bypass time, and outcomes were extracted by two independent authors (WW and SL). Numeric data were gathered directly from tables, or when presented in graphs only, were inferred by digitizing the figure with GetData Graph Digitizer 2.26 [6].

2.3 Study Outcomes

Researchers generally used biochemical and/or clinical outcomes to evaluate the myocardial protective effects. In this NMA, the outcomes included biochemical and clinical outcomes. Biochemical outcomes were the serum concentrations of the creatine kinase-myocardial band (CK-MB) 6 h postoperatively (IU/L) and cardiac troponin I (cTnI) 4, 12, and 24 h postoperatively (ng/ml). The clinical outcomes included spontaneous beating after declamping, postoperative arrhythmias, inotropic support (%), inotropic duration hours, mechanical ventilation hours, intensive care unit (ICU) stay in days, hospital stay in days, and risk of postoperative mortality.

2.4 Statistical Analysis

Before analyzing the data, the risk of trial bias of the included studies was assessed using the Cochrane Collaboration's Tool. Mean differences (MDs) and 95% confidence intervals (CIs) were used to report the 6-h CK-MB, 4-h cTnI, 12-h cTnI, 24-h cTnI, inotropic duration hours, mechanical ventilation hours, ICU stay in days, and hospital stay in days. Odds ratios (ORs) were used to report the risk of spontaneous beating after declamping, postoperative arrhythmias, inotropic support percentage, and mortality.

We evaluated the myocardial protection of various cardioplegia solutions using NMA. In the Bayesian NMA, random effects and consistency models were used for analyzing data and carrying out the network meta-analysis (4 chains, 50,000 iterations, and 20,000 per chain). We assessed inconsistency using the node-splitting method, and the inconsistency was reported by the Bayesian *P* value. The publication bias was evaluated using a comparison-adjusted funnel plot [7]. All analyses were conducted using the "gemtc" package of R (version 4.0.2; R Foundation) and Stata (version 16.0; StataCorp, College Station, TX, USA).

3 Results

Our exhaustive search strategy retrieved 536 potentially relevant publications from 7 databases. After screening, 22 RCTs s were included in our final analysis (Fig. 1 shows the PRISMA flow-chart) [8–29].

The 22 RCTs conducted in Europe, Asia, and the USA between 1994 and 2020 involved 1529 patients (Tab. 1). Six types of cardioplegia solutions were described in these studies, including cBCP, cCCP, DN, HTK, terminal warm blood cardioplegia, and warm blood cardioplegia (wBCP). Most cardioplegia solutions were delivered in an antegrade fashion. The temperature of cold cardioplegia solutions was 2°C–10°C. The temperature of warm cardioplegia solutions was 33°C–37°C. Additional details of the selected studies are shown in Tabs. S2–S4.

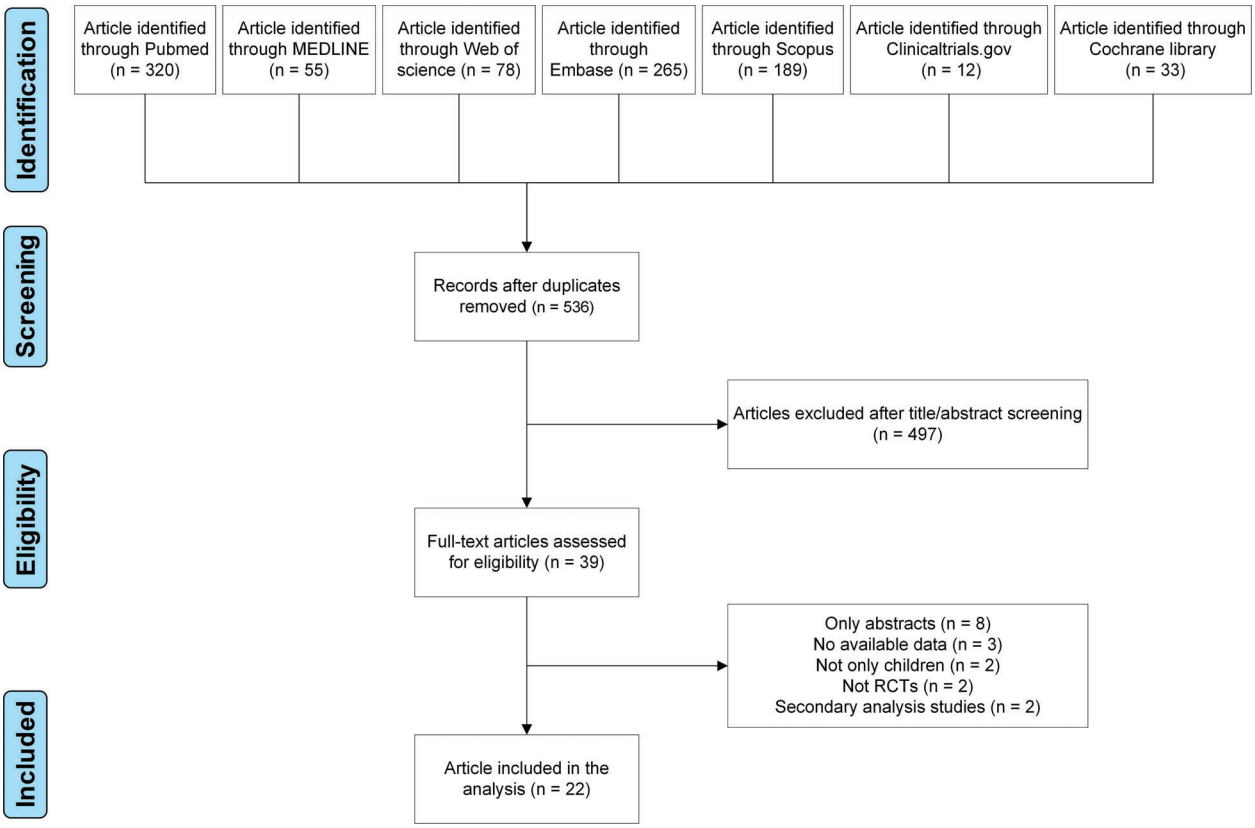

Figure 1: Flow-chart of study selection

Table 1: Characteristics of included studies

No.	Author (year)	Region	Median age (month)	Gender (male/ female)	Intervention	Number of participants	Temperature (°C)	Delivery method	Aortic cross −clamp time (min)	Cardiopulmonary bypass time (min)	Outcomes
1	Chen et al. 1994 [8]	China	NR (range: 36-120)	NR	cCCP	24	4	Antegrade	41 ± 8	89 ± 15	CK-MB, inotropic support
				NR	cBCP	21	4	Antegrade	38 ± 9	80 ± 19	
				NR	twBCP	12	4, terminal at 37	Antegrade	34 ± 8	75 ± 15	
				NR	wBCP	12	33–37	Antegrade	49 ± 2	86 ± 17	
2	Young et al. 1997 [9]	USA	36	75/63	cBCP	62	4	Antegrade	69 ± 3	NR	ICU stays, mortality
			29		cCCP	76	4	Antegrade	66 ± 4	NR	
3	Caputo et al. 2002 [10]	United Kingdom	5	11/10	cCCP	21	4–6	Antegrade	35 ± 24	62 ± 34	cTnI, postoperative arrhythmias, inotropic support, inotropic duration hours, mechanical ventilation hours, ICU stays, hospital stays, mortality*
			7	9/10	cBCP	19	4–6	Antegrade	29 ± 28	52 ± 34	
4	Toyoda et al. 2003 [11]	Japan	66	27/25	cBCP	52	9	Antegrade	83 ± 6	194 ± 12	Spontaneous beat after declamping, inotropic support, inotropic duration hours, mechanical ventilation hours, ICU stays, mortality
			67	33/18	twBCP	51	9, terminal at 35	Antegrade	82 ± 5	177 ± 9	
5	Modi et al. 2004 [12]	United Kingdom	34	17/15	cCCP	32	4	Antegrade	46 ± 13	80 ± 25	cTnI, inotropic duration hours, mechanical ventilation hours, ICU stays, hospital stays, mortality
			30	21/15	cBCP	36	4	Antegrade	51 ± 18	96 ± 36	
			25	19/16	twBCP	35	4, terminal at 37	Antegrade	50 ± 16	91 ± 29	
6	Amark et al. 2005 [13]	Sweden	4	4/11	cBCP	15	4	Antegrade	89 ± 6	135 ± 9	Inotropic support, mechanical ventilation hours, hospital stays, mortality*
			4	5/10	cCCP	15	4	Antegrade	88 ± 4	125 ± 5	
7	Duvan et al. 2009 [14]	Turkey	35	6/4	cCCP	10	4	Antegrade	35 ± 14	55 ± 16	Spontaneous beat after declamping, mechanical ventilation hours, ICU stays, hospital stays
			55	4/6	twBCP	10	4, terminal at 35	Antegrade	45 ± 22	63 ± 25	
8	Zhang et al. 2009 [15]	China	6	19/11	cCCP	10	4	Antegrade	30 ± 6	41 ± 9	Spontaneous beat after declamping, postoperative arrhythmias, inotropic support
					cBCP	20	4	Antegrade	33 ± 6	43 ± 8	
9	Poncelet et al. 2011 [16]	Belgium	24	NR	cCCP	22	5	Antegrade	NR	94 ± 30	cTnI, postoperative arrhythmias
			15		wBCP	25	36.5	Antegrade/ retrograde		90 ± 31	
10	Korun et al. 2013 [17]	Turkey	32	8/8	cCCP	16	4	Antegrade	50 ± 26	71 ± 30	Mortality
			47	11/5	HTK	16	4	Antegrade	41 ± 21	65 ± 26	
11	Ma et al. 2013 [18]	China	8	20/11	HTK	31	4	Antegrade	88 ± 17	NR	Spontaneous beat after declamping, postoperative arrhythmias, inotropic support, mortality
			7	40/24	cBCP	64	4	Antegrade	89 ± 18		
12	Kuşlu et al. 2015 [19]	Turkey	16	16/16	HTK	32	NR	Antegrade	55 ± 19	78 ± 21	CK-MB, cTnI, mechanical ventilation hours, ICU stays, hospital stays
			17	13/21	cCCP	34		Antegrade	53 ± 16	74 ± 18	

(Continued)

Table 1 (continued).

No.	Author (year)	Region	Median age (month)	Gender (male/female)	Intervention	Number of participants	Temperature (°C)	Delivery method	Aortic cross−clamp time (min)	Cardiopulmonary bypass time (min)	Outcomes
13	Mimic et al. 2016 [20]	Serbia	9	14/17	cCCP	31	4	Antegrade	49 ± 30	75 ± 28	cTnI, postoperative arrhythmias, inotropic support, mechanical ventilation hours, ICU stays, hospital stays, mortality
			11	15/16	cBCP	31	4	Antegrade	54 ± 28	79 ± 32	
14	Gorjipour et al. 2017 [21]	Iran	28	17/15	DN	32	NR	Antegrade	96 ± 31	137 ± 37	cTnI, mechanical ventilation hours, ICU stays
			24	9/18	cBCP	27		Antegrade	82 ± 24	128 ± 34	
15	Talwar et al. 2017 [22]	India	52	38/12	DN	50	NR	Antegrade	41 ± 13	67 ± 15	cTnI, mechanical ventilation hours, ICU stays, hospital stays, mortality
			65	33/17	cBCP	50		Antegrade	49 ± 16	78 ± 20	
16	Busro et al. 2018 [23]	Indonesia	23	32/23	HTK	55	4–10	NR	67 ± 27	118 ± 38	cTnI, mechanical ventilation hours, ICU stays, hospital stays, mortality
			26	29/25	twBCP	54	4–10, terminal at 34–36		64 ± 32	110 ± 41	
17	Panigrahi et al. 2018 [24]	India	36	15/15	DN	30	8–12	Antegrade	65 ± 30	93 ± 33	CK-MB, cTnI, mechanical ventilation hours, ICU stays, hospital stays
			27	16/14	cBCP	30	8–12	Antegrade	74 ± 39	105 ± 44	
18	Negi et al. 2019 [25]	India	8	15/11	cBCP	26	8–12	Antegrade	97 ± 28	147 ± 36	Spontaneous beat after declamping, mechanical ventilation hours, ICU stays, hospital stays, mortality
			9	18/12	DN	30	4–8	Antegrade	98 ± 38	144 ± 42	
19	Talwar et al. 2019 [26]	India	53	36/14	DN	50	8–10	NR	85 ± 13	126 ± 16	cTnI, mechanical ventilation hours, ICU stays, hospital stays, mortality
			61	17/33	HTK	50	4–8		87 ± 16	129 ± 17	
20	Valente et al. 2019 [27]	Brazil	29	9/16	HTK	25	5	Antegrade	58 ± 20	80 ± 22	Mortality
			19	10/15	cBCP	25	20	Antegrade	54 ± 18	80 ± 22	
21	Bigdelian et al. 2020 [28]	Iran	20	18/12	DN	30	NR	NR	71 ± 13	98 ± 14	Postoperative arrhythmias, inotropic support, inotropic duration hours, mechanical ventilation hours, ICU stays, hospital stays, postoperative arrhythmias
			22	16/14	cCCP	30			67 ± 9	92 ± 12	
22	Haranal et al. 2020 [29]	Malaysia	24	29/21	DN	50	2–8	Antegrade	60 ± 49	97 ± 74	Inotropic support, mechanical ventilation hours, ICU stays
			20	25/25	cBCP	50	2–8	Antegrade	57 ± 46	92 ± 60	

Note: cBCP: cold blood cardioplegia; cCCP: cold crystalloid cardioplegia; CK-MB: creatine kinase-myocardial band; cTnI: cardiac troponin I; DN: del Nido; HTK: Histidine-tryptophan-ketoglutarate; ICU: intensive care unit; NR: not reported; twBCP: terminal warm blood cardioplegia; wBCP: warm blood cardioplegia. *: there were no deaths in each group.

Evaluation of the bias risk for all RCTs is presented in the supplemental file (Figs. S1 and S2). Only two studies were high risk. Five studies were considered low risk and 14 studies were considered to have an unclear risk, which indicated that the selected RCTs were of good quality.

The geometry of the network is shown in Fig. S3 in the supplemental file. Ten studies with 5 types of cardioplegia solution involving the 24-h cTnI were included (Tab. 2). The serum concentration of the 24-h cTnI with wBCP (MD = −2.52, 95% CI: −4.74 to −0.27) was significantly lower than cCCP (Fig. 2). The serum concentration of the 24-h cTnI with HTK (MD = 4.91, 95% CI:2.84–7.24) was significantly higher than cCCP (Fig. 2). There was no significant difference in other biochemical outcomes among seven cardioplegia solutions (Fig. 3).

Table 2: Summary of the results of NMA and GRADE quality score assessment for the outcomes

Outcome	Number of studies	Number of participants	Conclusion	GRADE quality score
CK-MB 6-h (IU/L)	3	183	No difference when compared to cCCP	Moderate[#]
cTnI 4-h (ng/ml)	7	455	No difference when compared to cCCP	Moderate[#]
cTnI 12-h (ng/ml)	6	346	No difference when compared to cCCP	Moderate[#]
cTnI 24-h (ng/ml)	10	714	wBCP superior to cCCP	Moderate[#]
Spontaneous beat after declamping	5	304	No difference when compared to cCCP	Moderate[#]
Postoperative arrhythmias	6	334	No difference when compared to cCCP	Moderate[#]
Inotropic support (%)	9	589	No difference when compared to cCCP	Low[‡]
Inotropic duration hours	4	306	No difference when compared to cCCP	Moderate[#]
Mechanical ventilation hours	15	1068	No difference when compared to cCCP	Moderate[#]
ICU stays (days)	15	1176	No difference when compared to cCCP	Moderate[#]
Hospital stays (days)	12	806	No difference when compared to cCCP	Moderate[#]
Mortality	12	995	No difference when compared to cCCP	Low[‡]

Note: cBCP: cold blood cardioplegia; cCCP: cold crystalloid cardioplegia; CK-MB: creatine kinase-myocardial band; cTnI: cardiac troponin I; DN: del Nido; HTK: Histidine-tryptophan-ketoglutarate; ICU: intensive care unit; twBCP: terminal warm blood cardioplegia; wBCP: warm blood cardioplegia. # Rated down for serious imprecision; ‡ Rated down for serious inconsistency.

There was no significant difference in spontaneous beating after declamping, postoperative arrhythmias, inotropic support percentage, inotropic duration hours, mechanical ventilation hours, ICU stay in days, hospital stay in days, or mortality of the five cardioplegia solutions when compared with cCCP. The head-to-head comparisons of each outcome are shown in Tabs. S5–S16.

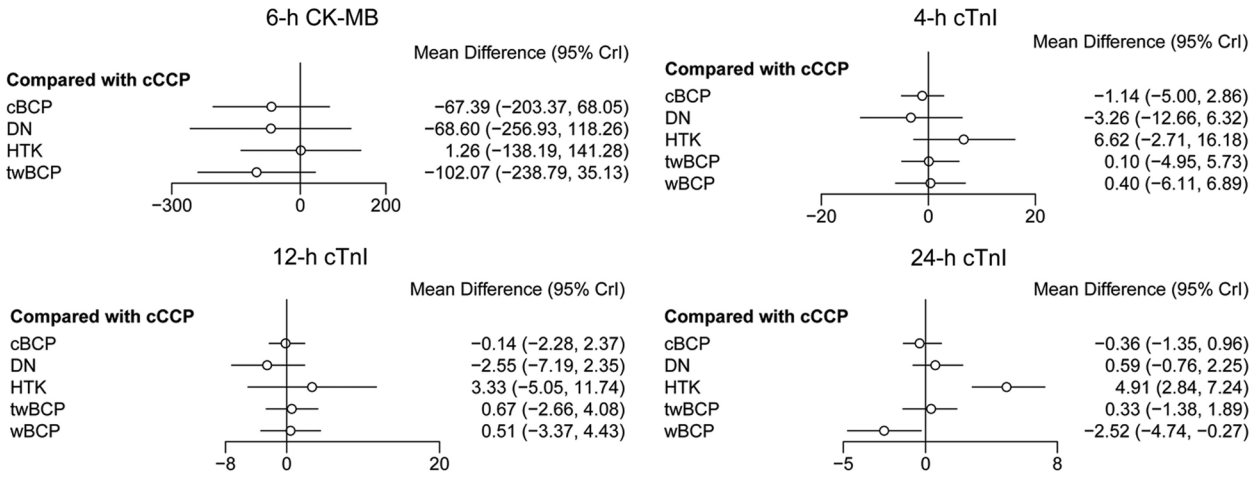

Figure 2: Forest plots of network meta-analysis of all trials for biochemical outcomes. cBCP: cold blood cardioplegia; cCCP: cold crystalloid cardioplegia; CK-MB: creatine kinase-myocardial band; cTnI: cardiac troponin I; DN: del Nido; HTK: Histidine-tryptophan-ketoglutarate; twBCP: terminal warm blood cardioplegia; wBCP: warm blood cardioplegia

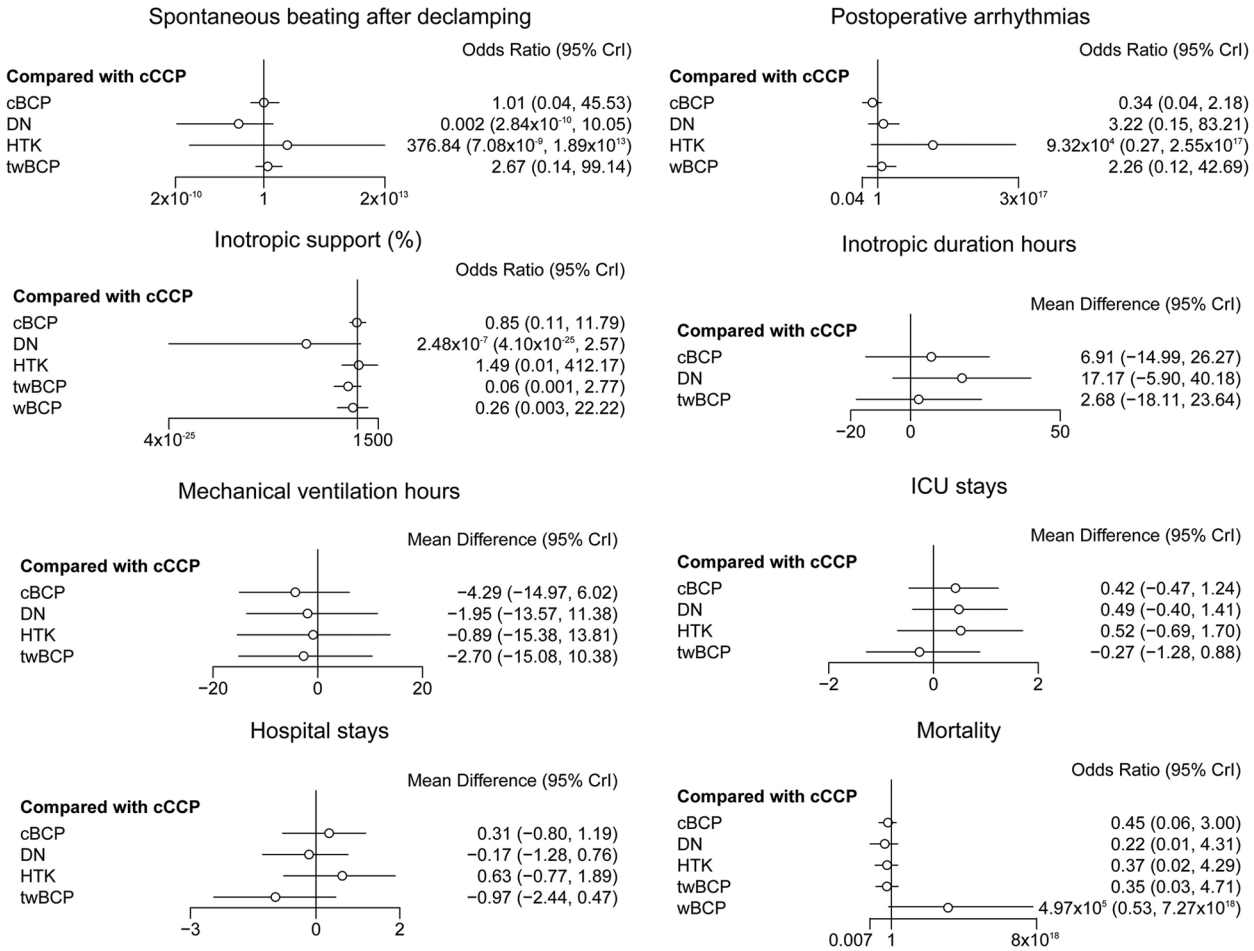

Figure 3: Forest plots of network meta-analysis of all trials for clinical outcomes. cBCP: cold blood cardioplegia; cCCP: cold crystalloid cardioplegia; DN: del Nido; HTK: Histidine-tryptophan-ketoglutarate; ICU: intensive care unit; twBCP: terminal warm blood cardioplegia; wBCP: warm blood cardioplegia

The results of evaluating inconsistencies for all outcomes are presented in Figs. S4–S12 in the supplemental file. We noted a significance level of $P > 0.05$ for most of cases, which indicated that inconsistency was not present for most comparisons. After comparison results were obtained, we used the GRADE system to evaluate the certainty of evidence (Tab. 2). No significant asymmetry was detected in the funnel plots of primary and secondary outcomes (Fig. S13).

4 Discussion

Based on this Bayesian NMA, cTnI measurements indicated that wBCP may afford better myocardial protection with lower cTnI levels 24 h postoperatively after cardiac surgery in children. The clinical outcomes were similar for various cardioplegia solutions. Indeed, this NMA is the first to compare the myocardial protective effects of various cardioplegia solutions during pediatric cardiac surgery.

There are several systematic reviews and meta-analyses that have compared cardioplegia during cardiac surgery over the years [30–33]. Fang et al. [30] compared cCCP and cBCP/wBCP in 5 RCTs and found that the 4-, 12-, and 24-h cTnI levels postoperatively, duration of mechanical ventilation, and ICU stays were not significantly different between groups. Mylonas et al. [31] concluded that the 4-h cTnI level was lower in the cBCP/wBCP group compared to cCCP based on 6 RCTs and 2 retrospective studies. Moreover, the duration of mechanical ventilation, length of hospital stay, and early mortality were similar in the analysis. Drury et al. [32] reported that the most common end points of cardioplegia in pediatric cardiac surgery were biomarkers of myocardial injury (cTnI [42.3%] and CK-MB [30.8%]), inotropic support (57.7%), and ICU stay (42.3%) in a systematic review involving 26 RCTs. Ler et al. [33] determined that the ICU stay and early mortality rate were similar when comparing DN and cCCP in three RCTs and one retrospective study.

The cTnI, cardiac troponin T, and CK-MB levels are specific and sensitive biomarkers of myocardial (ischemic–reperfusion) injury. Cardiac troponins are more specific markers of myocardial injury in pediatric cardiac surgery than CK-MB [34]. The diagnostic value of cTnI is similar to cardiac troponin T, but compared with cardiac troponin T, cTnI has the advantage of not being influenced by renal failure [35]. Several studies have shown the same trend; specifically, cTnI peaks at 4 h postoperatively and gradually decreases at 12 and 24 h [36–38]. Therefore, we chose 4, 12, and 24 h as the time points for cTnI in this NMA. cTnI values immediately postoperatively reflect the extent of myocardial damage from both incisional injury and intraoperative factors [39]. The 24-h cTnI level is also a good predictor for clinical outcomes following pediatric cardiac surgery, and correlated with ICU and hospital stays [39–41].

The advantages of wBCP during adult cardiac surgery were demonstrated as early as 1989 [42]. Since that time, wBCP has been shown to be safe and effective based on several RCTs involving adult cardiac surgery and widely used in clinical practice [43–45]; however, wBCP needs to be proven to become the standard method in pediatric patients. Two retrospective studies [46,47] and two RCTs [8,16] focused on wBCP during pediatric cardiac surgery. Chen et al. [8] published the first Chinese report which found that wBCP has a better myocardial protective effect with higher ATP and creatine phosphate, and lower inotropic support. Durandy et al. [46] published the first English report which showed that myocardial protection with wBCP during pediatric cardiac surgery was safe and effective in 1400 patients, with advantageous results in terms of fluid balance, sinus rhythm recovery, and time-to-extubation when compared to cBCP. Pouard et al. [47] reported that wBCP has a lower 24-h cTnI level, shorter duration of mechanical ventilation, and a trend to reduce the ICU length of stay. Poncelet et al. [16] confirmed that wBCP is as safe as cCCP through clinical outcomes, cardiac metabolic, and late neurologic and neuropsychologic assessments. The advantages of wBCP are as follows: (1) improved oxygen supply and reduced myocardial edema; and (2) easier to apply and cost-effective because cooling equipment is no longer required [48]. In addition, there is a RCT involving wBCP that is ongoing which may provide evidence to support the benefits of wBCP to clinical and biochemical outcomes during and after pediatric congenital heart surgery [48].

There were several limitations in this study. First, some of the selected studies were limited sample-sized, single-centered trials that could reduce the credibility of the results and conclusions. Second, the approach of administering cardioplegia, whether antegrade, retrograde, or a combination of both, was not analyzed in this NMA because most cardioplegia solutions were delivered in an antegrade fashion. Third, despite the use of NMA, some underlying confounders, such as the surgical complexity of the selected patients, surgical competence, and surgical proficiency may not be adjustable.

5 Conclusion

We are of the opinion that wBCP may have a superior myocardial protective effect with a lower 24-h cTnI level postoperatively and similar clinical outcomes after pediatric cardiac surgery.

Authors' Contributions: The authors' contributions were as follows: KZ participated in data collection, data analysis, and manuscript writing. DL participated in data collection and data analysis. XZ participated in data analysis. WW participated in data analysis. SL participated in project development. GS participated in project development, data analysis, and manuscript writing. All authors have read and approved the final manuscript.

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Appendix

Table S1: Strategy of this meta-analysis

Database	Strategy
PubMed	#1: (randomized controlled trial [Publication Type] OR controlled clinical trial [Publication Type] OR randomized [Title/Abstract] OR random [Title/Abstract] OR randomly [Title/Abstract] OR controlled [Title/Abstract] OR trial [Title/Abstract] OR placebo [Title/Abstract] OR groups [Title/Abstract]) NOT ((animals [Mesh] OR swine [Title/Abstract] OR pig [Title/Abstract] OR pigs [Title/Abstract] OR piglet*[Title/Abstract] OR rat [Title/Abstract] OR mouse [Title/Abstract]) NOT humans [Mesh]) #2: Cardioplegia [Title/Abstract] OR crystalloid cardioplegia [Title/Abstract] OR St. Thomas [Title/Abstract] OR Bretschneider[Title/Abstract] OR HTK[Title/Abstract] OR histidine-tryptophan-ketoglutarate[Title/Abstract] OR histidine tryptophan ketoglutarate [Title/Abstract] OR blood cardioplegia[Title/Abstract] OR del Nido[Title/Abstract] OR "Cardioplegic Solutions"[Mesh] OR "Heart Arrest, Induced"[Mesh] #3: infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby* OR babies OR girl* OR boy* OR kid OR kids OR child* OR paediatrics [mh] OR pediatric* OR paediatric* OR peadiatric* OR prematur* OR preterm* OR congenital* #4: #1 AND #2 AND #3
Medline	#1: (randomized controlled trial.pt OR controlled clinical trial.pt OR randomized.mp. OR placebo.mp. OR randomly.mp. OR trial.ti. OR Clinical Trials as Topic/) NOT (animals.sh. NOT humans.sh.) #2: (infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby* OR babies OR girl* OR boy* OR kid OR kids OR child* OR pediatric* OR paediatric* OR peadiatric* OR prematur* OR preterm* OR congenital*).mp. OR paediatrics.sh. #3: cardioplegia.sh. OR cardioplegia.ab. OR cardioplegia.ti. #4: #1 AND #2 AND #3
Web of science	#1: TS = (random* controlled trial OR random* OR placebo) #2: TS = (cardioplegia OR St. Thomas OR Bretschneider OR HTK OR histidine-tryptophan-ketoglutarate OR histidine tryptophan ketoglutarate OR del Nido) #3: TS = (infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby* OR babies OR girl* OR boy* OR kid OR kids OR child* OR paediatrics OR pediatric* OR paediatric*) OR peadiatric* OR prematur* OR preterm* OR congenital*) #4: #1 AND #2 AND #3

(Continued)

Table S1 (continued).

Database	Strategy
Embase	('random':ab,ti OR 'placebo':ab,ti OR 'double-blind':ab,ti OR 'randomized':ab,ti OR 'controlled':ab,ti OR 'group':ab,ti OR 'trial':ab,ti) AND ('Cardioplegia':ab,ti OR 'crystalloid cardioplegia':ab,ti OR 'blood cardioplegia':ab,ti OR 'St. Thomas':ab,ti OR 'Bretschneider':ab,ti OR 'HTK':ab,ti OR 'histidine-tryptophan-ketoglutarate':ab,ti OR 'histidine tryptophan ketoglutarate':ab,ti OR 'del Nido':ab,ti) AND ('infan*':ab,ti OR 'newborn*':ab,ti OR 'new-born*':ab,ti OR 'perinat*':ab,ti OR 'neonat*':ab,ti OR 'baby*':ab,ti OR 'babies':ab,ti OR 'girl*':ab,ti OR 'boy*':ab,ti OR 'kid':ab,ti OR 'kids':ab,ti OR 'child*':ab,ti OR 'pediatric*':ab,ti OR 'paediatric*':ab,ti OR 'peadiatric*':ab,ti OR 'prematur*':ab,ti OR 'preterm*':ab,ti OR 'congenital*':ab,ti)
Scopus	TITLE-ABS-KEY ("infan*" OR "newborn*" OR "new-born*" OR "adolescent*" OR "neonat*" OR "baby*" OR "babies" OR "kid" OR "kids" OR "child*" OR "pediatric*" OR "perinat*" OR "girl*" OR "boy*" OR "paediatric*" OR "peadiatric*" OR "prematur*" OR "preterm*" OR "congenital*") AND TITLE-ABS-KEY ("randomized" OR "controlled" OR "trial" "randomly" OR "random" OR "placebo" OR "groups") AND TITLE-ABS-KEY ("cardioplegia" OR "St. Thomas" OR "Bretschneider" OR "HTK" OR "histidine-tryptophan-ketoglutarate" OR "histidine tryptophan ketoglutarate" OR "del Nido") AND NOT TITLE-ABS-KEY((animal* OR swine OR pig OR pigs OR piglet* OR rat OR mouse) AND NOT human*)
ClinicalTrials.gov	(Cardioplegia) AND (Age group: Child (birth–17))
Cochrane library	(Cardioplegia) AND (pediatric)

Table S2: The detail of each subgroup of cardioplegic solutions

Type of cardioplegia	Number of participants	Reference
cBCP	528	[1–15]
cCCP	321	[1–3,5–7,9,16–20]
DN	272	[10–13,15,20,21]
HTK	209	[8,14,18,19,21,22]
twBCP	162	[1,4,5,16,22]
wBCP	37	[1,17]

Note: cBCP: cold blood cardioplegia; cCCP: cold crystalloid cardioplegia; DN: del Nido; HTK: Histidine-tryptophan-ketoglutarate; twBCP: terminal warm blood cardioplegia; wBCP: warm blood cardioplegia.

Table S3: The detail of distribution of cardioplegic solutions in each outcome

Outcome	Type of cardioplegia	Number of participants (percentage)
CK-MB 6-h (IU/L)		183
	cBCP	54 (29.5%)
	cCCP	55 (30.1%)
	DN	30 (16.4%)
	HTK	32 (17.5%)
	twBCP	12 (6.5%)
cTnI 4-h (ng/ml)		455
	cBCP	104 (22.9%)
	cCCP	130 (28.6%)
	DN	30 (6.5%)
	HTK	87 (19.1%)
	twBCP	79 (17.4%)
	wBCP	25 (5.5%)
cTnI 12-h (ng/ml)		346
	cBCP	104 (30.1%)
	cCCP	130 (37.6%)
	DN	30 (8.7%)
	HTK	32 (9.2%)
	twBCP	25 (7.2%)
	wBCP	25 (7.2%)
cTnI 24-h (ng/ml)		714
	cBCP	181 (25.4%)
	cCCP	130 (18.2%)
	DN	162 (22.6%)
	HTK	137 (19.2%)
	twBCP	79 (11.1%)
	wBCP	25 (3.5%)
Spontaneous beating after declamping		304
	cBCP	162 (53.3%)
	cCCP	20 (6.6%)
	DN	30 (9.9%)
	HTK	31 (10.2%)
	twBCP	61 (20.0%)
Postoperative arrhythmias		334
	cBCP	134 (40.1%)
	cCCP	114 (34.1%)
	DN	30 (9.0%)
	HTK	31 (9.3%)
	wBCP	25 (7.5%)

(Continued)

Table S3 (continued).

Outcome	Type of cardioplegia	Number of participants (percentage)
Inotropic support (%)		589
	cBCP	272 (46.2%)
	cCCP	131 (22.2%)
	DN	80 (13.6%)
	HTK	31 (5.3%)
	twBCP	63 (10.7%)
	wBCP	12 (2.0%)
Inotropic duration hours		306
	cBCP	107 (35.0%)
	cCCP	83 (27.1%)
	DN	30 (9.8%)
	twBCP	86 (28.1%)
Mechanical ventilation hours		1068
	cBCP	336 (31.5%)
	cCCP	173 (16.2%)
	DN	272 (25.5%)
	HTK	137 (12.8%)
	twBCP	150 (14.0%)
ICU stays (days)		1176
	cBCP	383 (32.6%)
	cCCP	234 (19.9%)
	DN	272 (23.1%)
	HTK	137 (11.6%)
	twBCP	150 (12.8%)
Hospital stays (days)		806
	cBCP	207 (25.7%)
	cCCP	173 (21.5%)
	DN	190 (23.5%)
	HTK	137 (17.0%)
	twBCP	99 (12.3%)
Mortality		995
	cBCP	346 (34.8%)
	cCCP	177 (17.8%)
	DN	130 (13.0%)
	HTK	177 (17.8%)
	twBCP	140 (14.1%)
	wBCP	25 (2.5%)

Note: cBCP: cold blood cardioplegia; cCCP: cold crystalloid cardioplegia; CK-MB: creatine kinase-myocardial band; cTnI: cardiac troponin I; DN: del Nido; HTK: Histidine-tryptophan-ketoglutarate; ICU: intensive care unit; twBCP: terminal warm blood cardioplegia; wBCP: warm blood cardioplegia.

Table S4: The RACHS-1 score of included studies

No.	Author (year)	Intervention	Number of participants	RACHS-1 score
1	Chen et al. 1994 [1]	cCCP	24	2
		cBCP	21	2
		twBCP	12	2
		wBCP	12	2
2	Young et al. 1997 [2]	cBCP	62	2.5 ± 0.9
		cCCP	76	
3	Caputo et al. 2002 [3]	cCCP	21	2
		cBCP	19	2
4	Toyoda et al. 2003 [4]	cBCP	52	NR
		twBCP	51	
5	Modi et al. 2004 [5]	cCCP	32	1.9 ± 0.5
		cBCP	36	2.0 ± 0.6
		twBCP	35	1.9 ± 0.5
6	Amark et al. 2005 [6]	cBCP	15	3
		cCCP	15	3
7	Duvan et al. 2009 [16]	cCCP	10	1.4 ± 0.5
		twBCP	10	1.6 ± 0.5
8	Zhang et al. 2009 [7]	cCCP	10	2
		cBCP	20	
9	Poncelet et al. 2011 [17]	cCCP	22	2.3 ± 0.6
		wBCP	25	2.1 ± 0.4
10	Korun et al. 2013 [18]	cCCP	16	NR
		HTK	16	
11	Ma et al. 2013 [8]	HTK	31	2.4 ± 0.8
		cBCP	64	
12	Kuşlu et al. 2015 [19]	HTK	32	NR
		cCCP	34	
13	Mimic et al. 2016 [9]	cCCP	31	2.0 ± 0.7
		cBCP	31	2.2 ± 0.7
14	Gorjipour et al. 2017 [10]	DN	32	2
		cBCP	27	2
15	Talwar et al. 2017 [11]	DN	50	2
		cBCP	50	2
16	Busro et al. 2018 [22]	HTK	55	2.4 ± 0.6
		twBCP	54	2.5 ± 0.7

(Continued)

Table S4 (continued).

No.	Author (year)	Intervention	Number of participants	RACHS-1 score
17	Panigrahi et al. 2018 [12]	DN	30	1 to 2
		cBCP	30	
18	Negi et al. 2019 [13]	cBCP	26	2
		DN	30	2
19	Talwar et al. 2019 [21]	DN	50	2
		HTK	50	2
20	Valente et al. 2019 [14]	HTK	25	2.4 ± 0.8
		cBCP	25	2.1 ± 0.6
21	Bigdelian et al. 2020 [20]	DN	30	2
		cCCP	30	2
22	Haranal et al. 2020 [15]	DN	50	NR
		cBCP	50	

Note: cBCP: cold blood cardioplegia; cCCP: cold crystalloid cardioplegia; DN: del Nido; HTK: Histidine-tryptophan-ketoglutarate; NR: not reported; RACHS: Risk Adjustment for Congenital Heart Surgery; twBCP: terminal warm blood cardioplegia; wBCP: warm blood cardioplegia.

Table S5: Head-to-head comparisons of CK-MB 6-h (IU/L)

cBCP	67.39 (–68.05, 203.37)	–1.22 (–130.45, 126.59)	68.32 (–125.47, 264.32)	–34.31 (–164.71, 95.7)
	cCCP	–68.60 (–256.93, 118.26)	1.26 (–138.19, 141.28)	–102.07 (–238.79, 35.13)
		DN	69.45 (–162.02, 305.28)	–33.13 (–217.13, 150.73)
			HTK	–103.11 (–300.24, 92.26)
				twBCP

Note: cBCP: cold blood cardioplegia; cCCP: cold crystalloid cardioplegia; CK-MB: creatine kinase-myocardial band; DN: del Nido; HTK: Histidine-tryptophan-ketoglutarate; twBCP: terminal warm blood cardioplegia.

Table S6: Head-to-head comparisons of cTnI 4-h (ng/ml)

cBCP	1.14 (–2.86, 5)	–2.11 (–10.81, 6.61)	7.75 (–2.02, 17.65)	1.23 (–3.98, 6.93)	1.54 (–6.12, 9.06)
	cCCP	–3.26 (–12.66, 6.32)	6.62 (–2.71, 16.18)	0.1 (–4.95, 5.73)	0.4 (–6.11, 6.89)
		DN	9.9 (–3.28, 23.07)	3.4 (–6.64, 13.7)	3.67 (–7.81, 15.02)
			HTK	–6.46 (–16.03, 2.96)	–6.19 (–17.75, 5.07)
				twBCP	0.29 (–8.39, 8.42)
					wBCP

Note: cBCP: cold blood cardioplegia; cCCP: cold crystalloid cardioplegia; cTnI: cardiac troponin I; DN: del Nido; HTK: Histidine-tryptophan-ketoglutarate; twBCP: terminal warm blood cardioplegia; wBCP: warm blood cardioplegia.

Table S7: Head-to-head comparisons of cTnI 12-h (ng/ml)

cBCP	0.14 (–2.37, 2.28)	–2.44 (–6.62, 1.72)	3.42 (–5.29, 12.08)	0.81 (–2.72, 4.03)	0.63 (–4.03, 5.02)
	cCCP	–2.55 (–7.19, 2.35)	3.32 (–5.05, 11.74)	0.67 (–2.66, 4.08)	0.51 (–3.37, 4.43)
		DN	5.86 (–3.73, 15.46)	3.23 (–2.24, 8.47)	3.06 (–3.2, 9.07)
			HTK	–2.65 (–11.61, 6.31)	–2.81 (–11.99, 6.37)
				twBCP	–0.17 (–5.32, 4.98)
					wBCP

Note: cBCP: cold blood cardioplegia; cCCP: cold crystalloid cardioplegia; cTnI: cardiac troponin I; DN: del Nido; HTK: Histidine-tryptophan-ketoglutarate; twBCP: terminal warm blood cardioplegia; wBCP: warm blood cardioplegia.

Table S8: Head-to-head comparisons of cTnI 24-h (ng/ml)

cBCP	0.36 (–0.96, 1.35)	0.96 (–0.09, 1.98)	5.26 (3.26, 7.33)	0.69 (–1.18, 2.13)	–2.17 (–4.78, 0.22)
	cCCP	0.59 (–0.76, 2.25)	4.91 (2.84, 7.24)	0.33 (–1.38, 1.89)	–2.52 (–4.74, –0.27)
		DN	4.32 (2.4, 6.28)	–0.26 (–2.33, 1.39)	–3.12 (–5.9, –0.55)
			HTK	–4.59 (–7.08, –2.42)	–7.44 (–10.67, –4.44)
				twBCP	–2.86 (–5.54, –0.02)
					wBCP

Note: cBCP: cold blood cardioplegia; cCCP: cold crystalloid cardioplegia; cTnI: cardiac troponin I; DN: del Nido; HTK: Histidine-tryptophan-ketoglutarate; twBCP: terminal warm blood cardioplegia; wBCP: warm blood cardioplegia.

Table S9: Head-to-head comparisons of spontaneous beating after declamping

cBCP	0.99 (0.02, 26.21)	0 (0, 3.81)	352.74 (0, 1.65×10^{13})	2.65 (0.61, 11.75)
	cCCP	0 (0, 10.05)	376.84 (0, 1.89×10^{13})	2.67 (0.14, 99.14)
		DN	8.85×10^{5} (0, 4.98×10^{16})	1517.89 (0.61, 9.26×10^{9})
			HTK	0.01 (0, 5.28×10^{8})
				twBCP

Note: cBCP: cold blood cardioplegia; cCCP: cold crystalloid cardioplegia; DN: del Nido; HTK: Histidine-tryptophan-ketoglutarate; twBCP: terminal warm blood cardioplegia.

Table S10: Head-to-head comparisons of postoperative arrhythmias

cBCP	2.95 (0.46, 23.22)	9.63 (0.27, 462.36)	2.78×10^{5} (1.01, 7.26×10^{17})	6.7 (0.22, 251.27)
	cCCP	3.22 (0.15, 83.21)	9.33×10^{4} (0.27, 2.56×10^{17})	2.26 (0.12, 42.69)
		DN	3.08×10^{4} (0.05, 8.56×10^{16})	0.69 (0.01, 49.91)
			HTK	0 (0, 12.89)
				wBCP

Note: cBCP: cold blood cardioplegia; cCCP: cold crystalloid cardioplegia; DN: del Nido; HTK: Histidine-tryptophan-ketoglutarate; wBCP: warm blood cardioplegia.

Table S11: Head-to-head comparisons of inotropic support (%)

cBCP	1.18 (0.08, 9.01)	0 (0, 3.3)	1.81 (0.02, 203.82)	0.07 (0, 1.97)	0.3 (0, 19.19)
	cCCP	0 (0, 2.57)	1.49 (0.01, 412.17)	0.06 (0, 2.77)	0.26 (0, 22.22)
		DN	7.40×10^6 (0.25, 5.56×10^{24})	2.56×10^5 (0.01, 1.69×10^{23})	1.11×10^6 (0.05, 8.07×10^{23})
			HTK	0.04 (0, 11.27)	0.17 (0, 82.53)
				twBCP	4.19 (0.03, 626.04)
					wBCP

Note: cBCP: cold blood cardioplegia; cCCP: cold crystalloid cardioplegia; DN: del Nido; HTK: Histidine-tryptophan-ketoglutarate; twBCP: terminal warm blood cardioplegia; wBCP: warm blood cardioplegia.

Table S12: Head-to-head comparisons of inotropic duration hours

cBCP	–6.91 (–26.27, 14.99)	10.24 (–19.16, 42.57)	–4.65 (–17.74, 13)
	cCCP	17.17 (–5.9, 40.18)	2.68 (–18.11, 23.64)
		DN	–14.53 (–45.49, 16.87)
			twBCP

Note: cBCP: cold blood cardioplegia; cCCP: cold crystalloid cardioplegia; DN: del Nido; twBCP: terminal warm blood cardioplegia.

Table S13: Head-to-head comparisons of mechanical ventilation hours

cBCP	4.29 (–6.02, 14.97)	2.35 (–6.8, 13.58)	3.39 (–11.64, 19.06)	1.57 (–10.67, 15.01)
	cCCP	–1.95 (–13.57, 11.38)	–0.89 (–15.38, 13.81)	–2.7 (–15.08, 10.38)
		DN	1.08 (–14.67, 15.18)	–0.77 (–16.2, 13.81)
			HTK	–1.82 (–18, 15)
				twBCP

Note: cBCP: cold blood cardioplegia; cCCP: cold crystalloid cardioplegia; DN: del Nido; HTK: Histidine-tryptophan-ketoglutarate; twBCP: terminal warm blood cardioplegia.

Table S14: Head-to-head comparisons of ICU stays

cBCP	–0.42 (–1.24, 0.47)	0.07 (–0.58, 0.82)	0.1 (–1.05, 1.29)	–0.69 (–1.62, 0.47)
	cCCP	0.49 (–0.4, 1.41)	0.52 (–0.69, 1.7)	–0.27 (–1.28, 0.88)
		DN	0.04 (–1.09, 1.09)	–0.76 (–1.83, 0.44)
			HTK	–0.79 (–1.98, 0.57)
				twBCP

Note: cBCP: cold blood cardioplegia; cCCP: cold crystalloid cardioplegia; DN: del Nido; HTK: Histidine-tryptophan-ketoglutarate; ICU: intensive care unit; twBCP: terminal warm blood cardioplegia.

Table S15: Head-to-head comparisons of hospital stays

cBCP	–0.31 (–1.19, 0.8)	–0.49 (–1.25, 0.42)	0.29 (–0.94, 1.75)	–1.28 (–2.66, 0.29)
	cCCP	–0.17 (–1.28, 0.76)	0.63 (–0.77, 1.89)	–0.97 (–2.44, 0.47)
		DN	0.78 (–0.37, 2.04)	–0.8 (–2.3, 0.8)
			HTK	–1.58 (–3.26, 0.1)
				twBCP

Note: cBCP: cold blood cardioplegia; cCCP: cold crystalloid cardioplegia; DN: del Nido; HTK: Histidine-tryptophan-ketoglutarate; twBCP: terminal warm blood cardioplegia.

Table S16: Head-to-head comparisons of mortality

cBCP	2.21 (0.33, 17.41)	0.48 (0.03, 5.76)	0.82 (0.09, 6.06)	0.78 (0.11, 6.84)	1.14×10^6 (0.97, 1.80×10^{19})
	cCCP	0.22 (0.01, 4.31)	0.37 (0.02, 4.29)	0.35 (0.03, 4.71)	4.97×10^5 (0.53, 7.27×10^{18})
		DN	1.7 (0.11, 30.45)	1.62 (0.09, 48.77)	2.47×10^6 (1.49, 4.19×10^{19})
			HTK	0.97 (0.11, 11.81)	1.50×10^6 (1.11, 2.26×10^{19})
				twBCP	1.48×10^6 (1.19, 2.48×10^{19})
					wBCP

Note: cBCP: cold blood cardioplegia; cCCP: cold crystalloid cardioplegia; DN: del Nido; HTK: Histidine-tryptophan-ketoglutarate; twBCP: terminal warm blood cardioplegia; wBCP: warm blood cardioplegia.

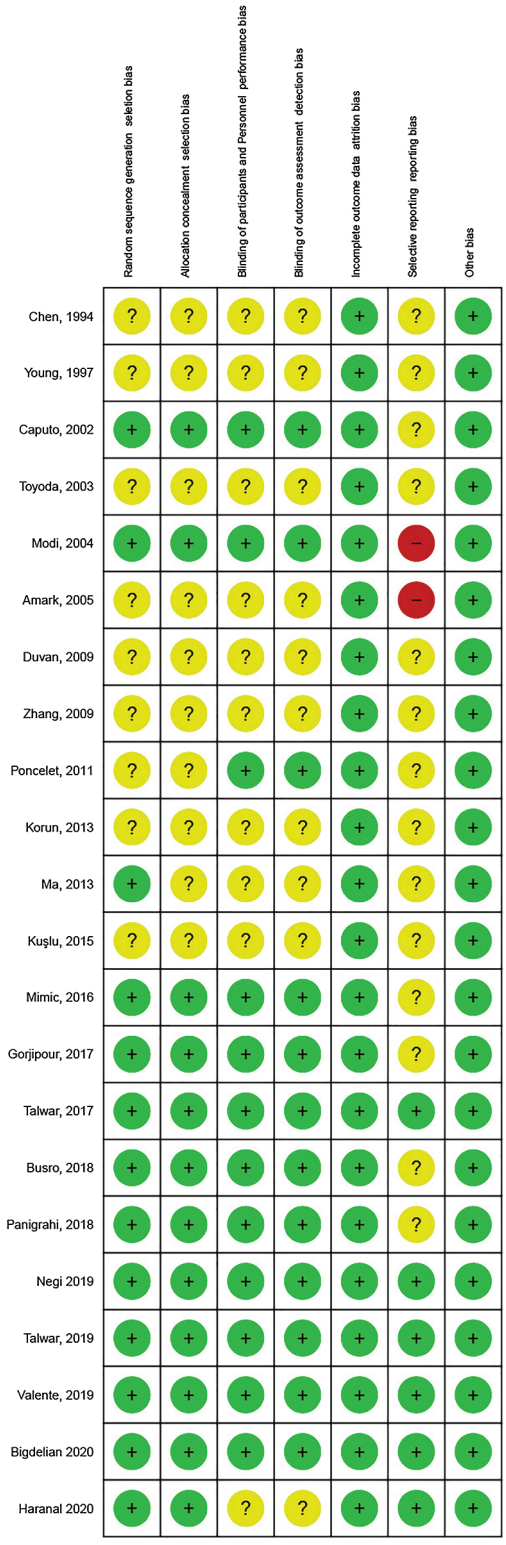

Figure S1: Risk of bias summary. +: low risk of bias; –: high risk of bias; ?: unclear risk of bias

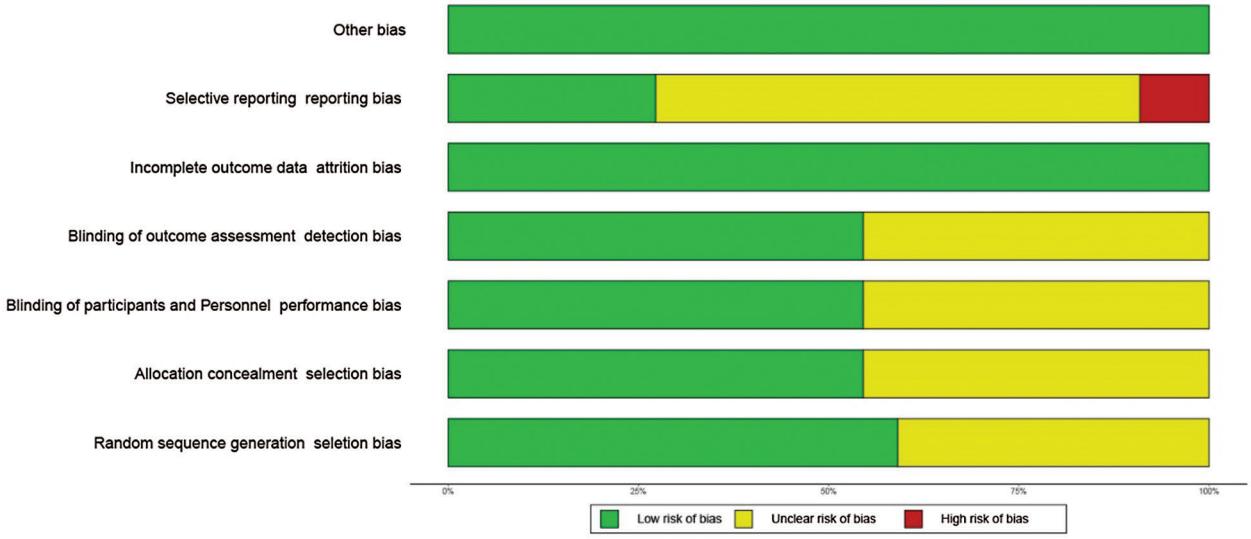

Figure S2: Risk of bias graph

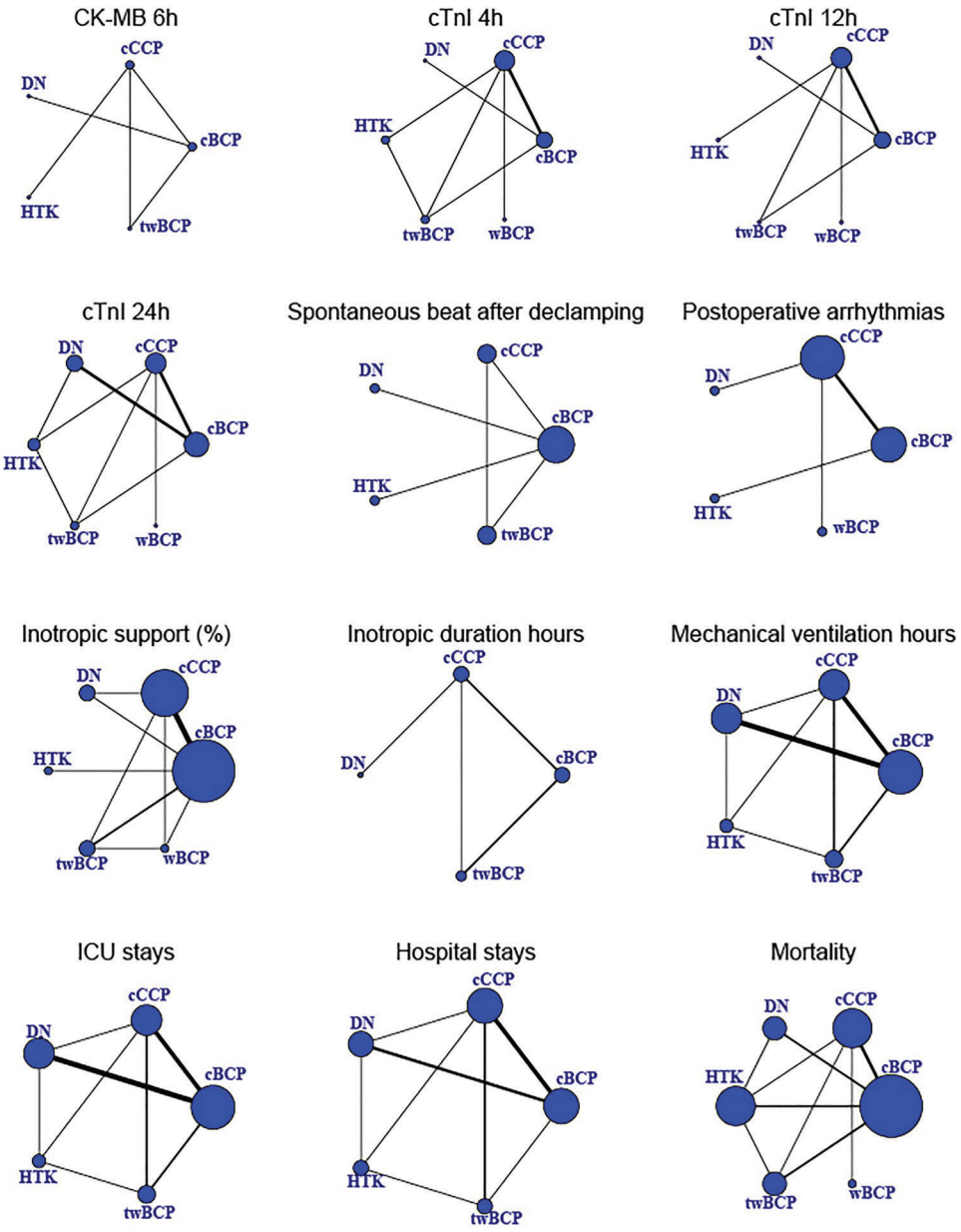

Figure S3: Geometry of the network. cBCP: cold blood cardioplegia; cCCP: cold crystalloid cardioplegia; CK-MB: creatine kinase-myocardial band; cTnI: cardiac troponin I; DN: del Nido; HTK: Histidine-tryptophan-ketoglutarate; ICU: intensive care unit; twBCP: terminal warm blood cardioplegia; wBCP: warm blood cardioplegia. Notes: circles represent the intervention as a node in the network, lines represent direct comparisons using randomized controlled trials (RCTs) and the thickness of lines corresponds to the number of RCTs included in each comparison

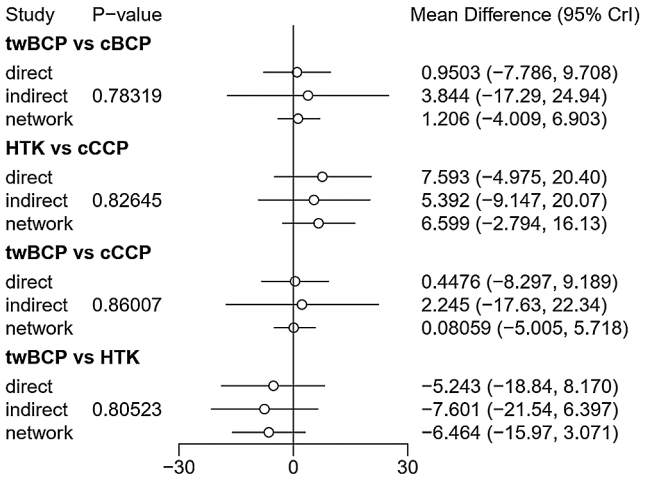

Figure S4: Inconsistency test of cTnI 4-h. cTnI: cardiac troponin I

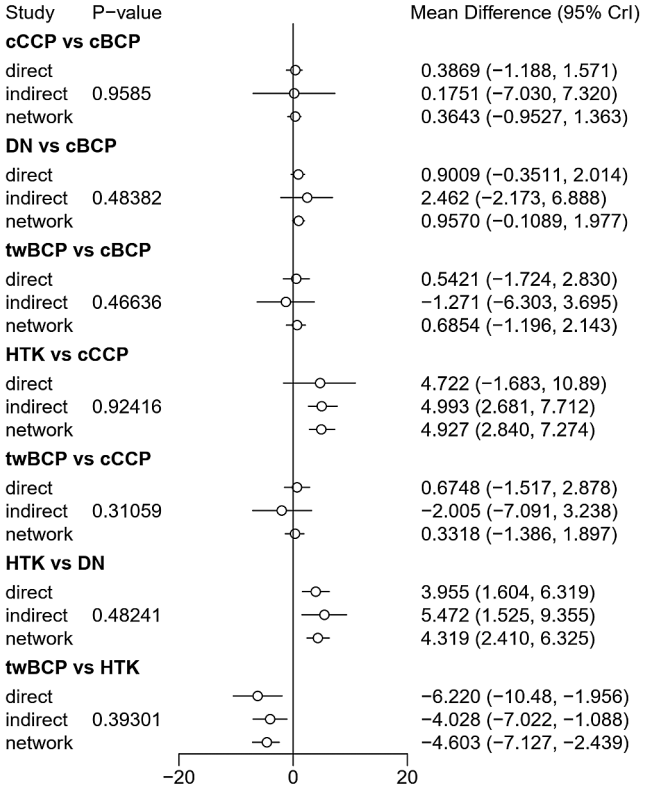

Figure S5: Inconsistency test of cTnI 24-h. cTnI: cardiac troponin I

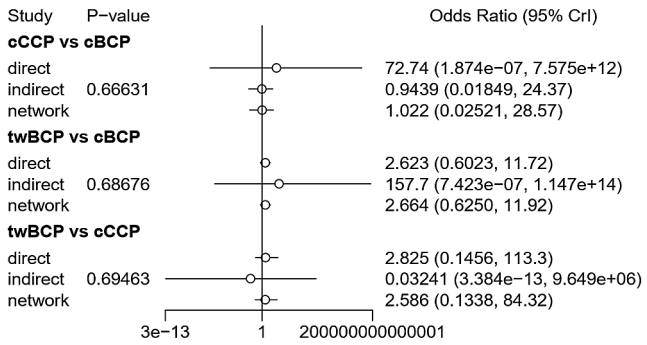

Figure S6: Inconsistency test of spontaneous beating after declamping

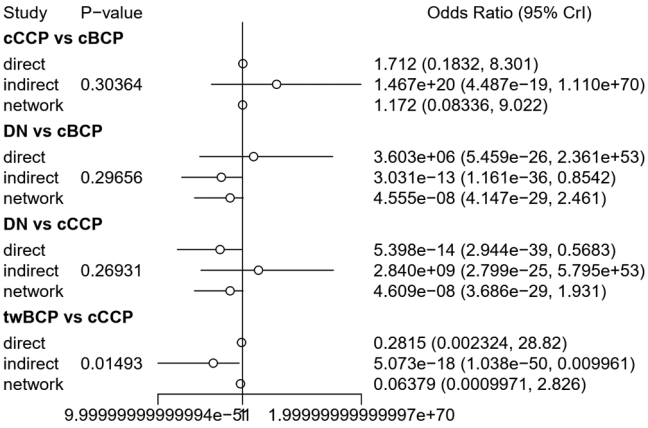

Figure S7: Inconsistency test of inotropic support (%)

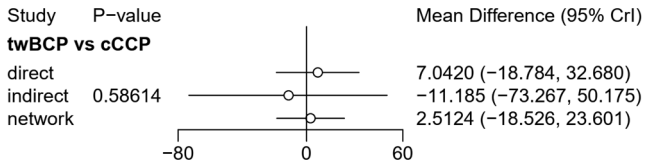

Figure S8: Inconsistency test of inotropic duration hours

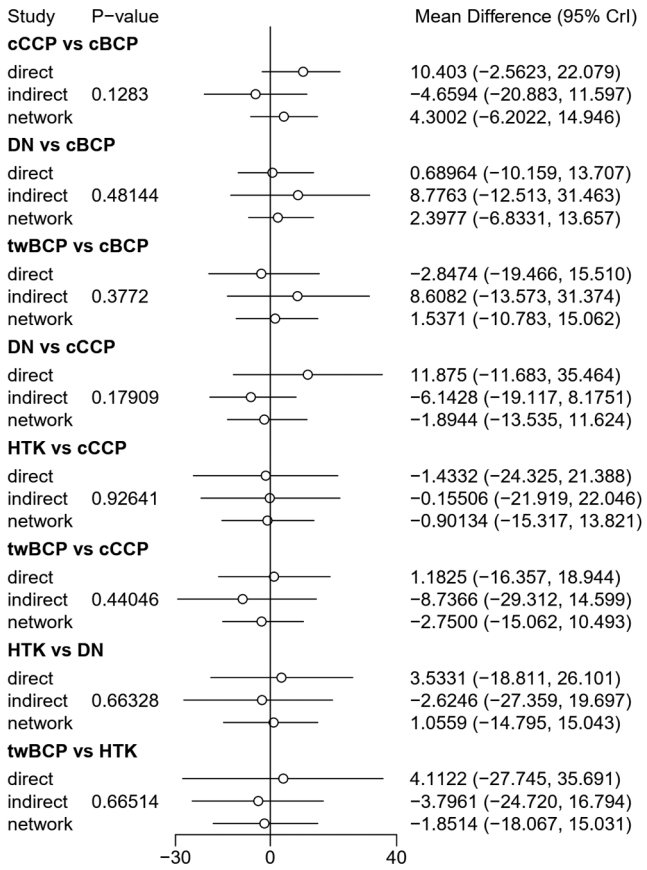

Figure S9: Inconsistency test of mechanical ventilation hours

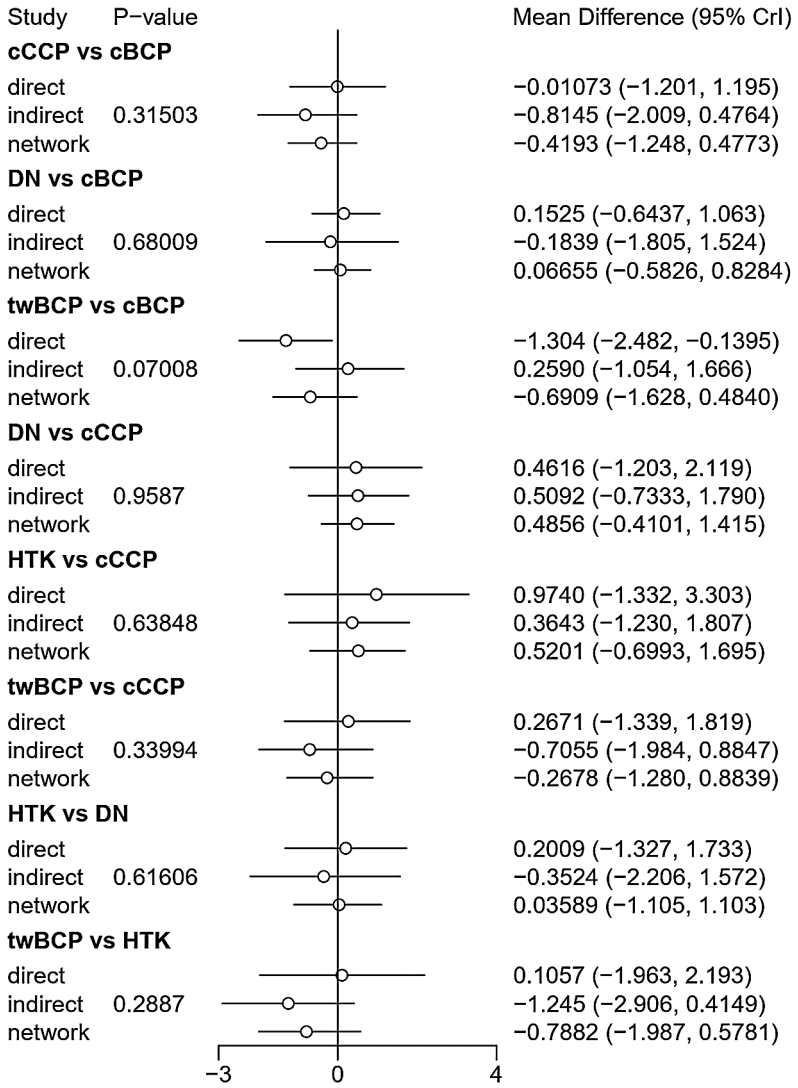

Figure S10: Inconsistency test of ICU stays. ICU: intensive care unit

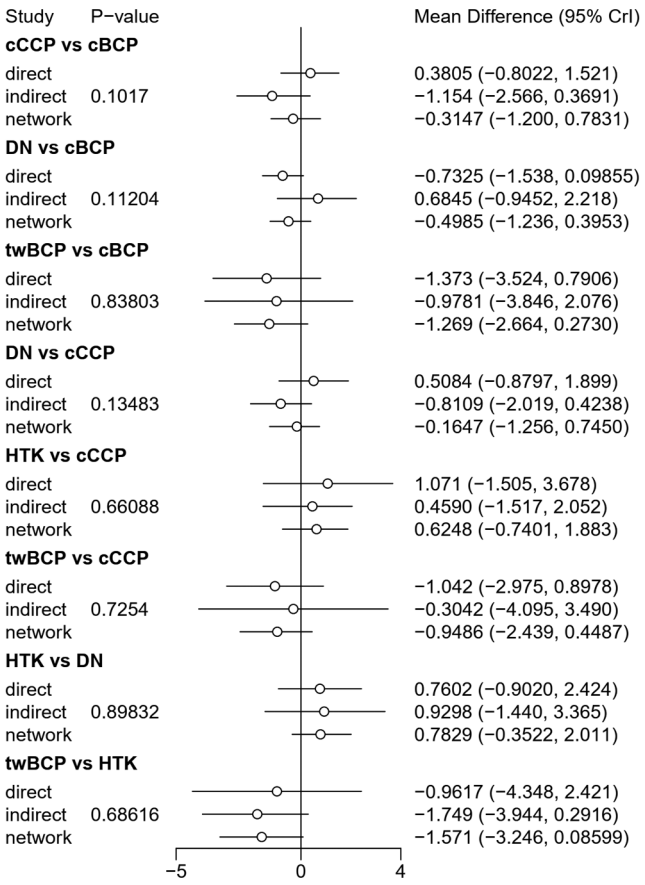

Figure S11: Inconsistency test of hospital stays

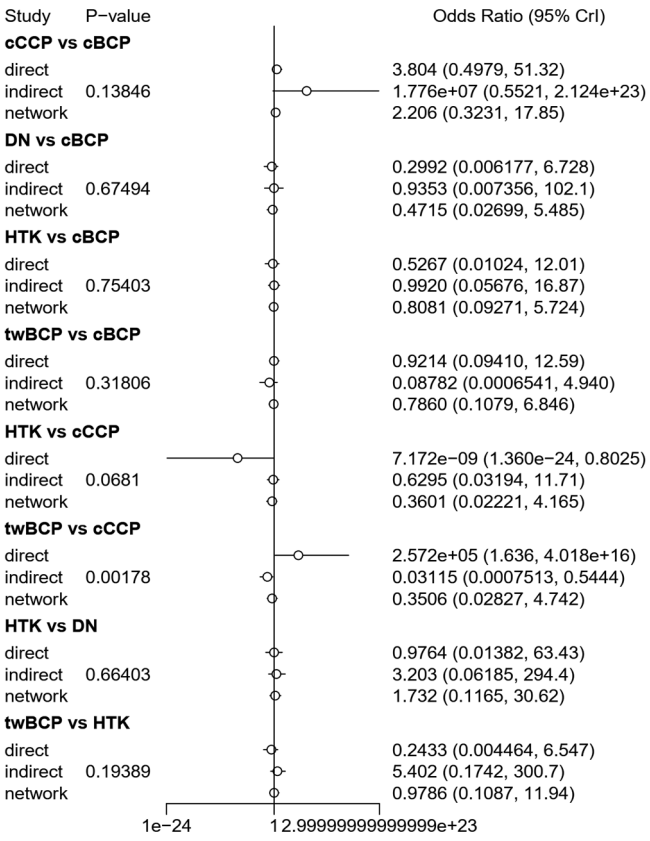

Figure S12: Inconsistency test of mortality

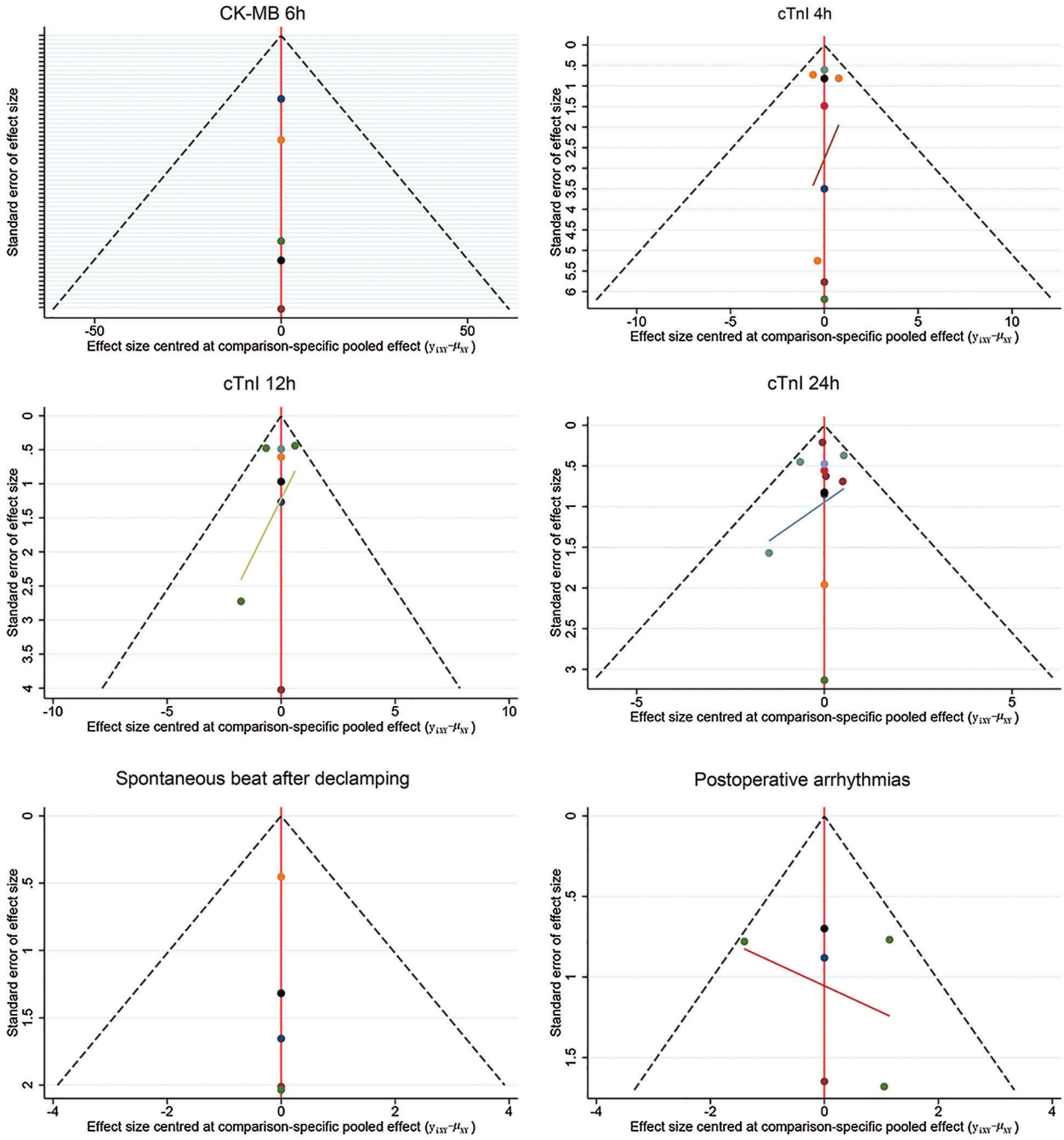

Figure S13: (continued)

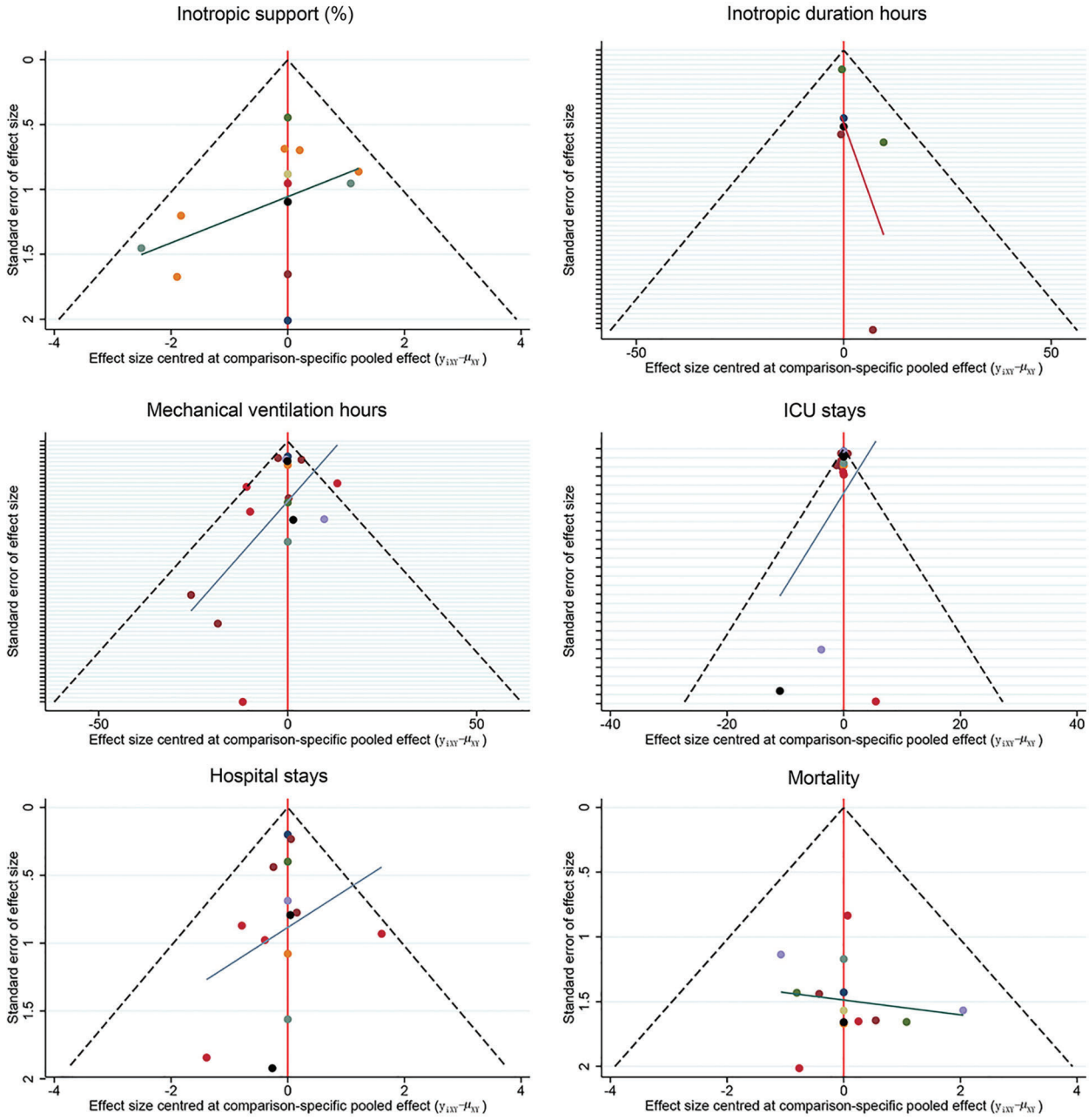

Figure S13: Funnel plot of outcomes. CK-MB: creatine kinase-myocardial band; cTnI: cardiac troponin I; ICU: intensive care unit.

e-References

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PRISMA NMA Checklist of Items to Include When Reporting a Systematic Review: Involving a Network Meta-Analysis

Section/Topic	Item #	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis)*.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis*. **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	Page 1

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Section/Topic	Item #	Checklist item	Reported on page #
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, *including mention of why a network meta-analysis has been conducted*.	Page 2
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 2
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	Pages 2–3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification)*.	Pages 2–3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Pages 2–3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Pages 2–3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Pages 2–3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Pages 2–3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Pages 2–3
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	Pages 2–3

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Section/Topic	Item #	Checklist item	Reported on page #
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Pages 2–3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses*.	Pages 2–3
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit*.	Pages 2–3
Assessment of inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	Pages 2–3
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Pages 2–3
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable)*.	/
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Pages 3–6
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Fig. S3

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Section/Topic	Item #	Checklist item	Reported on page #
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	Pages 3–6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Pages 3–6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Figs. S1–S2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks*.	Pages 3–6
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g., placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons*. If additional summary measures were explored (such as treatment rankings), these should also be presented.	Pages 3–6
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	Pages 3–6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Figs. S1–S2
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, *alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses*, and so forth).	/
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	Pages 6–7

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Section/Topic	Item #	Checklist item	Reported on page #
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	Pages 6–7
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 7
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	Page 7

Note: PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.