

Cardioplegia in paediatric cardiac surgery

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1 **Cardioplegia in paediatric cardiac surgery: a systematic review of randomised**
2 **controlled trials**

3

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6

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21

22 **Visual abstract**

23 *Key question:* What is the randomised controlled trial evidence for different cardioplegia
24 strategies in paediatric cardiac surgery?

25 *Key findings:* 26 small, single-centre trials identified. Heterogeneity of patients, interventions
26 & outcomes prohibited meta-analysis.

27 *Take-home message:* There are no late phase clinical trials of cardioplegia in children; high-
28 quality, multi-centre trials should be conducted to improve care.

29

30 *Central image:* PRISMA flow diagram of study selection.

31

32 **Abstract**

33 *Objectives:* Cardioplegia is the primary method for myocardial protection during cardiac
34 surgery. We conducted a systematic review of randomised controlled trials of cardioplegia in
35 children to evaluate the current evidence-base.

36 *Methods:* We searched MEDLINE, CENTRAL and LILACS, and manually screened retrieved
37 references and systematic reviews to identify all randomised controlled trials comparing
38 cardioplegia solutions or additives in children undergoing cardiac surgery published in any
39 language; secondary publications and those reporting inseparable adult data were excluded.
40 Two or more reviewers independently screened studies for eligibility and extracted data; the
41 Cochrane Risk of Bias tool was used to assess for potential biases.

42 *Results:* We identified 26 trials randomising 1,596 children undergoing surgery; all were
43 single centre, phase II trials, recruiting few patients (median 48, IQR 30-99). The most
44 frequent comparison was blood versus crystalloid in 10 (38.5%) trials and the most common
45 endpoints were biomarkers of myocardial injury (17, 65.4%), inotrope requirements (15,
46 57.7%) and length of stay in intensive care (11, 42.3%). However, the heterogeneity of
47 patients, interventions and reported outcome measures prohibited meta-analysis. Overall
48 risk of bias was high in 3 (11.5%), unclear in 23 (88.5%) and low in none.

49 *Conclusions:* The current literature on cardioplegia in children contains no late phase trials.
50 The small size, inconsistent use of endpoints and low quality of reported trials provides a
51 limited evidence-base to inform practice. A core outcome set of clinically important,
52 standardised, validated endpoints for assessing myocardial protection in children should be
53 developed to facilitate the conduct of high-quality, multi-centre trials.

54 *PROSPERO registration:* CRD42017080205

55 *Key words:* systematic review, clinical trials, cardioplegia, myocardial protection, paediatric
56 cardiac surgery

57 **Introduction**

58 The use of cardioplegia has been fundamental to the intracardiac repair of congenital heart
59 lesions for over 40 years. In conjunction with hypothermia, it remains the primary method for
60 myocardial protection against ischemia-reperfusion injury during cardiac surgery, inducing
61 electromechanical arrest to allow access to a still and bloodless field. Cardioplegic arrest
62 reduces myocardial oxygen uptake to only 10% of the perfused beating heart, and
63 progressive hypothermia leads to a further stepwise reduction [1]. However, myocardial
64 damage still occurs routinely following ischemia-reperfusion, as demonstrated by the
65 universal release of troponin [2]. Ventricular dysfunction may follow repair of even the
66 simplest lesions [3], manifesting as low cardiac output and requiring inotropic support in the
67 early postoperative period. The immature myocardium exhibits marked differences from the
68 adult heart, including substrate metabolism, calcium handling, insulin sensitivity and
69 antioxidant defence against free radicals [4]. Current cardioplegia techniques are primarily
70 derived from adult or laboratory models and may not be optimal for young children,
71 especially neonates and those with preoperative cyanosis [5-7].

72 Recent surveys of practice have shown marked variations in the use of commercially-
73 available and customised cardioplegia solutions in children in North America [8] and
74 worldwide [9]. The composition, dilution, dose, temperature, route of administration and time
75 interval between doses varied between surgeons and continents, but few surgeons adjusted
76 their technique according to the age of the patient [8]. These findings suggest that the choice
77 of solution is determined primarily by the individual surgeon, institution or country rather than
78 the physiology of the patient, and that this may be due to a lack of evidence to support one
79 technique over another. We therefore conducted a systematic review of all randomised
80 controlled trials (RCTs) of cardioplegia in paediatric cardiac surgery to evaluate the value
81 and quality of the current evidence-base.

82 **Methods**

83 This review was conducted with reference to the Cochrane handbook for systematic reviews
84 of interventions [10,11] and reported in accordance with the PRISMA statement [12]. All
85 eligibility criteria, search terms and data items were prespecified and the review was
86 prospectively registered on PROSPERO (CRD42017080205)
87 (<https://www.crd.york.ac.uk/PROSPERO>).

88

89 *Trial eligibility*

90 All randomised and quasi-randomised clinical trials comparing cardioplegia solutions or
91 additives in children undergoing cardiac surgery published in any language were included.
92 The definition of a child was based upon the authors' characterization and cardioplegia was
93 defined as a solution injected into the cardiac vasculature during surgery with the aim of
94 causing electromechanical arrest.

95 Trials were excluded if the outcome measures were not related to the use of cardioplegia for
96 myocardial protection. Those including both adults and children were only included if the
97 publication presented the paediatric data separately. Secondary publications, sub-studies or
98 long-term outcomes of previously reported trials were excluded unless the results were
99 specifically related to cardioplegia when the original report was not. Trials published only as
100 a conference abstract or for which all options to obtain the full text publication were
101 exhausted, were excluded due to insufficient data for analysis.

102

103 *Search strategy*

104 We searched international primary research databases (MEDLINE, CENTRAL, LILACS)
105 from inception to October 31, 2017 and reference lists of relevant articles, systematic

106 reviews and meta-analyses to identify all eligible studies. We combined previously validated
107 search strategies to identify randomised controlled trials, studies including children and
108 those using cardioplegia as an investigational medicinal product (see supplemental material
109 for detailed search terms). For example, to identify RCTs in MEDLINE, we used the
110 Cochrane Highly Sensitive Search Strategy for identifying randomised trials: sensitivity- and
111 precision-maximizing version [10] and to identify studies including children, we adapted the
112 improved Cochrane Childhood Cancer Group filter for PubMed developed by Leclercq and
113 colleagues [13].

114

115 *Study selection and data extraction*

116 Abstracts and then full text publications of all identified articles were screened independently
117 by two reviewers (IY and NED) to generate a database of included studies. Data were
118 extracted independently by two reviewers (two of IY, AJP, NKO, C-RC and NED) from the
119 full trial publication and any published protocols or supplemental material; any assessments
120 of trials in previous systematic reviews were corroborated. A full list of data items,
121 descriptors is available in the supplemental material. Any disagreements on study selection
122 or data extraction were resolved by consensus. Non-English language articles were
123 evaluated in conjunction with individuals with a clinical or research methodology background
124 and fluent in that language (C-RC for Chinese, see acknowledgements).

125

126 *Risk of bias assessment*

127 The Cochrane Risk of Bias Tool was used to define the risk of bias for each of the included
128 trials according to the following domains: sequence generation, allocation concealment,
129 blinding of participants, personnel and outcome assessors, incomplete outcome data,
130 selective outcome reporting and other potential threats to validity [11]. Trials were rated as

131 low risk, unclear or high risk of bias for each factor; overall risk of bias was determined for
132 each trial as low (low risk in all domains), high (high risk of bias in one or more domains) or
133 unclear (neither of the above).

134

135 *Statistical analysis*

136 Statistical analysis was performed using *R* (<https://www.r-project.org/>). All continuous data
137 were expressed as medians with interquartile ranges (IQR) and categorical data as counts
138 and percentages where relevant. Pearson correlation was used to assess the relationship
139 between the number of children randomised per trial and the year of publication.

140 The corresponding author had full access to all the data in the study and had final
141 responsibility for the decision to submit for publication.

142

143 **Results**

144 From 132 unique records, we identified 26 RCTs published to October 31, 2017,
145 randomising 1,596 children undergoing surgery with cardioplegic arrest, of whom 1549
146 (97.1%) were included in analysis of the primary endpoint. The flow of studies through the
147 systematic review process is documented in figure 1. All full text articles were sourced
148 online, via national libraries or directly from the authors; references of included trials are
149 listed in the supplementary material.

150 Characteristics of the included trials are shown in table 1. All studies were single centre,
151 phase II trials, originating from 11 countries, with China (9, 34.6%), Japan (4, 15.4%) and
152 Turkey (3, 11.5%) being the most frequent and only one (3.8%) from the United States. Eight
153 (30.7%) trials were published in a language other than English: 7 (26.9%) in Chinese and
154 one (3.8%) in Turkish. Trials were most commonly published in specialist cardiothoracic
155 surgery journals (14, 53.8%) with none reaching high-impact cardiovascular or general
156 medical journals.

157 The number of children randomised ranged between 20 and 138 with a median of 48 (IQR
158 30-99). Only 4 (15.4%) trials analysed fifty or more patients per arm and the median duration
159 of recruitment was 12 months (IQR 6-16.5). The median age of patients was 29.5 months
160 (IQR 18.2-54.0) and just 21 (1.4%) neonates (confirmed or probable) were included; no trial
161 specifically assessed the use of cardioplegia in neonates. There was no significant
162 correlation between the number of patients recruited per trial and the year of publication ($R =$
163 0.19). Most surgical procedures were low risk with 255 (16.4%) children undergoing
164 operations with a Risk Adjusted classification for Congenital Heart Surgery (RACHS-1) score
165 of 3 or above [14] and the mean aortic cross-clamp time across studies was 60 minutes. The
166 most frequent comparison was blood versus crystalloid cardioplegia in 10 (38.5%) trials
167 followed by various additives in 6 (23.1%) trials (table 1).

168

169 *Outcome measures*

170 Thirteen trials (50.0%) had a defined primary endpoint, one of which (cardiac index) was a
171 clinical outcome; none reported mortality as the primary endpoint. The most common
172 outcome measures were biomarkers of myocardial injury (17, 65.4%), inotrope requirements
173 (15, 57.7%) and length of stay in intensive care (11, 42.3%) (table 2). However, there was
174 marked heterogeneity within endpoints relating to the metrics of assessment used (table 3).

175 Serum biomarker assays of myocardial injury were: cardiac troponin (cTn) in 13 (50.0%),
176 specifically the cTn-I subunit in 11 (42.3%) and cTn-T subunit in 3 (11.5%); serum creatine
177 kinase MB isoenzyme (CK-MB) in 8 (30.8%); and heart-type fatty acid binding protein (h-
178 FABP) in 2 (7.7%). These measures were inconsistently reported as concentrations at
179 timepoints from reperfusion to 48 hours, peak value, total release/activity, and area under
180 the time-concentration curve (AUC); scheduling of sample collection was variable and timed
181 from reperfusion, end of CPB, end of surgery or arrival on ICU. Similarly, inotrope use was
182 reported as binary need for support, dose at the end of surgery or postoperative intervals,
183 maximal dose, total dose in the first 24 hours, duration of use and various inotrope scores
184 over differing time periods. The heterogeneity of patients, interventions and reported
185 outcome measures thereby prohibited meta-analysis. Only short-term outcomes up to
186 discharge or 30 days were reported.

187

188 *Quality of trials*

189 Regarding standards for the conduct and reporting of clinical trials, [15] 4 (15.4%) performed
190 a sample size calculation, 2 (7.7%) were prospectively registered on a publicly-accessible
191 trial database, and 2 (7.7%) published a CONSORT flow diagram. None of the 26 trials were
192 overseen by an independent Data Monitoring Committee and none were stopped early or
193 extended.

194 Risk of bias assessment for each of the eight domains and overall is shown in figure 2.
195 Overall risk of bias was high in 3 (11.5%) trials, unclear in 23 (88.5%) and low in none; the
196 high proportion of unclear resulted from poor reporting of randomisation and masking
197 procedures, and an inability to exclude selective reporting due to a lack of trial registration or
198 published protocol.

199

200 **Discussion**

201 RCTs represent the gold standard in evaluating healthcare interventions through rigorous
202 testing of a predefined protocol and minimization of bias [15]. Yet in this systematic review of
203 the published literature, we identified only 26 RCTs of cardioplegia in paediatric cardiac
204 surgery; these were exclusively single centre, phase II trials that were rarely prospectively
205 registered, recruited small numbers of patients, lacked independent oversight and were not
206 reported to international standards [15-16]. Furthermore, the heterogeneity of patients,
207 interventions and reported outcome measures across trials precluded the pooling of results
208 for meta-analysis. Of concern is the finding that studies included few neonates, in whom
209 myocardial metabolism and cellular homeostasis differ from the more mature heart and the
210 effects of cardioplegia are less well understood [4]. As a result, these trials provide a limited
211 evidence-base to support clinical decision-making on cardioplegia, a technique which is so
212 fundamental to the surgical management of children with congenital heart disease. Whilst all
213 cardioplegia solutions are efficacious in arresting the heart, differences in their effectiveness
214 to reduce ischaemia-reperfusion injury and therefore improve outcomes, are unknown.

215

216 Our findings reflect those of a previous, more limited meta-analysis of cardioplegia trials in
217 children. Fang et al compared the efficacy of blood versus crystalloid cardioplegia and
218 identified 5 RCTs published in English prior to mid-2013, recruiting 358 children in total [17].
219 They found no difference in cTn-I release at 4-6, 12 or 24 hours (3 trials), duration of
220 ventilation (3 trials) or length of ICU stay (4 trials). Only blood lactate following CPB (4 trials)
221 was significantly lower in the blood cardioplegia group but this difference was prejudiced by
222 one study, without which there was no effect. Inotrope use was reported in all 5 trials, but the
223 reviewers were unable to pool data due to the diverse metrics used. Risk of bias was
224 assessed using the modified Jadad scale, a flawed method of quality assessment, with all
225 trials classified as 'high quality' despite only one scoring >5 on the 8-point scale. They

226 concluded that there was no evidence of improvement in myocardial injury or clinical
227 outcomes but were limited by the small number of patients and variability in age,
228 preoperative cyanosis and techniques used. Similarly, Mylonas et al recently identified many
229 non-randomised or retrospective studies on paediatric cardioplegia but few RCTs [18], a
230 finding that is commonplace throughout the global paediatric cardiac surgery literature. In a
231 recent systematic review of RCTs published since 2000, we identified few late-phase clinical
232 trials; most were small, single-centre studies of low value, uncertain quality and at risk of
233 systematic bias [19]. This lack of evidence to guide clinical practice fosters uncertainty and
234 predisposes to variability in patient care.

235

236 Low cardiac output syndrome following surgery is the commonest premonitory complication in
237 children and the most frequent seminal event leading to death [20]. The ubiquitous release
238 of troponin following aortic cross-clamping in children demonstrates that myocardial injury
239 occurs *routinely* and is therefore not a problem solved [2,4]. Myocardial protection remains
240 an area of active research; 18% of recent clinical trials in paediatric cardiac surgery
241 evaluated cardioplegia, ischemic conditioning or other drugs to reduce myocardial injury [19].
242 However, the wide range of variables in cardioplegia technique has led to a potpourri of
243 studies evaluating different aspects of practice. Of the papers identified in this review, blood
244 versus crystalloid cardioplegia was the most common comparison (10, 38.5%) but was often
245 combined with other differences between groups, such as warm versus cold or autologous
246 versus allogenic blood, making direct comparison between studies more difficult and limiting
247 meta-analysis. This variability in the techniques evaluated by clinical trials reflects the
248 current state of clinical practice; the second most commonly used formulations of
249 cardioplegia for children in North America are customised solutions (34%) unique to each
250 centre [8], essentially a ‘none of the above’ homebrew, emphasizing the lack of evidence for
251 an optimal cardioplegia solution. As such the widespread adherence to local solutions may
252 also provide a barrier to conducting multi-centre clinical trials.

253

254 To facilitate the synthesis of findings from multiple studies, clinical trials must report valid
255 and comparable outcome measures. We found marked variation in the reporting of
256 endpoints between trials with inconsistent use of metrics to evaluate the same outcome
257 (table 3). Biomarkers of myocardial injury were the most commonly used outcome measure
258 but included one or more of serum troponin-I, troponin-T, CK-MB and h-FABP, measured at
259 varying timepoints up to 48 hours, and variably reported as measured concentrations, peak
260 or AUC. This disparity reflects the absence of a standardized method for reporting biomarker
261 release after ischemia-reperfusion in children as it is unknown which metric has greatest
262 discriminatory power. Following coronary surgery in adults, cumulative AUC troponin at 72
263 hours has been shown to best predict mid-term mortality [21]. However, obtaining blood
264 samples even up to 48 hours is more problematic in children, especially with expedited
265 removal of venous lines during an uneventful recovery [22]. Newer measures of myocardial
266 injury, such as h-FABP and high-sensitivity troponin, may have an earlier peak and greater
267 positive predictive value [23-25] but currently lack validation in this cohort [26]. Other
268 outcome measures also differed in their definition, timing and measurement. Inotropic
269 support in the early postoperative period was reported using various metrics of dose,
270 duration or a combination through an inotrope score; recently, maximum vasoactive-inotropic
271 score has been identified as the optimal measure of pharmacologic cardiovascular support
272 after cardiac surgery in infants and is strongly associated with morbidity and mortality [27].
273 Length of stay on ICU was usually recorded as actual time elapsed rather than assessed
274 against objective criteria such as fitness for discharge. Furthermore, all trials reported only
275 short-term endpoints with no functional or long-term outcomes.

276

277 Heterogeneity of outcome measures is a common problem in systematic reviews and limits
278 the ability to conduct meta-analyses of pooled data. The Core Outcome Measures in

279 Effectiveness Trials (COMET) initiative is an international effort to develop core outcome
280 sets for clinical trials, defined as ‘the minimum that should be measured and reported in all
281 clinical trials of a specific condition’ [28]. Yet there are currently no core outcome sets
282 relevant to any aspect of children’s heart surgery registered on the COMET database.
283 Endpoints such as vasoactive inotrope score [27] and duration of postoperative mechanical
284 ventilation [29] have been validated in large datasets and should form the basis of such an
285 endeavour. A set of standardized, evidence-based endpoints would have enabled selection
286 of the same metrics across trials, reduced the risk of outcome reporting bias, and increased
287 the value of individual studies by facilitating evidence synthesis. To approve new drugs, the
288 FDA looks for endpoints that are clinically meaningful and ideally measure directly how a
289 patient ‘feels, functions or survives’ [30]; however, none of the trials reported outcomes
290 beyond discharge or 30 days and there is little evidence to correlate perioperative variables
291 to the long-term functional outcomes that are most important to patients, such as exercise
292 tolerance and quality of life.

293

294 The strengths of this systematic review include the comprehensive search strategy,
295 independent review procedures and obtainment of the full text of all potential articles in all
296 languages. The limitations include: a risk of reporting bias, although unpublished studies
297 would be expected to be of lower value; an inability to perform any meta-analyses to inform
298 clinical practice due to the paucity of comparable studies; and limiting the scope to RCTs,
299 which are not the only source of valuable evidence to inform clinical practice.

300

301 *Conclusions*

302 This comprehensive systematic review demonstrates that the current literature on
303 cardioplegia in children contains no late phase trials. The small size, inconsistent use of
304 endpoints and low quality of reported trials provides a limited evidence-base to inform clinical

305 practice; neonates were particularly poorly represented. This lack of evidence combined with
306 marked variations in care [8,9] demonstrates clinical equipoise and the need for high-quality,
307 late phase, multi-centre clinical trials to determine which of the current cardioplegic solutions
308 provide the best myocardial protection for defined patient groups. An agreed core outcome
309 set of clinically important, standardized, validated endpoints for assessing myocardial
310 protection in children should be developed to facilitate the conduct of such trials and the
311 meta-analysis of pooled data. Improving our understanding of how these perioperative
312 endpoints relate to long-term functional outcomes will be key to improving myocardial
313 protection, especially in those who have cumulative exposure to ischemia-reperfusion
314 through multiple operations.

315

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319

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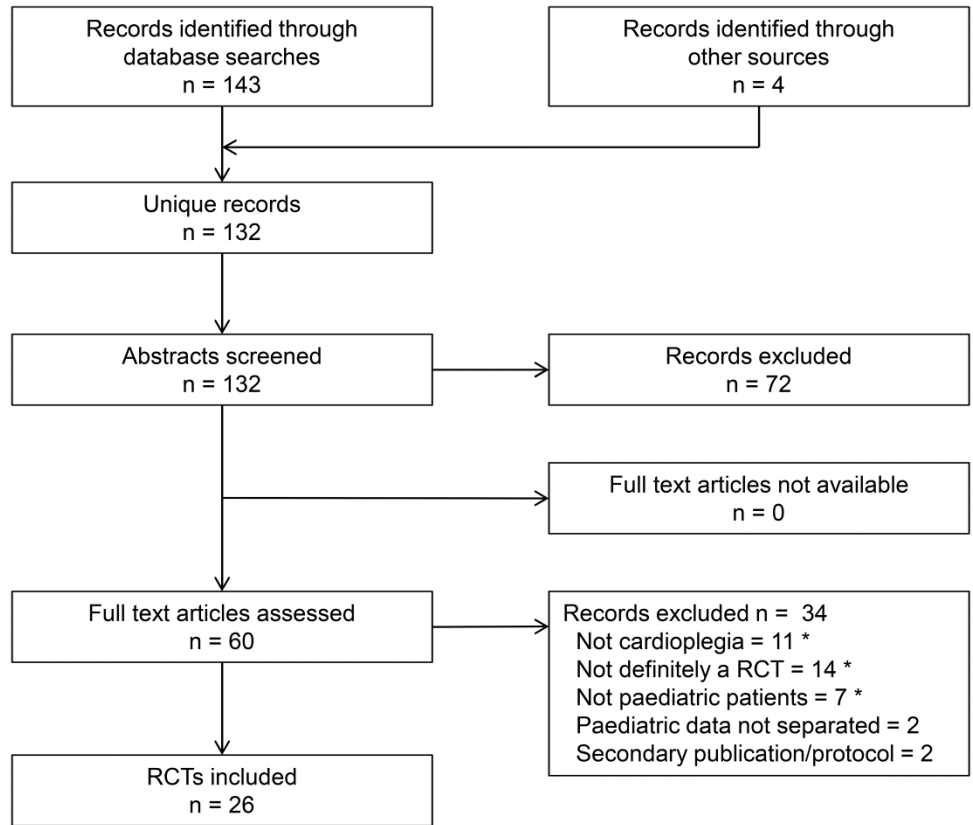
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324 **Conflict of interest:** none declared.

325

326 **Figures**

327

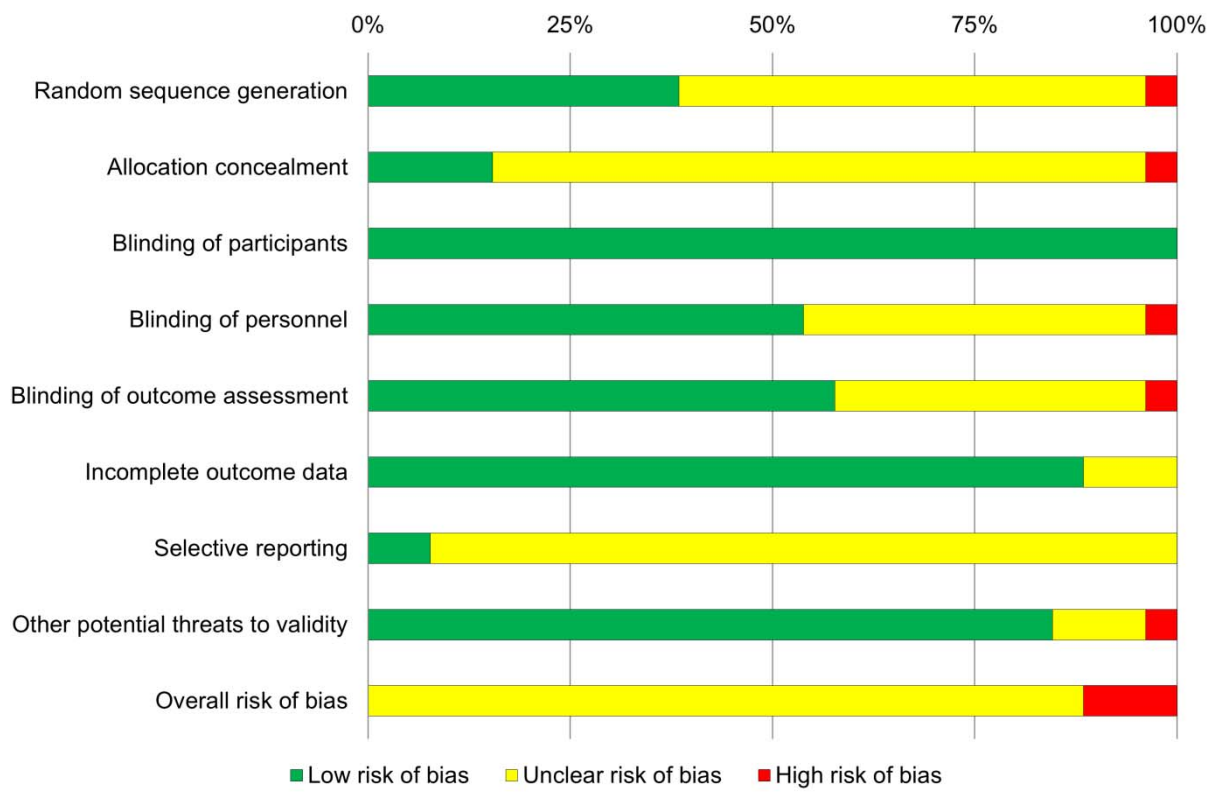


328

329 **Figure 1.** PRISMA flow diagram of study selection.

330 RCT, randomised controlled trial. * includes multiple counting.

331



332

333 **Figure 2.** Cochrane Risk of bias scores for included trials.

334

335 **Table 1.** Characteristics of included trials.

336

Characteristic	n (%)	Characteristic	n (%)
Phase II, single-centre	26 (100%)	Design	
Country of origin		Parallel groups	25 (96.2%)
China	9 (34.6%)	Factorial	1 (3.8%)
Japan	4 (15.4%)	Randomisation	
Turkey	3 (11.5%)	Simple unrestricted	11 (42.3%)
Iran	2 (7.7%)	Block/stratified	1 (3.8%)
United Kingdom	2 (7.7%)	Unclear	14 (53.8%)
Belgium	1 (3.8%)	Intervention comparisons	
India	1 (3.8%)	Blood v crystalloid *	10 (38.5%)
Italy	1 (3.8%)	Additives	6 (23.1%)
Serbia	1 (3.8%)	Herbal additive	3 (11.5%)
Sweden	1 (3.8%)	Non-herbal additive	3 (11.5%)
United States	1 (3.8%)	Warm terminal dose (hot shot) *	3 (11.5%)
Language of publication		Autologous v allogenic blood *	2 (7.7%)
English	18 (69.2%)	Custodiol HTK v St. Thomas'	2 (7.7%)
Chinese	7 (26.9%)	del Nido v St. Thomas'	2 (7.7%)
Turkish	1 (3.8%)	Warm v cold *	2 (7.7%)
Number of arms		Celsior v St. Thomas'	1 (3.8%)
Two	20 (76.9%)	Leukocyte depletion	1 (3.8%)
Three	6 (23.1%)	Potassium concentration	1 (3.8%)

337

338 * includes multiple counting. HTK: Histidine-Tryptophan-Ketoglutarate.

339

340 **Table 2.** Defined outcome measures most frequently reported in included trials.

341

Outcome measure	n (%)
Clinical	
Inotrope requirements	15 (57.7%)
Length of stay in ICU	11 (42.3%)
Duration of mechanical ventilation	10 (38.5%)
Length of stay in hospital	7 (26.9%)
Cardiac output/index	4 (15.9%)
LV function on echocardiography	4 (15.9%)
Non-clinical	
Biomarkers of myocardial injury	17 (65.4%)
Arterial lactate	8 (30.8%)
Myocardial biopsy histology	5 (19.2%)
Myocardial biopsy ATP	4 (15.9%)
Biomarkers of systemic inflammation	4 (15.9%)
Coronary sinus lactate	3 (11.5%)

342

343 ATP: adenosine triphosphate; ICU: intensive care unit; LV: left ventricle.

344

345 **Table 3.** Outcome metrics for serum biomarkers and inotropes reported in included trials.

346

Authors	Year	Biomarkers of myocardial injury	Inotropes
Matsuda H et al	1989	CK-MB: peak *	-
Mori F et al	1990	CK-MB: 1, 3, 6, 12, 24, 48 h, total release/activity *	Use
Young JN et al	1997	-	Inotrope score, total dose 8 h
Hayashi Y et al	2000	CK-MB: peak (6, 12, 18, 24 h) h-FABP: 50 min	Peak dose
Caputo M et al	2002	cTnI: AUC 48 h (4, 12, 24, 48 h)	Use, duration
Toyoda Y et al	2003	cTnT: reperfusion, 1, 3, 6, 18 h h-FABP: reperfusion, 1, 2, 3 h	-
Han HG et al	2004	-	-
Modi P et al	2004	cTnI: AUC 48 h (1, 4, 12, 24, 48 h)	Duration, total dose
Amark K et al	2006	-	Total dose 24 h
Cuccurullo L et al	2006	-	-
Deng YK et al	2006	CK-MB: end op, 6, 12, 24, 48 h cTnI: end op, 6, 12, 24, 48 h cTnT: end op, 6, 12, 24, 48 h	-
Deng YK et al	2007	-	-
Jin ZX et al	2008	cTnI: 1, 3, 6, 12, 24 h	Duration, inotrope score: 1, 3, 6, 12, 24, 48 h
Deng YK et al	2009	-	-
Duvan I et al	2009	CK-MB: reperfusion, 4, 12, 24, 48 h cTnT: reperfusion, 4, 12, 24, 48 h	Use, duration
Zhang Q et al	2009	-	Use
Poncelet AJ et al	2011	cTnI: reperfusion, 6, 12, 24 h	Use
Liu Y et al	2012	cTnI: 1, 3, 6, 12, 24 h *	Inotrope score: 1, 3, 6, 12, 24, 48 h
Cheng GC et al	2013	CK: 30 min, 24 h	-
Korun O et al	2013	-	-

Ma C et al	2013	CK-MB: end CPB cTnl: end CPB	Use
Nezafati MH et al	2013	-	-
Kuşlu S et al	2015	CK-MB: end op, 4, 16, 24, 48 h cTnl: end op, 4, 16, 24, 48 h *	Peak dose, dose: end op, 4, 8, 12, 16, 20, 24, 48 h
Mimic B et al	2016	cTnl: reperfusion, 1, 4, 12, 24 h *	Level 24 h, duration
Gorjipour F et al	2017	cTnl: reperfusion, 24 h	-
Talwar S et al	2017	cTnl: end CPB, 24 h	VIS: 1, 2, 3, 4 d

347

348 * indicates defined primary outcome. AUC: area under the curve; CK: creatine kinase; CK-
349 MB: creatine kinase MB isoenzyme; CPB: cardiopulmonary bypass; cTnl: cardiac troponin I
350 subunit; cTnT: cardiac troponin T subunit; h-FABP: heart-type fatty acid binding protein; VIS:
351 vasoactive inotrope score.

352

353

354 **References**

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356 of the effects of hypothermia on regional myocardial blood flow and metabolism during
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