Single- versus multidose cardioplegia in adult cardiac surgery patients: A meta-analysis

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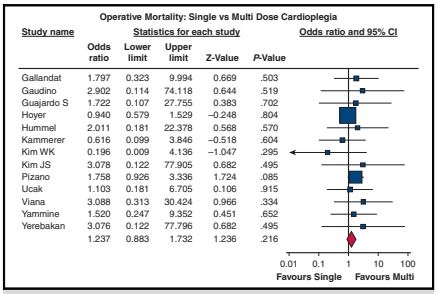
ABSTRACT

Objective: To compare outcomes of single (intervention group: del Nido [DN], and histamine–tryptophan–ketoglutarate) versus multidose (control group) cardioplegia in the adult cardiac surgery patients.

Methods: Medical search engines were interrogated to identify relevant randomized controlled trials and propensity-score matched cohorts. Meta-analysis was conducted for primary (in-hospital/30-day mortality) and secondary (ischemic and cardiopulmonary bypass [CPB] times, reperfusion fibrillation, peak of cardiac enzymes, myocardial infarction) endpoints. Subgroup analyses were conducted for study design and type of intervention, and meta-regression for primary outcome included type of surgery and left ventricular ejection fraction as moderators.

Results: Ten randomized controlled trials and 13 propensity-score matched cohorts were included, reporting on 5516 patients. Estimates are expressed as (parameter value [OR, odds ratio; MD, mean difference; SMD, standardized mean difference]/unit of measure [95% confidence interval], *P* value). DN reduced ischemic time (MD, −7.18 minutes [−12.52 to −1.84], $P < .01$), CPB time (MD, −10.44 minutes [−18.99 to −1.88], *P* .01), reperfusion fibrillation (OR, 0.16 [0.05-0.54], $P < .01$), and cardiac enzymes (SMD −0.17 [−0.29, 0.05], $P < .01$) compared with multidose cardioplegia. None of these beneficial effects were reproduced by histamine–tryptophan–ketoglutarate, which instead increased CPB time (MD, 2.04 minutes [0.73-3.37], $P < .01$) and reperfusion fibrillation (OR, 1.80 [1.20-2.70], $P < .01$). There was no difference in mortality and myocardial infarction between single and multidose, independently of type of surgery or left ventricular ejection fraction.

Conclusions: DN decreases operative times, reperfusion fibrillation, and surge of cardiac enzymes compared with multidose cardioplegia. (J Thorac Cardiovasc Surg 2020;160:1195-202)



Operative mortality: single- versus multidose cardioplegia. Forest plot for the primary endpoint of operative mortality comparing single- with multidose cardioplegia. Meta-analysis of the aggregated evidence showed no statistical difference in operative mortality between the compared groups.

Central Message

Single-dose cardioplegia, only in the form of del Nido but not of HTK solution, reduced operative times, reperfusion fibrillation, and surge of cardiac enzymes compared with multidose cardioplegia.

Perspective

The evidence provided by this meta-analysis is based on a sample of 5516 patients, from 10 randomized controlled trials and 13 propensity-score matched cohorts. This evidence suggested that although clinical outcomes were not affected by the use of single- versus multidose cardioplegia, del Nido solution was effective in reducing operative times, reperfusion fibrillation, and surge of cardiac enzymes.

See Commentaries on pages 1203 and 1205.

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Abbreviations and Acronyms

CPB = cardiopulmonary bypass
DN = del Nido cardioplegia
FE = fixed effect
HTK = histidine–tryptophan–ketoglutarate cardioplegia
MD = mean difference
MI = myocardial infarction
OR = odds ratio
PSMC = propensity-score matched cohort
RCT = randomized controlled trial
RE = random effect
SMD = standardized mean difference

Scanning this QR code will take you to the article title page to access supplementary information.

Myocardial protection is a necessary component of cardiac surgery. Over the decades, cardioplegia has allowed surgeons to operate safely during cardiac arrest.[1] Many iterations of cardioplegia have been proposed and compared according to solute content (depolarizing vs hyperpolarizing),[2] solvent composition (blood cardioplegia vs crystalloid cardioplegia),[3] temperature,[4] delivery (antegrade vs retrograde),[5] and so on. Regardless, all these comparisons based on mechanisms of action, and their metabolic effects are very intriguing, but ultimately surgeons are interested in (1) the best cardiac protection (2) that can be delivered in the least cumbersome fashion, to optimize results and streamline the operative process. Point (2) is best fulfilled by solutions that only require a single dose to complete most cardiac operations, such as Del Nido cardioplegia[6] (DN) and histidine–tryptophan–ketoglutarate (HTK) cardioplegia.[7] But do the latter also fulfill point (1)? To answer this question with the greatest level of evidence, we performed a meta-analysis of only randomized controlled trials (RCTs) and propensity score matched cohorts (PSMCs) that directly compared single- versus multidose cardioplegia in the adult population with acquired disease.

METHODS

Methodology of Literature Search and Synthesis

The protocol for this meta-analysis was prospectively registered with number CRD42019119751 at the International Prospective Register of Systematic Reviews in Health and Social Care (PROSPERO). The systematic literature review was undertaken according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses[8] guidelines (Appendix E1), whose PICOS components (ie, participants, interventions, comparisons, outcomes, and study design) were used to frame our objectives, including the primary endpoint (in-hospital or 30-day operative mortality) and secondary endpoints (ischemic time, cardiopulmonary bypass [CPB] time, reperfusion fibrillation, cardiac enzymes [creatine kinase-muscle/brain, troponin I], and myocardial infarction [MI]). Multiple electronic health database engines (MEDLINE, Embase, Cochrane Library, Google Scholar) were searched with no date limitation up until October 2018. The data items defined the information of interest to be extracted from the literature, which was selected according to eligibility criteria. The mentioned objectives, data items, and eligibility criteria, along with details of the methodology of review and related bibliographic references, are detailed in Appendix E1.

Data Analysis

Assessment of methodologic quality and reporting bias. The methodologic quality of the selected studies was assessed with the Cochrane risk-of-bias tool for RCTs and with the Newcastle–Ottawa scale scoring for PSMCs. The risk of reporting bias was evaluated quantitatively with the Egger's regression intercept and visually by plotting the standard error and pooled estimate (funnel plot) for each endpoint. Details of the assessment for methodological quality and publication bias, along with bibliographic references, are reported in Appendix E1.

Measures of treatment effect and heterogeneity. Analysis of dichotomous variable endpoints (reperfusion fibrillation, MI, and mortality) was carried out using the odds ratio (OR). Analysis of continuous variable endpoints was carried out using the mean difference (MD) if they presented homogeneous units of measure (ischemic and CPB times), or the standardized difference of means (SMD) if they presented heterogeneous units of measure (cardiac enzymes). The summary statistic was the 95% confidence intervals for all the endpoints. Pooled estimates were calculated with the Mantel–Haenszel fixed and random effect models, which were both reported in the absence of univocal rules on their preferential usage. Cochrane recommendations suggest preferential regard to either fixed or random effect models, if respectively there is absence or presence of publication heterogeneity. Relevantly, in-between study heterogeneity was examined with the Cochrane's Q (χ^2) test, and we further quantified inconsistency by calculating I^2, interpreted using the following guide: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% may represent considerable heterogeneity (Appendix E1).

Subgroup analysis I: Study design. A meta-analysis (fixed/random effect models) of all the endpoints was restricted to RCTs only. This analysis was extended to the entire sample and its subsets according to type of intervention.

Subgroup analysis II: Type of intervention. A meta-analysis (fixed/random effect models) of all the endpoints was carried out to separately compare the 2 types of intervention (DN and HTK) with the control group.

Sensitivity Analysis

Sensitivity analysis was performed for all the endpoints by determining whether consequent removal of one study at a time led to influential observations according to quantitative and qualitative criteria. We deemed an observation to be influential according to quantitative criteria if: (1) it inverted the direction of the pooled treatment effect (ie, if ORs were inverted from >1 to <1, or differences of means were inverted from positive to negative values, and vice versa) at a significant degree ($P \leq .05$), or (2) conferred new statistical significance ($P \leq .05$) to the pooled treatment effect of which it was previously lacking. The clinical meaningfulness of such quantitative criteria had to be contextualized in view of the characteristics of the study

that was the culprit of the influential observation (eg, subgroup of intervention, study design) and of the results of subgroup analyses and meta-regression (qualitative criteria).

Meta-Regression

Multivariable meta-regression with mixed effects models (method of moments) was performed for the primary endpoint using as moderators type of surgery (coronary and valve surgery), type of surgical approach (full sternotomy vs minimally invasive approach, which consisted of either right thoracotomy or mini-sternotomy), and left ventricular function (preserved = ≥55%, impaired ventricle = <55%). The moderating effect of left ventricular ejection fraction was additionally evaluated as a continuous variable.

Statistical Analysis

We used the Comprehensive Meta-Analysis (CMA) software (Biostat Inc, Englewood, NJ).

RESULTS

Selected Publications and Preintervention Analysis

Characteristics of studies. The 23 articles finally selected[9-31] were published over a 2-decade period (1988-2018) and were composed of 10 RCTs and 13 PSMCs reporting on a total of 5516 patients. Details of study design, along with type of intervention, control, and surgery from the specific institutions are reported in Table 1. The flow chart of the literature search and selection, along with assessments of the methodologic quality of the included studies, are available in Appendix E1.

Perioperative variables. Intervention and control groups presented no significant differences in terms of demography (age and sex), myocardial performance status (New York Heart Association status and ejection fraction), comorbidities (hypertension, diabetes mellitus, peripheral arterial disease, chronic lung disease, cerebrovascular disease), nonelective, and reintervention status. The typologies of cardiac surgery procedure were equivalently represented in the compared groups. There was also no statistical difference regarding number of grafts in CABG, rate of repair, and minimally invasive approach in valve operations (Table 2).

Analysis of Endpoints

Comparison estimates are expressed as (parameter/value/unit of measure [95% confidence interval], *P* value; model:

TABLE 1. Series selected for quantitative analysis

Author	Journal	Date	Patients	Design	Intervention	Control	Operation
Ad et al[9]	*J Thorac Cardiovasc Surg.**	2017	89	RCT	DN	BC	Mixed
Arslan et al[10]	*Transplant Proc.*	2005	42	RCT	HTK	CC	CABG
Beyersdorf et al[11]	*Thorac Cardiovasc Surg.*	1990	24	RCT	HTK	BC	CABG
Braathen et al[12]	*J Thorac Cardiovasc Surg.*	2011	76	RCT	HTK	BC	MVR/r
Careaga et al[13]	*Arch Med Res.*	2001	30	RCT	HTK	CC	Mixed
Demmy et al[14]	*Int J Angiol.*	2008	136	RCT	HTK	CC	CABG
Gallandat et al[15]	*Thorac Cardiovasc Surg.*	1988	249	RCT	HTK	CC	CABG
Gaudino et al[16]	*Scand Cardiovasc J.*	2013	60	RCT	HTK	BC	MVR/r
Guajardo Salinas et al[17]	*Perfusion.*	2017	364	PSMC	DN	BC	CABG
Hoyer et al[18]	*Eur J Cardiothorac Surg.*	2017	1650	PSMC	HTK	BC	AVR
Hummel et al[19]	*Innovations (Phila).*	2016	362	PSMC	HTK	BC	AVR-MVR/r
Kammerer et al[20]	*Arch Clin Exp Surg.*	2012	107	RCT	HTK	BC	MVR/r
Kim et al[21]	*Interact Cardiovasc Thorac Surg.*	2018	208	PSMC	DN	BC	Mixed
Kim et al[22]	*J Thorac Dis.*	2016	78	PSMC	DN	BC	Mixed
Koeckert et al[23]	*J Card Surg.*	2018	118	PSMC	DN	BC	AVR
Mick et al[24]	*J Thorac Cardiovasc Surg.*	2015	390	PSMC	DN	BC	AVR-MVR/r
Ota et al[25]	*Perfusion.*	2016	108	PSMC	DN	BC	AVR
Pizano et al[26]	*Heart Surg Forum.*	2018	584	PSMC	HTK	BC	Mixed
Timek et al[27]	*Ann Thorac Surg.*	2016	164	PSMC	DN	BC	CABG
Ucak et al[28]	*Ann Thorac Cardiovasc Surg.*	2018	297	RCT	DN	BC	CABG
Viana et al[29]	*Eur J Cardiothorac Surg.*	2013	142	PSMC	HTK	BC	Mixed
Yammine et al[30]	*J Card Surg.*	2014	158	PSMC	DN	BC	Mixed
Yerebakan et al[31]	*J Cardiothorac Surg.*	2014	80	PSMC	DN	BC	CABG

RCT, Randomized controlled trial; *DN*, del Nido cardioplegia; *BC*, blood cardioplegia; *HTK*, histidine–tryptophan–ketoglutarate cardioplegia; *CC*, crystalloid cardioplegia; *CABG*, coronary artery bypass grafting; *MVR/r*, mitral valve replacement/repair; *mixed*, series of mixed cardiac and proximal aorta operations; *PSMC*, propensity-score matched cohort; *AVR*, aortic valve replacement. *All journals are listed according to Index Medicus abbreviations.

TABLE 2. Pre- and intraoperative variables in the single-dose and multidose cardioplegia groups

Variable	Single-dose (2829)	Multidose (2687)	*P* value
Preoperative			
Age, y ± SD	64.17 ± 4.75	64.18 ± 4.39	.99
Male sex, n (%)	1707 (62.48)	1586 (61.23)	.85
HTN, n (%)	1337 (65.57)	1291 (65.43)	.96
DM, n (%)	568 (26.71)	591 (27.66)	.95
NYHA ≥III, n (%)	623 (33.38)	565 (31.88)	.89
EF, % ± SD	55.13 ± 3.54	54.38 ± 4.45	.63
PAD, n (%)	320 (18.25)	254 (15.96)	.73
CPD, n (%)	175 (10.12)	187 (10.77)	.90
CVD, n (%)	189 (11.31)	170 (10.74)	.87
Nonelective, n (%)	412 (29.21)	403 (28.44)	.97
Reintervention, n (%)	173 (11.22)	177 (11.48)	.97
Intraoperative			
Isolated CABG, n (%)	829 (29.3)	675 (25.1)	.67
Isolated valve, n (%)	1657 (58.57)	1631 (60.69)	.98
Multiple valve, n (%)	114 (4.02)	110 (4.09)	.96
Valve + CABG, n (%)	116 (4.1)	113 (4.2)	.96
Proximal aorta, n (%)	123 (4.34)	112 (4.16)	.92
Other, n (%)	20 (0.7)	16 (0.59)	.84
Minimally invasive, n (%)	680 (48.02)	671 (47.28)	.67
Valve repair, n (%)	206 (14.91)	204 (14.77)	.97
No. grafts,* mean ± SD	3.66 ± 0.47	3.6 ± 0.47	.86

SD, Standard deviation; *HTN*, hypertension; *DM*, diabetes mellitus; *NYHA*, New York Heart Association class; *EF*, ejection fraction; *PAD*, peripheral arterial disease; *CPD*, chronic pulmonary disease; *CVD*, cerebrovascular disease; *CABG*, coronary artery bypass grafting. *Mean number of grafts per CABG operation.

fixed effect [FE], random effect [RE]). None of the endpoints was affected by reporting bias. The clinical endpoints of operative mortality (primary) and MI presented homogeneity of publication, whereas the other endpoints were affected by significant heterogeneity (Table 3). We discursively summarized below the pooled estimates, which are detailed along with publication bias and heterogeneity in Table 3.

Meta-analysis of the entire sample. There was no difference in clinical endpoints (operative mortality OR 1.24 [0.88-1.73], $P = .22$, FE; myocardial infarction OR 1.34 [0.52-3.42], $P = .54$, FE) between the intervention and control groups. Single-dose cardioplegia was able to decrease ischemic time (MD −4.53 minutes [−8.33 to −0.73], $P = .01$, RE), reperfusion fibrillation (OR 0.49 [0.50-1.94], $P = .02$, RE), and surge of cardiac enzymes (SMD −0.13 [−0.22 to 0.03], $P < .01$, FE) compared with multidose cardioplegia (Table 3). Sensitivity analysis detected no influential observations, and its results are detailed along with graphical assessment of reporting bias in Appendix E1.

Subgroup analysis I: Study design. The greater level of evidence provided by RCTs showed similarity in all endpoints between intervention and control groups, according to the random effect model that we would advise as preferable in the presence of significant heterogeneity. Table 3 details the results of subgroup analysis I, including FE model estimates and the evidence provided by PSMCs.

Subgroup analysis II: Type of intervention. Compared with multidose cardioplegia, DN was able to reduce ischemic time (MD −7.18 minutes [−12.52 to −1.84], $P < .01$, RE) (Figure 1), CPB time [MD −10.44 minutes [−18.99 to −1.88], $P = .01$, RE], reperfusion fibrillation (OR 0.16 [0.05-0.54], $P < .01$, RE) (Figure 2), and cardiac enzymes (SMD −0.17 [−0.29 to 0.05], $P < .01$, FE). None of these beneficial effects were reproduced by HTK, which instead increased CPB time (MD 2.04 minutes [0.73-3.37], $P < .01$, FE) and reperfusion fibrillation (OR 1.80 [1.20-2.70], $P < .01$, FE) compared with multidose cardioplegia (Table 3).

Meta-regression. Multivariable regression showed that the operative mortality was similar between single and multidose cardioplegia, regardless of the type of surgical approach and operation (coronary operation OR −0.19 [−1.87 to 1.49], $P = .82$; valve operation via full sternotomy OR −0.12 [−1.60 to 1.35], $P = .86$; valve operation with minimally invasive approach OR −1.03 [−3.93, 1.86], $P = .48$), whether patients had a preserved (OR −0.56 [−2.76, 1.64], $P = .61$) or impaired (OR −0.07 [−1.78, 1.62], $P = .92$) left ventricular function (Table 4). The latter finding also was maintained when left ventricular ejection fraction was analyzed as a continuous variable (OR −0.08 [−0.21, 0.04], $P = .19$) (Figure 3).

DISCUSSION

Overview

Although this meta-analysis cannot assess the intuitive advantage of single-dose cardioplegia in streamlining the operative flow and facilitating the surgeon's focus, it showed a quantifiable reduction in operative times with its usage. This decrease was eminently driven by the capability of DN to reduce both ischemic and CPB times, when compared with standard multidose cardioplegia. This finding is of interest, as ischemic time is reported as an independent risk factor for operative mortality in the literature.[32] Regardless DN and HTK are both delivered with a single dose, but only the former significantly reduced ischemic time compared with multidose cardioplegia. This can be explained by the fact that DN is infused more rapidly (commonly a volume of 1000 mL with a rate of 250-450 mL/min) than HTK (commonly a volume 2000-4000 mL with either controlled pressure ≤50 mm Hg, or with liberal hydrostatic pressure from a bag placed at a height of 2 meters).[6-31] Using single-arm estimates, in our sample crossclamp times were specifically 63.74 minutes (95% CI 54.47-73.02) for DN and 75.55 minutes (95% CI 65.86-85.23) for HTK.

The fact that DN was also able to reduce reperfusion fibrillation could be due to (1) its capability to decrease the ischemic cardiac time, of which reperfusion fibrillation

TABLE 3. Meta-analysis of the entire sample and subgroup analyses, comparing single versus multidose cardioplegia

	Meta-analysis of the endpoints			Publications analysis					
				Studies	Reporting bias			Heterogeneity	
	Model	Estimate (95% CI)	*P* value	No.	Intercept	SE	*P* value	*P* value	I^2, %
Entire sample: single- vs multidose cardioplegia									
Ischemic time, min (MD)	Fixed	−1.95 (−2.87, −1.03)	<.01	17	−1.32	1.11	.27	<.01	90
	Random	−4.53 (−8.33, −0.73)	.01						
CPB time, min (MD)	Fixed	−0.34 (−1.49, 0.79)	.54	17	−1.40	1.03	.19	<.01	89
	Random	−4.43 (−9.32, 0.46)	.07						
Reperfusion fibrillation (OR)	Fixed	0.49 (0.50-1.94)	.02	10	−1.47	2.80	.61	<.01	93
	Random	0.49 (0.14-1.74)	.27						
Cardiac enzymes (SMD)	Fixed	−0.13 (−0.22, 0.03)	<.01	13	−0.08	1.60	.96	<.01	68
	Random	−0.13 (−0.31, 0.05)	.14						
Myocardial infarction (OR)	Fixed	1.34 (0.52-3.42)	.54	5	−1.17	0.64	.16	.86	0
	Random	1.34 (0.52-3.42)	.54						
Operative mortality (OR)	Fixed	1.24 (0.88-1.73)	.22	13	0.31	0.32	.35	.90	0
	Random	1.24 (0.88-1.73)	.22						

		Randomized controlled trials		Propensity-score matched cohorts	
	Model	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
Subgroup analysis I: study design					
Ischemic time, min (MD)	Fixed	−1.29 (−2.29, −0.28)	.01	−5.56 (−7.89, −3.23)	<.01
	Random	−1.92 (−6.97, 3.11)	.45	−7.69 (−14.20, −1.17)	.02
CPB time, min (MD)	Fixed	0.60 (−0.62, 1.83)	.33	−6.22 (−9.27, −3.17)	<.01
	Random	0.68 (−4.95, 6.31)	.81	−11.01 (−21.65, −0.36)	.04
Reperfusion fibrillation (OR)	Fixed	1.63 (1.11-2.39)	.01	0.09 (0.05-0.17)	<.01
	Random	1.15 (0.33-4.00)	.82	0.06 (0.02-0.22)	<.01
Cardiac enzymes (SMD)	Fixed	−0.03 (−0.14, 0.07)	.49	−0.42 (−0.62, −0.23)	<.01
	Random	−0.06 (−0.25, 0.13)	.51	−0.42 (−0.62, −0.23)	<.01
Myocardial infarction (OR)	Fixed	1.41 (0.37-5.41)	.62	1.27 (0.34-4.73)	.71
	Random	1.41 (0.37-5.41)	.62	1.27 (0.34-4.73)	.71
Operative mortality (OR)	Fixed	1.20 (0.45-3.19)	.72	1.24 (0.86-1.77)	.23
	Random	1.20 (0.45-3.19)	.72	1.24 (0.86-1.77)	.23

		Del Nido		HTK	
	Model	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
Subgroup analysis II: type of intervention					
Ischemic time, min (MD)	Fixed	−7.60 (−9.25, −5.95)	<.01	−0.59 (−0.51, 1.70)	.29
	Random	−7.18 (−12.52, −1.84)	<.01	−1.95 (−6.44, 2.54)	.39
CPB time, min (MD)	Fixed	−7.25 (−9.50, −5.00)	<.01	2.04 (0.73-3.37)	<.01
	Random	−10.44 (−18.99, −1.88)	.01	0.71 (−4.55, 5.97)	.79
Reperfusion fibrillation (OR)	Fixed	0.14 (0.08-0.24)	<.01	1.80 (1.20-2.70)	<.01
	Random	0.16 (0.05-0.54)	<.01	1.08 (0.24-4.86)	.92
Cardiac enzymes (SMD)	Fixed	−0.17 (−0.29, 0.05)	<.01	−0.06 (−0.21, 0.08)	.41
	Random	−0.22 (−0.48, 0.03)	.09	−0.05 (−0.32, 0.21)	.69
Myocardial infarction (OR)	Fixed	0.55 (0.02-13.53)	.71	1.46 (0.55-3.89)	.45
	Random	0.55 (0.02-13.53)	.71	1.46 (0.55-3.89)	.45
Operative mortality (OR)	Fixed	1.29 (0.48-3.45)	.61	1.23 (0.86-1.76)	.26
	Random	1.29 (0.48-3.45)	.61	1.23 (0.86-1.76)	.26

The superior third of the table shows the treatment effect for all the endpoints in the entire sample, comparing single- with multidose cardioplegia; additionally, a breakdown of publication bias and heterogeneity of publication is detailed. The middle third of the table shows a first subgroup analysis distinguishing studies according to its design: randomized controlled trials versus propensity score matched cohorts. The lower third of the table shows a second subgroup analysis, which distinguishes the type of intervention in the 2 forms of single-shot cardioplegia: del Nido and HTK. *CI*, Confidence interval; *SE*, standard error; *MD*, mean difference; *CPB*, cardiopulmonary bypass; *OR*, odds ratio; *SMD*, standardized mean difference; *HTK*, histidine–tryptophan–ketoglutarate.

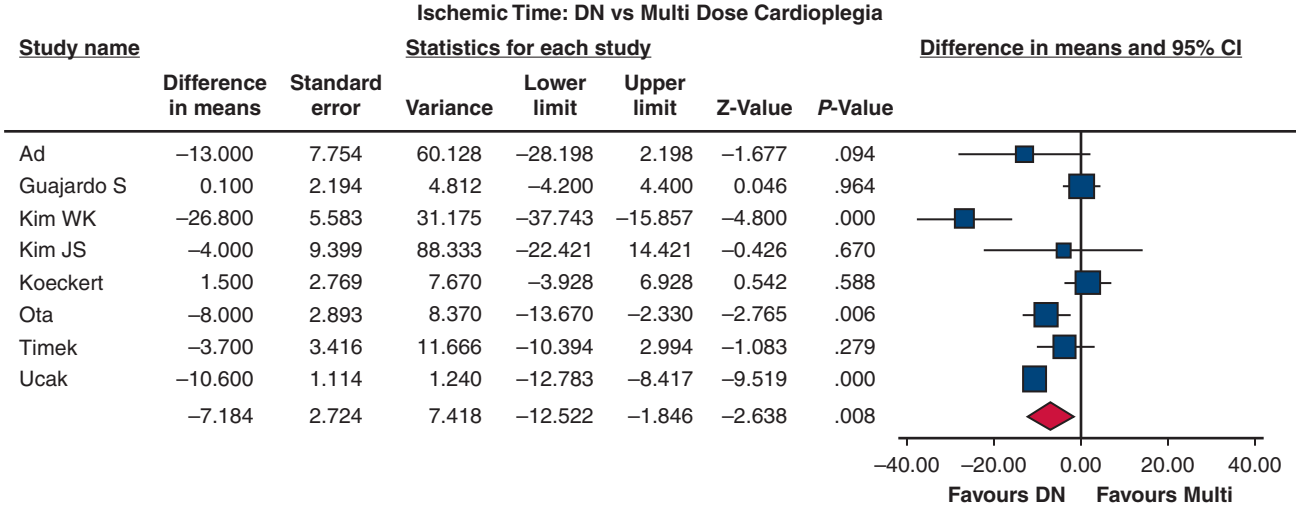

FIGURE 1. Ischemic time: DN versus multidose cardioplegia. Forest plot for ischemic time comparing DN with multidose cardioplegia. Meta-analysis of the aggregated evidence showed that ischemic time was reduced by adoption of DN cardioplegia. *DN*, del Nido; *CI*, confidence interval.

is a consequence, and (2) its intrinsic content of lidocaine, which has been shown to reduce reperfusion fibrillation.[33]

The improvement of such surrogated measures of intraoperative ischemia (ie, ischemic time and reperfusion fibrillation) was reflected in the biochemical evidence (ie, cardiac enzymes) of a better myocardial protection, but it did not translate in an amelioration of clinical outcomes (ie, MI and mortality). None of the aforementioned advantages of DN were replicated by HTK, which on the contrary increased CPB time and reperfusion fibrillation. Postoperative echocardiographic data could have been useful to detect subclinical differences in ventricular performance between intervention and control groups, but they were insufficiently reported to be considered as an endpoint.

We aimed to validate with an enhanced quality of evidence the results of previous meta-analyses that compared standard multidose cardioplegia with either DN[34] or HTK.[35] This purpose was first achieved by improving the profile of their literature sample, with inclusion of RCTs and PSMCs, and exclusion of cohort studies where propensity-score matching was either not performed or its results were not quantified separately. Bibliographic references to the studies, which were included or excluded in respect to previous meta-analyses, are reported in Appendix E1. In addition, we analyzed such an improved literature sample with paradigms able to discern the evidence coming only from randomized models (ie, subgroup analysis by study design), and the influence of multiple moderators on the treatment effect (ie, multivariate meta-regression).

Consequently, we confirm the findings of Li and colleagues,[34] who showed that although DN was able to reduce ischemic (MD −5.74 minutes [−10.14 to −1.34], $P = .01$) and CPB (MD −7.52 [−14.76 to −0.29], $P = .04$) times,

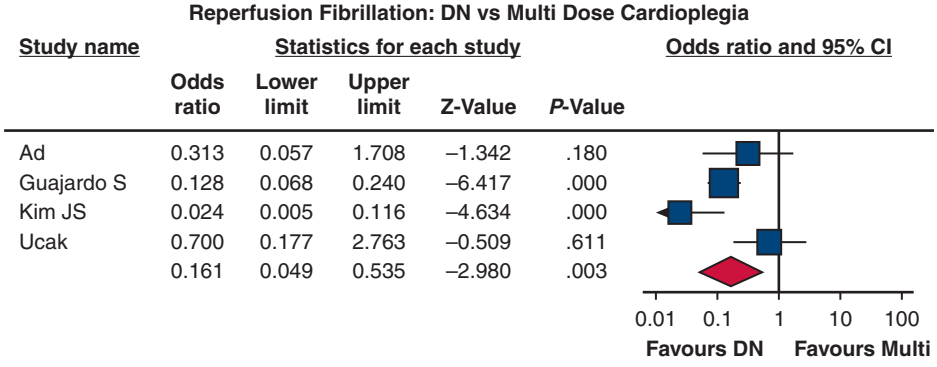

FIGURE 2. Reperfusion fibrillation: DN versus multidose cardioplegia. Forest plot for reperfusion fibrillation comparing DN with multidose cardioplegia. Meta-analysis of the aggregated evidence showed that reperfusion fibrillation was reduced by adoption of DN cardioplegia. *DN*, del Nido; *CI*, confidence interval.

TABLE 4. Multivariable meta-regression for operative mortality

Covariate	Coefficient	SE	*P* value
Intercept	0.67 (−1.01, 2.37)	0.86	.43
Surgery			
Coronary	−0.19 (−1.87, 1.49)	0.85	.82
Valve—full sternotomy	−0.12 (−1.60, 1.35)	0.75	.86
Valve—minimally invasive	−1.03 (−3.93, 1.86)	1.48	.48
Left Ventricle			
Good	−0.56 (−2.76, 1.64)	1.12	.61
Impaired	−0.07 (−1.78, 1.62)	0.86	.92

Meta-regression showed that the employment of single- versus multidose cardioplegia did not affect operative mortality regardless of type of surgery (coronary vs valve operation, independently of minimally invasive approach) and status of the left ventricle (good = ejection fraction ≥55%, impaired = ejection fraction <55%). *SE*, Standard error.

this did not lead to a decreased surge of cardiac enzymes (SMD −0.16 [−0.41 to 0.08], $P = .18$) or mortality (risk difference 0.00 [−0.01 to 0.01], $P = .53$) compared with multidose cardioplegia. Furthermore, our evidence corroborates the findings of Edelman and colleagues,[35] who concluded that reperfusion fibrillation (risk ratio 1.84 [0.91-3.74], $P = .09$), cardiac enzymes (creatine kinase-muscle/brain = MD −4.15 [−12.41 to 4.10], $P = .32$; troponin I = MD 0.90 [−4.68 to 6.48], $P = .75$), MI (risk ratio 1.72 [0.82-3.60], $P = .15$), and operative mortality (risk ratio 1.05 [0.59-1.88], $P = .86$) were similar between HTK and multidose cardioplegia.

Therefore, single-dose cardioplegia seemed to be advantageous over multidose cardioplegia. However, this advantage was limited to a specific type of intervention (DN only) and constrained to secondary endpoints that do not affect clinical outcomes.

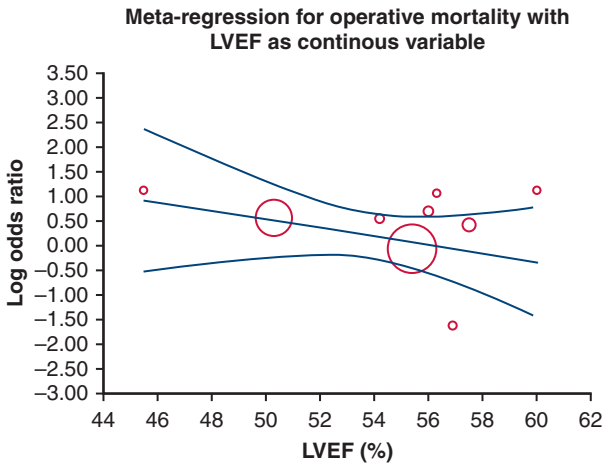

FIGURE 3. Meta-regression for operative mortality with LVEF as moderator. Meta-regression showed that operative mortality was not affected by the usage of single versus multidose cardioplegia, and this finding was independent of LVEF analyzed as a continuous variable. The *curved lines* represent 95% confidence intervals. *LVEF*, Left ventricular ejection fraction.

Limitations

We could have limited our meta-analysis only to RCTs. Nonetheless, we believed that increasing the overall sample pool with the addition of the greatest-quality cohort studies (ie, PSMCs) would have optimized detection of significant trends. To avoid any confusion, the level of evidence (whether from randomized studies or not) is clearly indicated throughout the body of the text and tables/figures. Notably, the evidence from RCTs was predominantly corroborative of the evidence from the overall sample. Despite the power gained from meta-analysis, difference in endpoints between intervention and control arms may not have been captured because of the sample size required to detect adverse outcomes with low incidence. For instance, overall operative mortality for coronary and valve surgery (isolated and combined) in the Society of Thoracic Surgery registry is 2.5%: even if the intervention led to a 25% reduction in the primary outcome, the detection of this effect would still require more than 8500 patients in each arm for a power of 80% at an alpha of 0.05.

CONCLUSIONS

Compared with multidose cardioplegia, there were advantages in adopting single-dose cardioplegia only in the form of DN solution. Indeed, DN was able to reduce operative times, reperfusion fibrillation, and peak of cardiac enzymes. These effects were not replicated by HTK, which on the contrary increased CPB time and reperfusion fibrillation. No significant difference was detected in terms of MI and operative mortality between single- and multidose cardioplegia. It is warranted to confirm the latter finding over time with accumulating registry data, as differences in adverse outcomes with low incidence can only be detected by a proportionally increasing sample size.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: cardioplegia, cardiac protection, cardiac surgery, coronary surgery, valve surgery, del Nido, HTK, minimally invasive surgery

APPENDIX E1. REGISTRATION

The study protocol for this meta-analysis was registered with the number CRD42019119751 at the International Prospective Register of Systematic Reviews in Health and Social Care (PROSPERO), developed and maintained by the Centre for Reviews and Dissemination of the University of York, United Kingdom.[E1] The systematic literature review was undertaken according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and summarized in Table E1. Objectives, data items, and eligibility criteria are detailed in Table E2.

CRITERIA FOR ASSESSMENT OF BIAS AND HETEROGENEITY

The methodologic quality was assessed with the Cochrane risk-of-bias tool[E2] for randomized controlled trials (RCTs) and with the Newcastle–Ottawa scale[E3] scoring for propensity-score matched cohorts (PSMCs). The risk of reporting bias was evaluated quantitatively with the Egger's regression intercept. The risk of bias assessment was performed by 2 authors as standardized practice (I.G., M.G.). In-between study heterogeneity was examined with the Cochrane's Q (χ^2) test, and we further quantified inconsistency by calculating I^2, interpreted using the following guide: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% may represent considerable heterogeneity.[E2,E4]

INFORMATION SOURCES AND SEARCH STRATEGY

Multiple electronic health database engines (MEDLINE, Embase, Cochrane Library, Google Scholar) were searched with unrestricted strategy up till October 2018. Exploded Medical Subject Headings (MeSH) were employed and key words combined with the Boolean operator AND to retrieve relevant reports: ''Del Nido cardioplegia''; ''Custodiol cardioplegia''; ''Bretschneider cardioplegia''; ''HTK cardioplegia''; ''single dose cardioplegia''; 'multiple-dose cardioplegia', ''blood cardioplegia''; ''crystalloid cardioplegia''; and ''adult cardiac surgery''. A second-level search included a manual review of the reference lists of the articles identified through the electronic search.

SELECTION AND ASSESSMENT OF PUBLICATIONS

Eligibility assessment was performed independently in an unblinded standardized manner by 2 reviewers (I.G. and B.W.); disagreements between reviewers were resolved by majority consensus with a third reviewer (M.G.). A total of 955 studies were identified according to the search strategy. This initial pool was screened according to the prespecified eligibility criteria, and consequently a number of articles were excluded as detailed by the flow chart in Figure E1.

The data retrieved from the primary sources were entered into a spreadsheet, which was pilot-tested in 3 randomly selected articles and refined accordingly. One author extracted the data from the included studies (I.G.) and a second author checked the extracted information (B.W.). Disagreements were resolved by discussion with a third author (M.G.). Data were identified in published material only. The methodologic quality of the 23 articles finally selected is depicted in the Figure E2 for PSMCs and Figure E3 for RCTs.

PUBLICATION BIAS AND HETEROGENEITY

Sensitivity Analysis and Visual Assessment of Publication Bias

Sensitivity analysis was performed for all the endpoints by determining whether consequent removal of one study at a time led to influential observations according to quantitative and qualitative criteria. We deemed an observation to be influential according to quantitative criteria if: (1) it inverted the direction of the pooled treatment effect (ie, if odds ratios were inverted from >1 to <1, or differences of means were inverted from positive to negative values, and vice versa) at a significant degree ($P \leq .05$), or (2) conferred new statistical significance ($P \leq .05$) to the pooled treatment effect, of which it was previously lacking. The clinical meaningfulness of such quantitative criteria had to be contextualized in view of the characteristics of the study that was culprit of the influential observation (eg, subgroup of intervention, study design) and of the results of subgroup analyses and meta-regression (qualitative criteria). Sensitivity analysis detected no influential observations. More specifically, quantitative criteria of influential analysis were met only for Hoyer's study, whose removal showed a greater operative mortality of single- over multiple-shot cardioplegia (odds ratio, 1.59 [0.99-2.54], $P = .05$). Qualitative criteria of influential analysis were not instead met for this study, which was a PSMC with histidine–tryptophan–ketoglutarate (HTK) as type of intervention. Indeed, considering the subgroup analysis of RCTs (ie, qualitatively greater ranking studies) with HTK as type of intervention, the latter presented similar mortality compared with multidose cardioplegia (odds ratio, 1.24 [0.38-3.98], $P = .72$). ''Leave one out'' plots detailing the sensitivity analysis, along with funnel plots providing a visual assessment of reporting bias, are available for the endpoints of ischemic time (Figure E4), cardiopulmonary bypass time (Figure E5), reperfusion fibrillation (Figure E6), cardiac enzymes (Figure E7), myocardial infarction (Figure E8), and operative mortality (Figure E9).

Relation with Previous Meta-Analyses

Regarding the meta-analysis on del Nido versus multidose cardioplegia by Li and colleagues,[E5] we improved the quality of the literature sample by including RCTs[E6,E7] and PSMCs[E8,E9] and by excluding cohort studies in which propensity-score matching was either not performed[E10] or its results were not quantified separately.[E11] Regarding the meta-analysis on HTK versus multidose cardioplegia by Edelman and colleagues,[E12] we improved the quality of the literature sample by including PSMCs[E13-E15] and excluding cohorts without propensity-score matching.[E16-E20] In addition, we analyzed such improved literature samples with paradigms able to discern the evidence coming only from randomized models (ie, subgroup analysis by study design), and the influence of multiple moderators on the treatment effect (ie, multivariate meta-regression).

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E14. Hummel BW, Buss RW, DiGiorgi PL, Laviano BN, Yaeger NA, Lucas ML, et al. Myocardial protection and financial considerations of Custodiol cardioplegia in minimally invasive and open valve surgery. *Innovations (Phila)*. 2016;11:420-4.

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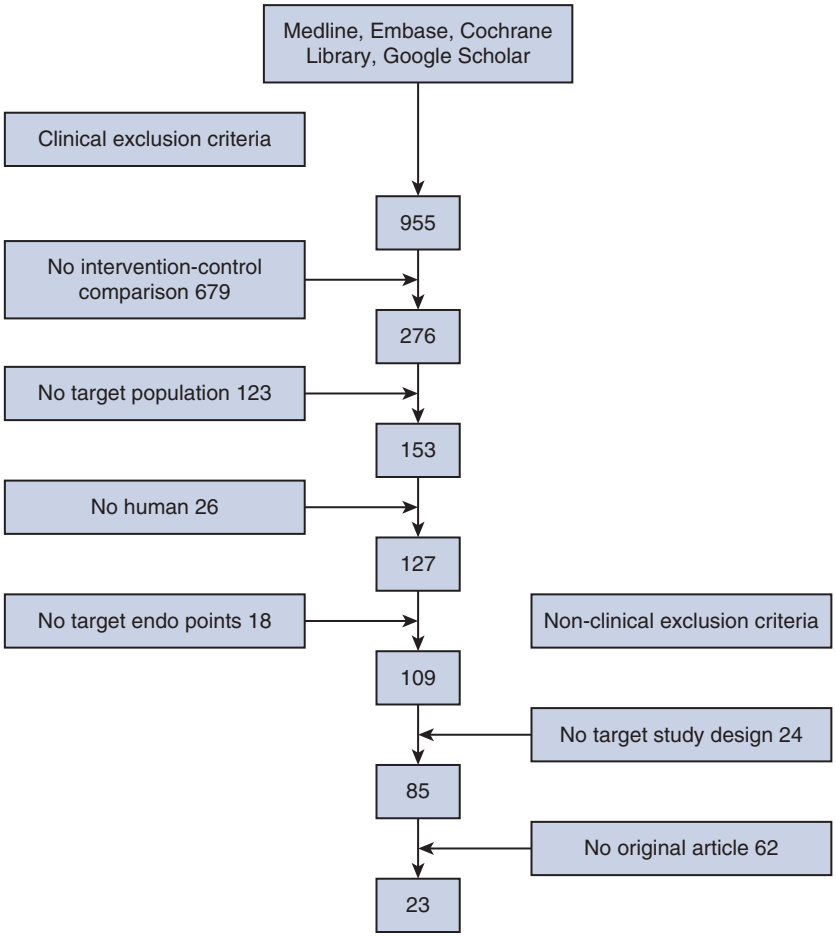


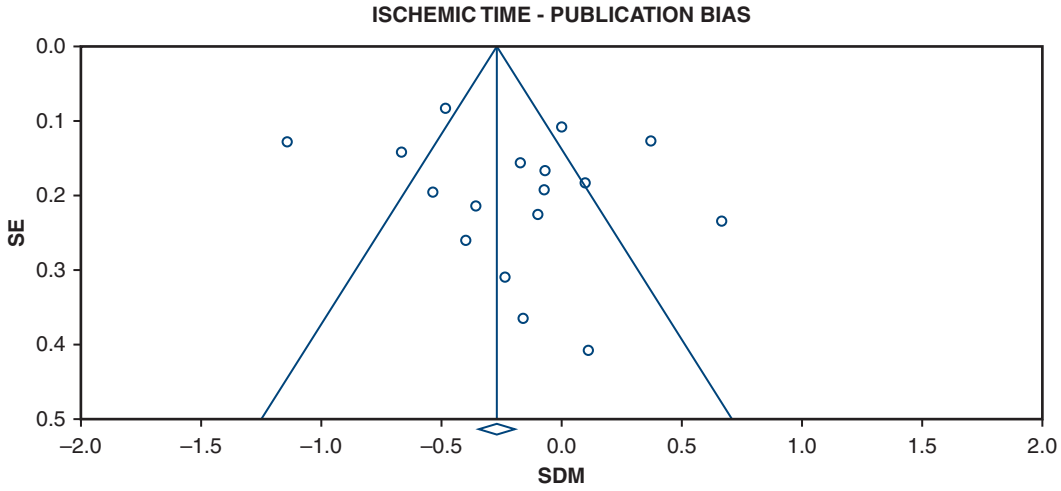
FIGURE E1. Flowchart of literature search and selection process. "No intervention-control comparison" indicates no direct comparison of intervention of interest (ie, single-dose cardioplegia) versus control (ie, multidose cardioplegia); "no target population" indicates pediatric, adult congenital, and cardiac transplant cases were not part of the target population (ie, acquired adult cardiac and proximal aorta disease); "no target endpoints" indicates no clear quantification of end-points as described in the section "Objectives"; "no target study design" indicates the study was not a randomized controlled trial or a propensity-score matched cohort.

Newcastle-Ottawa scale													
Criteria	Guajardo S.	Hoyer	Hummel	Kim WK	Kim JS	Koeckert	Mick	Ota	Pizano	Timek	Viana	Yammine	Yerebakan
I Selection													
IA	*	*	*	*	*	*	*	*	*	*	*	*	*
IB	*	*	*	*	*	*	*	*	*	*	*	*	*
IC	*	*	*	*	*	*	*	*	*	*	*	*	*
ID	*	*	*	*	*	*	*	*	*	*	*	*	*
II Comparability													
II	**	**	**	**	**	**	**	**	**	**	**	**	**
III Outcomes													
IIIA	*	*	*	*	*	*	*	*	*	*	*	*	*
IIIB	*	*	*	*	*	*	*	*	*	*	*	*	*
IIIC	*	*	*	*	*	*	*	*	*	*	*	*	*
IIID	*	*	*	*	*	*	*	*	*	*	*	*	*
Stars, total	10	10	10	10	10	10	10	10	10	10	10	10	10

FIGURE E2. Newcastle–Ottawa Scale. Newcastle–Ottawa scale for the included propensity-score matched cohorts. Criteria: IA, representativeness of the exposed cohort; IB, selection of the non-exposed cohort; IC, ascertainment of exposure; ID, demonstration that outcome of interest was not present at start of study; II, comparability; IIIA, assessment of outcome; IIIB, was follow-up long enough for outcomes to occur; IIIC, complete follow-up, ie, all subjects accounted for; IIID, subjects lost to follow-up unlikely to introduce bias. Score: *asterisk*, the study meets the specified criterion; *dash*, the criterion is not applicable to the study.

Cochrane risk of bias tool										
Criteria	Ad	Arslan	Beyersdorf	Braathen	Careaga	Demmy	Gallandat	Gaudino	Kammerer	Ucak
I	+	+	+	+	+	+	+	+	+	+
II	+	?	?	?	?	–	–	?	?	+
III	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
IV	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
V	+	+	+	+	+	+	+	+	+	+
VI	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
VII	+	+	+	+	+	+	+	+	+	+

FIGURE E3. Cochrane risk of bias tool. Cochrane risk of bias tool for the included randomized controlled trials. Criteria: I, random sequence generation (selection bias); II, allocation concealment (selection bias); III, blinding of participants and personnel (performance bias); IV, blinding of outcome assessment (detection bias) (patient-reported outcomes); V, incomplete outcome data addressed (attrition bias) (short-term outcomes 2-6 weeks); VI, incomplete outcome data addressed (attrition bias) (long-term outcomes >6 weeks); VII, selective reporting (reporting bias). Score: +, low risk of bias; –, high risk of bias; ?, unclear risk of bias. *N/A*, Not available.



ISCHEMIC TIME - SENSITIVITY ANALYSIS

Study name	Statistics with study removed							Difference in means (95% CI) with study removed
	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	*P*-Value	
Ad	–4.218	1.976	3.906	–8.092	–0.345	–2.134	.033	
Arslan	–4.720	2.051	4.207	–8.740	–0.700	–2.301	.021	
Beyersdorf	–4.804	1.989	3.958	–8.703	–0.905	–2.415	.016	
Braathen	–5.128	2.018	4.071	–9.082	–1.173	–2.542	.011	
Careaga	–4.542	1.974	3.895	–8.410	–0.673	–2.301	.021	
Gallandat	–5.504	1.986	3.942	–9.395	–1.612	–2.772	.006	
Gaudino	–4.834	2.221	4.931	–9.186	–0.482	–2.177	.029	
Guajardo S	–4.943	2.084	4.345	–9.029	–0.858	–2.372	.018	
Kammerer	–4.673	2.006	4.022	–8.604	–0.742	–2.330	.020	
Kim WK	–3.352	1.896	3.593	–7.067	0.363	–1.768	.077	
Kim JS	–4.554	1.978	3.911	–8.430	–0.678	–2.303	.021	
Koeckert	–5.019	2.052	4.210	–9.041	–0.998	–2.446	.014	
Ota	–4.278	2.032	4.128	–8.260	–0.296	–2.105	.035	
Pizano	–3.480	1.896	3.594	–7.196	0.235	–1.836	.066	
Timek	–4.609	2.040	4.161	–8.606	–0.611	–2.259	.024	
Ucak	–3.798	1.773	3.144	–7.273	–0.323	–2.142	.032	
Viana	–4.553	1.975	3.901	–8.424	–0.682	–2.305	.021	
	–4.534	1.941	3.768	–8.339	–0.730	–2.336	.019	

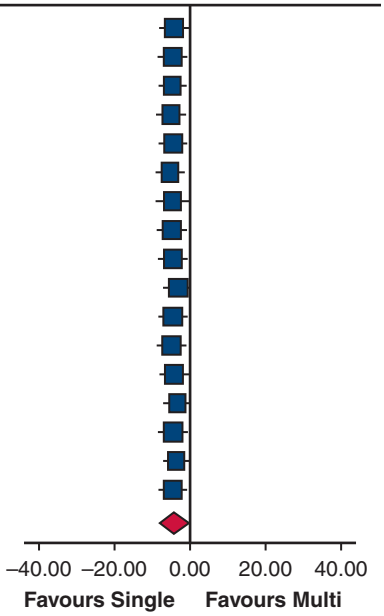
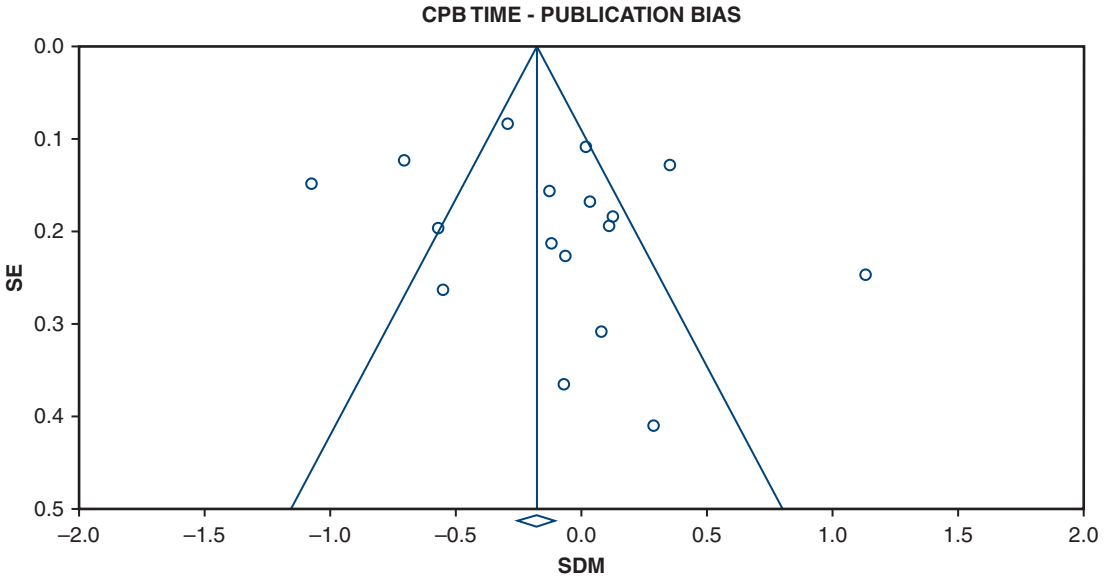


FIGURE E4. Publication bias and sensitivity analysis of the secondary endpoint "ischemic time." The funnel plot in the upper half of the figure depicts graphically the publication bias. The forest plot in the lower half of the figure represents a sensitivity analysis, where each row displays not the results of a single study, but rather the summary values computed when that row's study is removed from the meta-analysis. *SE*, Standard error; *SDM*, standard difference of means; *CI*, confidence interval.



CPB TIME - SENSITIVITY ANALYSIS

Study name	Statistics with study removed							Difference in means (95% CI) with study removed
	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	*P*-Value	
Ad	–4.378	2.552	6.514	–9.380	0.625	–1.715	.086	
Arslan	–4.820	2.602	6.773	–9.921	0.280	–1.852	.064	
Beyersdorf	–4.876	2.555	6.530	–9.885	0.133	–1.908	.056	
Braathen	–5.264	2.666	7.110	–10.490	–0.038	–1.974	.048	
Careaga	–4.484	2.541	6.457	–9.464	0.496	–1.765	.078	
Gallandat	–5.709	2.566	6.583	–10.738	–0.680	–2.225	.026	
Gaudino	–4.639	2.954	8.725	–10.429	1.150	–1.571	.116	
Guajardo S	–4.892	2.721	7.402	–10.224	0.440	–1.798	.072	
Kammerer	–4.859	2.566	6.586	–9.889	0.171	–1.893	.058	
Kim WK	–1.763	2.104	4.425	–5.886	2.360	–0.838	.402	
Kim JS	–4.443	2.537	6.434	–9.415	0.529	–1.752	.080	
Koeckert	–5.005	2.634	6.938	–10.168	0.158	–1.900	.057	
Ota	–3.771	2.571	6.611	–8.810	1.268	–1.467	.142	
Pizano	–3.612	2.550	6.501	–8.610	1.385	–1.417	.157	
Timek	–4.522	2.633	6.934	–9.683	0.639	–1.717	.086	
Ucak	–3.953	2.590	6.708	–9.030	1.123	–1.526	.127	
Viana	–4.596	2.535	6.424	–9.564	0.372	–1.813	.070	
	–4.430	2.498	6.240	–9.326	0.466	–1.773	.076	

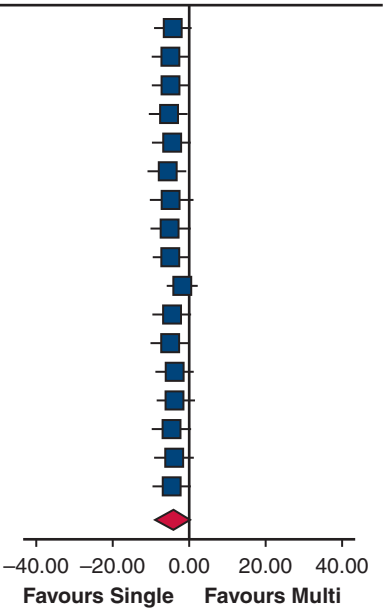
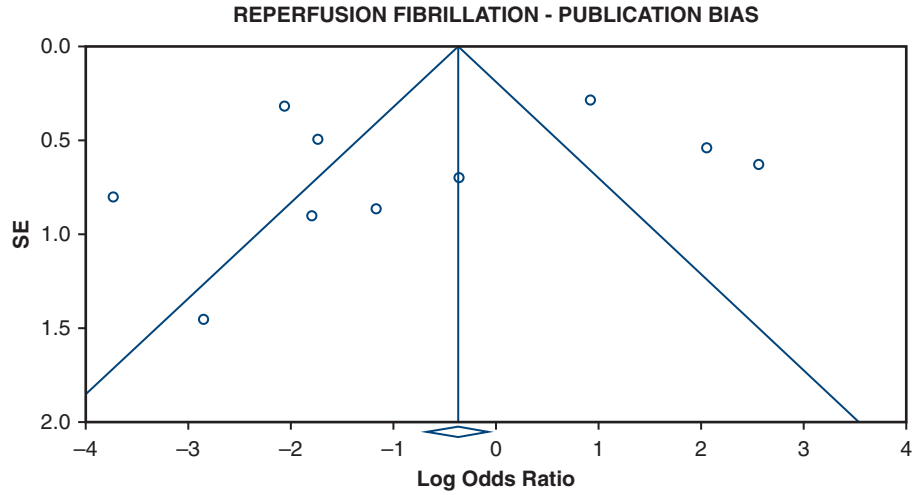


FIGURE E5. Publication bias and sensitivity analysis of the secondary endpoint "CBP time." The funnel plot in the upper half of the figure depicts graphically the publication bias. The forest plot in the lower half of the figure represents a sensitivity analysis, where each row displays not the results of a single study, but rather the summary values computed when that row's study is removed from the meta-analysis. *CPB*, Cardiopulmonary bypass; *SE*, standard error; *SDM*, standard difference of means; *CI*, confidence interval.



REPERFUSION FIBRILLATION - SENSITIVITY ANALYSIS

Study name	Statistics with study removed					Odds ratio (95% CI) with study removed
	Point	Lower limit	Upper limit	Z-Value	*P*-Value	
Ad	0.514	0.132	1.998	–0.961	.336	
Beyersdorf	0.549	0.143	2.107	–0.875	.382	
Demmy	0.552	0.138	2.211	–0.840	.401	
Gallandat	0.398	0.098	1.609	–1.293	.196	
Gaudino	0.340	0.096	1.201	–1.676	.094	
Guajardo S	0.585	0.158	2.170	–0.801	.423	
Hoyer	0.581	0.156	2.155	–0.812	.417	
Kammerer	0.356	0.098	1.295	–1.568	.117	
Kim JS	0.686	0.193	2.438	–0.582	.560	
Ucak	0.469	0.118	1.874	–1.071	.284	
	0.492	0.139	1.738	–1.102	.271	

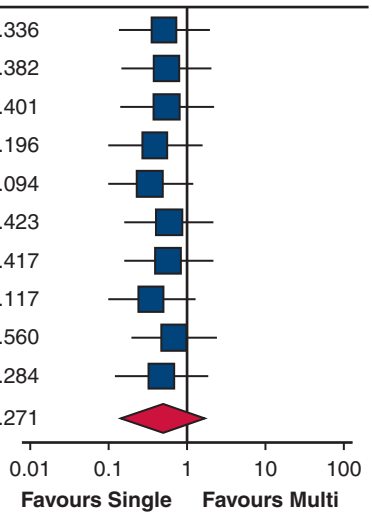
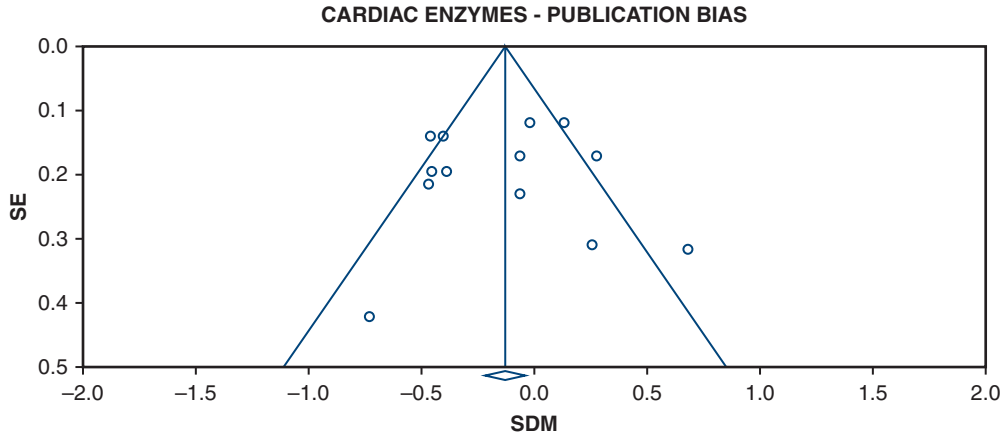


FIGURE E6. Publication bias and sensitivity analysis of the secondary endpoint "reperfusion fibrillation." The funnel plot in the upper half of the figure depicts graphically the publication bias. The forest plot in the lower half of the figure represents a sensitivity analysis, where each row displays not the results of a single study, but rather the summary values computed when that row's study is removed from the meta-analysis. *SE*, Standard error; *CI*, confidence interval.



CARDIAC ENZYMES - SENSITIVITY ANALYSIS

Study name	Subgroup within study	Statistics with study removed: Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	*P*-Value
Ad	Trop-I	–0.107	0.095	0.009	–0.293	0.079	–1.131	.258
Arslan	CK-MB	–0.155	0.094	0.009	–0.339	0.029	–1.647	.100
Arslan	Trop-I	–0.174	0.087	0.008	–0.345	–0.004	–2.003	.045
Beyersdorf	CK-MB	–0.113	0.092	0.008	–0.294	0.068	–1.224	.221
Braathen	CK-MB	–0.138	0.098	0.010	–0.330	0.053	–1.418	.156
Demmy	CK-MB	–0.140	0.100	0.010	–0.335	0.056	–1.399	.162
Demmy	Trop-I	–0.173	0.092	0.008	–0.353	0.007	–1.883	.060
Kammerer	CK-MB	–0.111	0.097	0.009	–0.301	0.078	–1.155	.248
Kammerer	Trop-I	–0.106	0.095	0.009	–0.293	0.080	–1.117	.264
Kim WK	CK-MB	–0.099	0.094	0.009	–0.283	0.084	–1.062	.288
Kim WK	Trop-I	–0.105	0.096	0.009	–0.294	0.084	–1.092	.275
Ucak	CK-MB	–0.164	0.096	0.009	–0.352	0.024	–1.709	.087
Ucak	Trop-I	–0.146	0.102	0.010	–0.347	0.055	–1.423	.155
		–0.134	0.091	0.008	–0.313	0.046	–1.461	.144

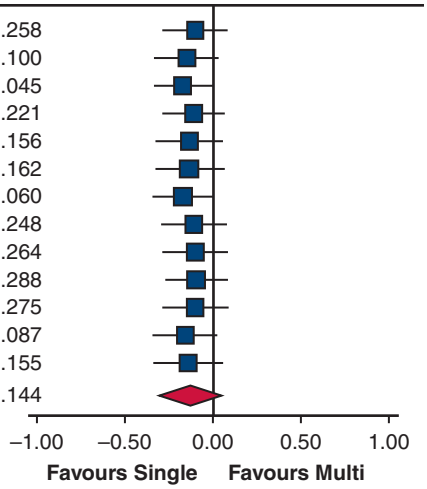
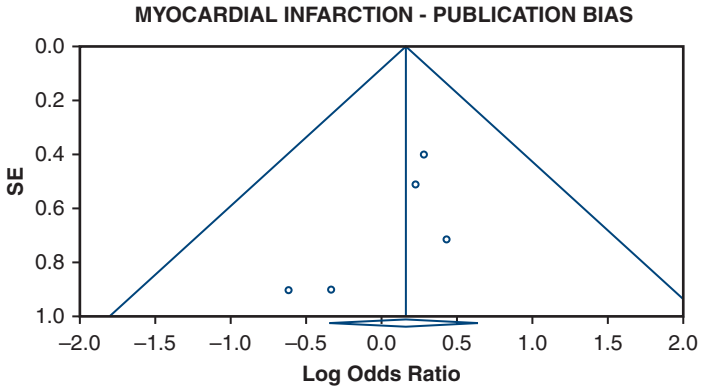


FIGURE E7. Publication bias and sensitivity analysis of the secondary endpoint "cardiac enzymes." The funnel plot in the upper half of the figure depicts graphically the publication bias. The forest plot in the lower half of the figure represents a sensitivity analysis, where each row displays not the results of a single study, but rather the summary values computed when that row's study is removed from the meta-analysis. *SE*, Standard error; *SDM*, standard difference of means; *CI*, confidence interval.



MYOCARDIAL INFARCTION - SENSITIVITY ANALYSIS

Study name	Statistics with study removed					Odds ratio (95% CI) with study removed
	Point	Lower limit	Upper limit	Z-Value	*P*-Value	
Beyersdorf	1.239	0.451	3.400	0.416	.678	
Demmy	1.278	0.427	3.822	0.439	.660	
Hoyer	1.135	0.328	3.926	0.200	.842	
Ucak	1.456	0.546	3.886	0.750	.453	
Viana	1.526	0.572	4.072	0.844	.399	
	1.339	0.524	3.424	0.610	.542	

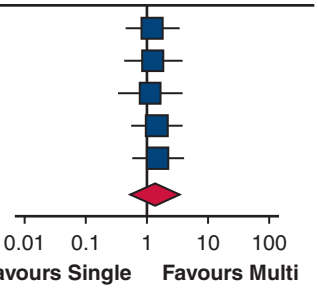
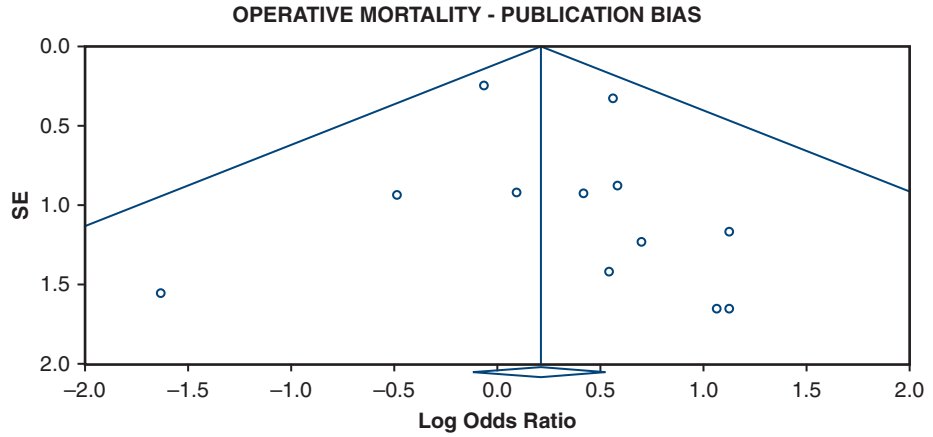


FIGURE E8. Publication bias and sensitivity analysis of the secondary endpoint "myocardial infarction." The funnel plot in the upper half of the figure depicts graphically the publication bias. The forest plot in the lower half of the figure represents a sensitivity analysis, where each row displays not the results of a single study, but rather the summary values computed when that row's study is removed from the meta-analysis. *SE*, Standard error; *CI*, confidence interval.



OPERATIVE MORTALITY - SENSITIVITY ANALYSIS

Study name	Statistics with study removed					Odds ratio (95% CI) with study removed
	Point	Lower limit	Upper limit	Z-Value	*P*-Value	
Gallandat	1.218	0.864	1.718	1.127	.260	
Gaudino	1.225	0.873	1.719	1.175	.240	
Guajardo S	1.231	0.876	1.728	1.199	.231	
Hoyer	1.595	0.999	2.546	1.955	.051	
Hummel	1.225	0.872	1.721	1.168	.243	
Kammerer	1.267	0.900	1.785	1.355	.176	
Kim WK	1.265	0.901	1.776	1.360	.174	
Kim JS	1.224	0.873	1.718	1.171	.241	
Pizano	1.081	0.728	1.607	0.387	.698	
Ucak	1.242	0.881	1.750	1.238	.216	
Viana	1.212	0.862	1.704	1.106	.269	
Yammine	1.228	0.871	1.730	1.173	.241	
Yerebakan	1.224	0.873	1.718	1.171	.241	
	1.237	0.883	1.732	1.236	.216	

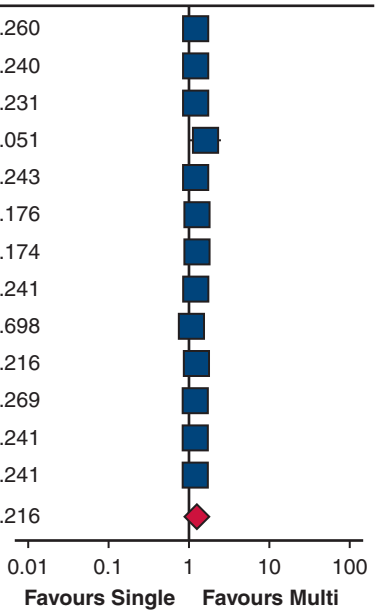


FIGURE E9. Publication bias and sensitivity analysis for the primary endpoint. The funnel plot in the upper half of the figure depicts graphically the publication bias. The forest plot in the lower half of the figure represents a sensitivity analysis, where each row displays not the results of a single study, but rather the summary values computed when that row's study is removed from the meta-analysis. *SE*, Standard error; *CI*, confidence interval.

TABLE E1. A review of randomized controlled trials and cohort studies with propensity match scoring, which directly compared single- versus multidose cardioplegia, was undertaken according to the components of PRISMA

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a literature review.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings.	1
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known about your topic.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2, Appendix E1, Table E1
Methods			
Eligibility criteria	5	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	Appendix E1, Table E1
Information sources	6	Describe all information sources (eg, databases with dates of coverage) in the search and date last searched.	2, Appendix E1
Search	7	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix E1, Figure E1
Study selection	8	State the process for selecting studies (ie, screening, eligibility).	Appendix E1, Table E1, Figure E1
Risk of bias in individual studies	9	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level).	7, Appendix E1
Risk of bias across studies	10	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	2, Appendix E1
Results			
Study selection	11	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.	Appendix E1, Table E1
Study characteristics	12	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	3, Table 1, Appendix E1
Synthesis of results of individual studies	13	For all outcomes considered (benefits or harms), present, for each study: (1) summary of results and (2) relationship to other studies under review (eg, agreements or disagreements in methods, sampling, data collection or findings).	3-4
Discussion			
Summary of evidence	14	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, health care providers, users, and policy makers).	4-7
Limitations	15	Discuss limitations at study and outcome level (eg, risk of bias), and at review-level (eg, incomplete retrieval of identified research, reporting bias).	7
Conclusion			
Conclusions	16	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	7

PICOS, Participants, interventions, comparisons, outcomes, and study design

TABLE E2. PICOS, data items, and eligibility criteria

PICOS	
Participants	Patients with age ≥18 years and no sex limitation requiring surgical intervention for acquired cardiac or proximal aorta disease with the exclusion of transplantation
Interventions	Single-dose cardioplegia (intervention group) vs multidose cardioplegia (control group)
Comparisons	Intervention group [DN or HTK] vs control group [conventional blood or crystalloid multidose cardioplegia]
Outcomes	Primary: operative mortality. Secondary: ischemic time, CPB bypass time; reperfusion fibrillation, peak of cardiac enzymes, MI.
Study design	Meta-analysis of RCTs (level IA evidence), and of PSMCs + RCTs (high-quality evidence).
Data items	
Series details	First author; publication year; journal; patients, n; study design; intervention type; control type; operation.
Preoperative variables	Age; male sex; HTN; DM; NYHA class ≥III; LVEF; PAD; chronic pulmonary disease; CVD; nonelective status; reintervention.
Intraoperative variables	Isolated CABG; isolated valve surgery; multiple valve surgery; valve + CABG; proximal aortic surgery; other; minimally invasive approach; valve repair %; number of grafts.
Outcomes	Ischemic time; CPB time; reperfusion fibrillation; cardiac enzyme levels (creatine kinase-muscle/brain and troponin I); MI; operative mortality
Eligibility criteria	
Inclusion criteria	Original articles directly comparing the outcomes of intervention and control groups in RCTs and PSMC, with no limit to date of publication
Clinical exclusion criteria	Pediatric, adult congenital, and cardiac transplant patients; no quantification of the outcomes of PICOS; no direct comparison of intervention and control groups
Nonclinical exclusion criteria	Publication reporting other than RCTs or PSMCs; overlapping series (only the latest publication on serial reports of a certain cohort was included); no original article (eg, editorial, review)

The objectives of the review were framed according to the PICOS components of PRISMA guidelines. The data items defined the information of interest to extract from the literature, which was selected according to the eligibility criteria. *PICOS*, Participants, interventions, comparisons, outcomes, and study design; *DN*, del Nido; *HTK*, histidine–tryptophan–ketoglutarate; *CPB*, cardiopulmonary bypass; *MI*, myocardial infarction; *RCT*, randomized controlled trial; *PSMC*, propensity-score matched cohort; *HTN*, hypertension; *DM*, diabetes mellitus; *NYHA*, New York Heart Association; *LVEF*, left ventricular ejection fraction; *PAD*, peripheral arterial disease; *CVD*, cerebrovascular disease; *CABG*, coronary artery bypass grafting.