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Original Article

Propofol-Supplemented Cardioplegic Solution Effect on Myocardial Protection: A Systematic Review and Bayesian Meta-analysis of Randomized Controlled Trials

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Objectives: To determine the probability of a clinically relevant reduction in postoperative myocardial injury following the use of propofol-supplemented cardioplegia.
Design: Systematic review and Bayesian meta-analysis.
Setting: Perioperative cardiac surgery.
Participants: Adult patients (N = 523) undergoing cardiac surgery requiring cardiopulmonary bypass.
Interventions: Propofol-supplemented cardioplegic solution versus standard cardioplegia.
Measurements and Main Results: The primary endpoint was postoperative troponin levels. A Bayesian hierarchical random-effects model using weakly informative priors yielded a pooled standardized mean difference (SMD) of −0.05 (95% credible interval [CrI], −0.33 to 0.24). The posterior probability of any reduction in postoperative troponin levels (SMD < 0) was 70.8%. Secondary endpoints showed similarly uncertain evidence of benefit, including postoperative creatinine levels (SMD, −0.06; 95% CrI, −0.71 to 0.46; probability of benefit, 59.8%), serious complications (risk ratio [RR], 0.77; 95% CrI, 0.18 to 2.28; probability of benefit, 70.3%), and postoperative arrhythmias (RR, 0.96; 95% CrI, 0.51 to 1.62; probability of benefit, 56.4%).
Conclusions: Current evidence suggests moderate posterior probabilities of benefit across endpoints. However, substantial uncertainty remains regarding the magnitude and direction of the true treatment effects. These findings do not provide convincing evidence to support routine addition of propofol to standardized cardioplegic protocols, and the use of propofol-supplemented cardioplegia should remain at the discretion of the heart surgery team.

Key Words: propofol; cardioplegia; cardiopulmonary bypass; cardiac surgery; cardioprotection

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CARDIAC SURGERY REQUIRING cardiopulmonary bypass (CPB), including coronary artery bypass grafting (CABG) and aortic valve replacement (AVR), inevitably exposes the myocardium to global ischemia followed by reperfusion, a process that remains a major determinant of postoperative myocardial injury despite advances in cardioplegic techniques.[1,2] The pathophysiology of ischemia-reperfusion injury is multifactorial, involving oxidative stress, calcium overload, mitochondrial dysfunction, and activation of inflammatory cascades, ultimately leading to myocardial stunning and irreversible cellular injury.[2,3] Clinically, this process is reflected by postoperative elevation of cardiac biomarkers, particularly cardiac troponins, which have been consistently associated with increased short- and long-term mortality after cardiac surgery.[4] Furthermore, troponin has demonstrated superior prognostic performance compared with creatine kinase−MB, reinforcing its role as a robust surrogate marker of myocardial injury in this setting. Despite the central role of cardioplegic arrest in myocardial protection, these observations underscore the persistent need for adjunctive strategies to further attenuate perioperative myocardial damage.[5]

Propofol, a widely used intravenous anesthetic, has emerged as a candidate cardioprotective agent because of its antioxidant, anti-inflammatory, and antiapoptotic properties.[6,7] Experimental studies have shown that propofol attenuates lipid peroxidation, reduces reactive oxygen species generation, and inhibits mitochondrial permeability transition pore opening, thereby limiting myocardial injury during ischemia-reperfusion.[7-9] However, translation into clinical benefit remains uncertain. Early randomized evidence, including the single-center Propofol for Myocardial Protection Trial (ProMPT), suggested that propofol-supplemented cardioplegia may reduce postoperative troponin release.[10] Additional randomized data in valvular surgery populations have also shown reductions in myocardial injury biomarkers, although in some cases, systemic administration appeared more effective than cardioplegic supplementation.[11] In contrast, more recent high-quality evidence challenges these findings. The multicenter Propofol for Myocardial Protection Trial 2 (ProMPT2) demonstrated no significant reduction in postoperative troponin levels with either low- or high-dose propofol supplementation of cardioplegia compared with placebo, despite confirming its safety.[12] Taken together, these conflicting findings highlight substantial uncertainty regarding the magnitude and clinical relevance of the cardioprotective effect of propofol when used as a cardioplegic additive. Existing meta-analyses in cardiac anesthesia have primarily compared volatile anesthetics with systemic propofol-based anesthesia during cardiac surgery rather than evaluating propofol administered within cardioplegic solutions.[13,14] Consequently, they do not address the clinically relevant question of whether propofol supplementation of cardioplegia improves myocardial protection. Moreover, the randomized controlled trials (RCTs) specifically evaluating this strategy remain limited and heterogeneous with respect to surgical populations, dosing strategies, and timing of biomarker assessment, which limits interpretability and generalizability.[10-12] Therefore, a systematic review and Bayesian meta-analysis of RCTs was performed to determine whether propofol-supplemented cardioplegic solutions improve myocardial protection in adult patients undergoing cardiac surgery, with a primary focus on postoperative troponin levels measured within the clinically relevant 12- to 24-hour window.

Methods

Study Design

This systematic review and meta-analysis was performed and reported in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines.[15,16] The prospective protocol was registered on PROSPERO on April 3, 2026.

Search Strategy

The authors systematically searched the PubMed, Cochrane, and Web of Science databases from inception to April 2026. The following search terms were used: “heart surgery,” “coronary artery bypass,” “propofol,” “cardioplegia,” “cardioplegic solutions.” The complete search strategy is available in the Supplementary Appendix. In addition, the references of all included studies were searched manually for any additional eligible studies.

Eligibility Criteria

Inclusion in this meta-analysis was restricted to studies that met all of the following criteria: (1) RCT, (2) inclusion of patients aged ≥ 18 years undergoing cardiac surgery with cardiac bypass, (3) comparison of propofol-supplemented cardioplegic solution with placebo (saline solution), (4) reporting of a minimum follow-up of 24 hours, and (5) reporting of at least 1 outcome of interest. Studies were excluded if (1) they were nonrandomized (observational cohorts, registries, case-control studies, case series, or case reports); (2) no outcomes of interest were reported; (3) there was no sufficient data to be extracted; or (4) overlapping populations were included.

Endpoints and Subgroup Analysis

The primary endpoint was postoperative cardiac troponin levels. Other endpoints evaluated were postoperative arrhythmias, postoperative creatinine levels, intensive care unit (ICU) length of stay, hospital length of stay, and serious complications. Definitions of all endpoints are provided in Supplementary Table 2.

Prespecified subgroup analyses were conducted to explore potential sources of clinical and methodological heterogeneity. First, all endpoints were stratified by surgical procedure (isolated CABG, isolated AVR, or combined). This stratification was prespecified because the baseline myocardial pathophysiology (eg, concentric ventricular hypertrophy in AVR *v* chronically ischemic myocardium in CABG) and typical aortic

cross-clamp durations differ fundamentally between these procedures, potentially altering the efficacy of cardioprotective adjuvants. Second, the primary endpoint of postoperative cardiac troponin levels was further stratified by biomarker subtype (troponin T *v* troponin I) to account for inherent differences in cytosolic release kinetics, molecular weights, and assay-specific reference thresholds.

Data Extraction

Two authors independently extracted the data using Rayyan software[17] (Rayyan Systems, Cambridge, MA) following predefined forms. A template was developed for data extraction of relevant items, including study details (first author, publication year, study design, sample size), participant baseline characteristics (history of cardiac surgery with cardiac bypass), population characteristics, age, sex, intervention (propofol), control (specific cardioplegic protocols including vehicle base, such as blood or crystalloid, composition, and temperature), and outcome measures. Disagreements were resolved by consensus with a third reviewer after discussing reasons for discrepancy.

Quality Assessment

The risk of bias in randomized studies was evaluated using the Cochrane risk-of-bias assessment tool, version 2. Studies were assessed across 5 domains: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, and (5) bias in selection of the reported result.[18] Two authors independently completed the risk-of-bias assessment, with disagreements resolved by consensus with a third author. Publication bias could not be reliably assessed because of the low number of studies included.

The certainty of evidence for each outcome was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[19] The overall certainty of evidence for each outcome was classified as high, moderate, low, or very low. GRADE assessments were performed independently by 2 reviewers. Disagreements were resolved by consensus with a third author.

Sensitivity Analysis

Leave-one-out sensitivity analyses were performed for all endpoints to assess the effects of influential studies on the pooled analysis. Studies were sequentially removed, and the data were reanalyzed to ensure the stability of the pooled effects. Furthermore, given the anticipated clinical heterogeneity regarding the cardioplegic vehicles used across the primary trials, this sequential exclusion strategy was specifically applied to explore whether the underlying cardioplegic protocol modulated the magnitude of the treatment effect or drove the observed between-study statistical heterogeneity.

Statistical Analysis

For dichotomous outcomes, risk ratios (RRs) with 95% confidence intervals (CIs) were calculated. For continuous outcomes, mean differences (MDs) or standardized mean differences (SMDs) with standard deviations were estimated. When standard deviations were not reported, they were imputed from standard errors, CIs, or interquartile ranges using Cochrane-recommended methods. All pooled estimates were derived using a random-effects model with restricted maximum-likelihood estimation to account for between-study variability and provide conservative effect estimates. Statistical heterogeneity was assessed using the Cochran Q test and quantified using the I^2 statistic, interpreted as low (25%-49%), moderate (50%-74%), or high ($\geq$75%).

A complementary Bayesian random-effects meta-analysis was conducted in adherence to the Bayesian Analysis Reporting Guidelines.[20] Posterior distributions of the pooled effect sizes were generated via Markov chain Monte Carlo (MCMC) sampling. The MCMC algorithm was executed using 4 parallel chains, each consisting of 4,000 iterations (including 1,000 warm-up iterations discarded for adaptation), with an adapt_-delta of 0.99, to ensure stringent sampling

To stabilize the variance estimates while minimizing subjective bias, the authors formulated weakly informative prior distributions that do not dominate the likelihood—specifically, a Normal prior for the global effect size Normal (0, 1.5) for log-ratios and Normal (0, 5) for continuous mean differences. For the between-study standard deviation (τ), a half-Cauchy prior, Cauchy (0, 1), was assigned, as recommended for hierarchical models with a limited number of included studies. Furthermore, a prior sensitivity analysis was conducted to assess the robustness of the authors' Bayesian inferences. The authors systematically compared the posterior estimates derived from their primary weakly informative (neutral) priors against those obtained using skeptical (strict) priors (which are tightly centered at 0 [eg, Normal (0, 0.5)]) to heavily penalize large treatment effects. This approach ensured that their posterior probabilities of benefit were primarily data driven and not an artifact of the prior specification.

Results are reported as posterior medians accompanied by 95% credible intervals (CrIs), communicating the precise 95% probability that the true parameter lies within the specified range. Furthermore, to directly address the clinical question, the authors computed the posterior probability of clinical benefit based on the area under the posterior curve exceeding prespecified clinical thresholds (SMD $<$ 0 or RR $<$ 1). Importantly, whereas a frequentist p value and CI provide a strict, binary test of the null hypothesis, the posterior probability directly quantifies the continuous likelihood of a treatment effect; hence, a 95% CrI may cross the line of no effect while the underlying posterior distribution continues to indicate probability of clinical benefit. The predefined categorical thresholds used to interpret the clinical significance of the posterior probabilities are detailed in Supplementary Table 3.

Comprehensive Bayesian diagnostics were performed to ensure the validity of the inferences. MCMC chain convergence and optimal mixing were verified via visual inspection of trace plots and

rank histograms. The adequacy of the model fit was examined through posterior predictive checks, and shrinkage plots were used to visualize the degree of partial pooling across the individual trials. Results of the Bayesian analysis are provided in the Supplementary Appendix. All statistical analyses were performed using R statistical software (version 4.2.3).[21]

Results

Study Selection and Baseline Characteristics

A total of 3,163 studies were identified through database searches. After removal of duplicates (n = 1,009), 2,154 titles and abstracts were screened, and 2,139 records were excluded. Fifteen full-text articles were assessed for eligibility, of which 10 were excluded. The reasons for exclusion were incorrect interventions, different patient populations, and outcomes of interest not reported (Fig 1).

Finally, 5 RCTs were included in this systematic review and meta-analysis, representing a total of 523 patients, of whom 261 (49.9%) received propofol-supplemented cardioplegia and 262 (50.1%) were managed with placebo.[10-12,22,23] The studies were conducted in the United Kingdom, Egypt, and Iran and enrolled patients undergoing CABG, AVR, or mixed cardiac surgical procedures requiring CPB. The mean age of participants ranged from 39 to 71 years, and the prevalence of

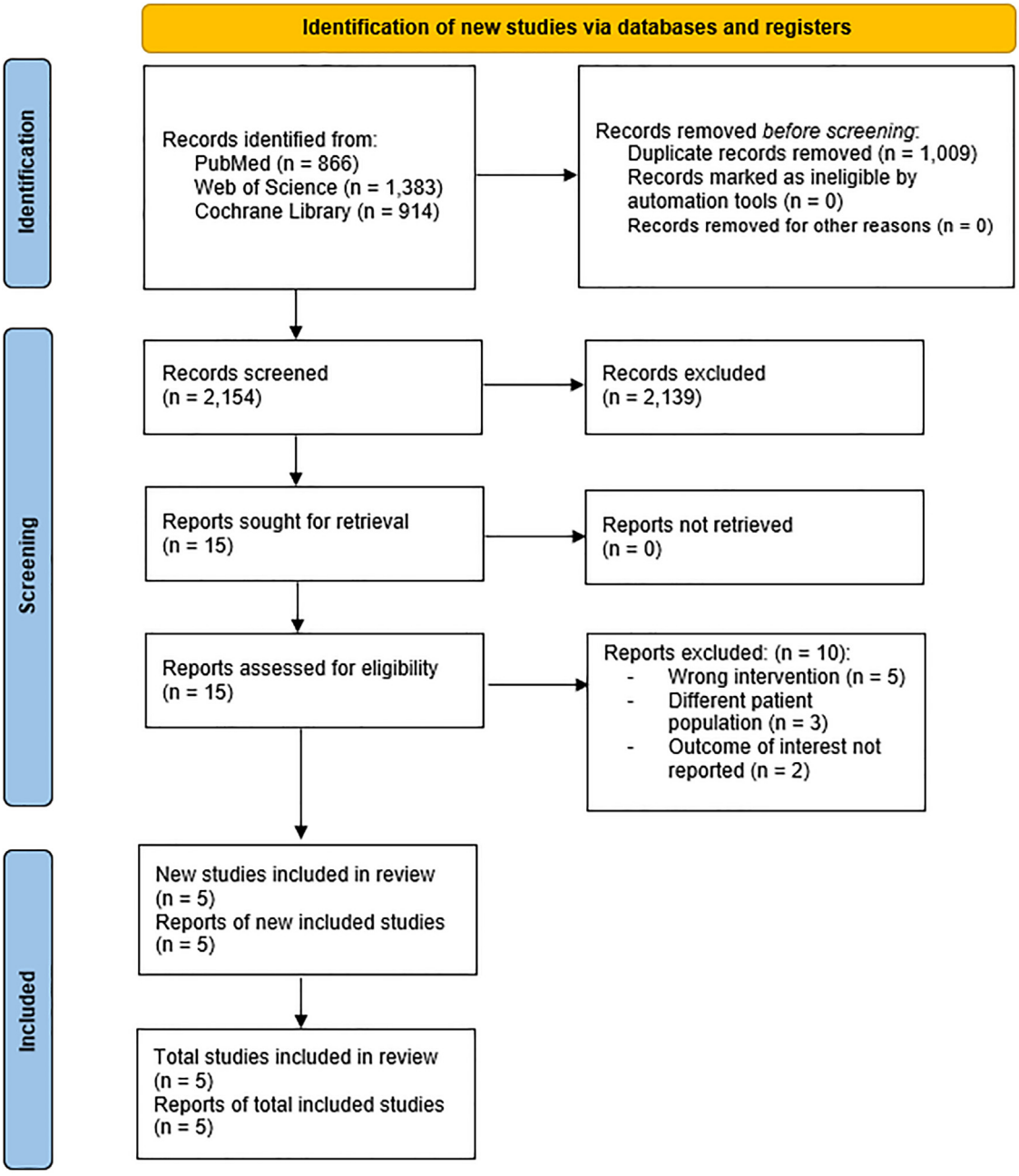

Fig 1. Detailed flow diagram of systematic literature search, screening, and study selection process in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

cardiovascular risk factors was similar across study arms. Propofol concentrations ranged from 4 to 10 μg/mL, and different cardioplegia formulations were used, including warm blood, cold blood, cold crystalloid, and St. Thomas cardioplegia. Control solutions consisted predominantly of saline solution, although Intralipid (Fresenius Kabi, Uppsala, Sweden) was used in 1 trial. Detailed baseline and operative characteristics of the included studies are summarized in Table 1. A comprehensive statistical summary of all primary and secondary endpoints, including frequentist estimates and Bayesian posterior probabilities, is presented in Table 2.

Primary Endpoint

Postoperative troponin levels were evaluated across 5 studies and showed no significant differences between the propofol-supplemented cardioplegia and placebo groups in the frequentist analysis (SMD, −0.05; 95% CI, −0.22 to 0.12; I^2 = 0%; p = 0.4596; Table 2). Bayesian analysis showed a pooled SMD of −0.05 (95% CrI, −0.33 to 0.24; Fig 2, A). The posterior probability of any reduction in postoperative troponin levels (SMD < 0) was 70.8% in patients receiving propofol-supplemented cardioplegia (Fig 2, B). Subgroup analysis based on specific cardiac biomarker assay did not find significant differences between studies reporting troponin T and troponin I levels (p for interaction = 0.4176; Supplementary Fig 1, A). Subgroup analysis based on type of procedure revealed that the overall test for subgroup differences remained nonsignificant (p for interaction = 0.8743; Supplementary Fig 1, B). Leave-one-out sensitivity analysis confirmed the robustness of the findings (Supplementary Fig 1, C).

Secondary Endpoints

Postoperative Creatinine Levels

Postoperative creatinine levels were reported in 3 studies and showed no significant differences between groups in the frequentist analysis (SMD, −0.06; 95% CI, −0.26 to 0.15; I^2 = 14.3%; p = 0.5917). Subgroup analysis based on type of surgery showed no significant differences between CABG and AVR studies (p for interaction = 0.1347; Supplementary Fig 2, A). Sensitivity analysis confirmed the stability of the findings, although the exclusion of the study by Attia et al.[11] reduced heterogeneity from 14.3% to 0% (Supplementary Fig 2, B). Bayesian analysis found a pooled SMD of −0.06 (95% CrI, −0.61 to 0.46; Supplementary Fig 2, C) with a posterior probability of any beneficial effect (SMD < 0) of 59.8% in patients receiving propofol-supplemented cardioplegia (Supplementary Fig 2, D).

Serious Complications

Serious complications were evaluated across 4 studies and showed no significant differences between groups in the frequentist analysis (RR, 0.84; 95% CI, 0.40 to 1.76; I^2 = 73.6%; p = 0.6480). Subgroup analyses based on type of procedure showed no significant differences between studies involving AVR and those involving both surgical procedures (p for interaction = 0.5026; Supplementary Fig 3, A). Leave-one-out sensitivity analysis confirmed the robustness of the findings (Supplementary Fig 3, B). Bayesian analysis showed a pooled RR of 0.77 (95% CrI, 0.18 to 2.28; Supplementary Fig 3, C). The posterior probability of any beneficial effect (RR < 1) was 70.3% in patients receiving propofol-supplemented cardioplegia (Supplementary Fig 3, D).

Postoperative Arrhythmias

Postoperative arrhythmia incidence was reported across 5 studies and showed no significant differences in the frequentist analysis between the propofol-supplemented cardioplegia and placebo groups (RR, 0.96; 95% CI, 0.77 to 1.19; I^2 = 52.9%, p = 0.6976). Subgroup analysis based on type of procedure did not show a significant reduction in postoperative arrhythmias between subgroups (p for interaction = 0.9343; Supplementary Fig 4, A). Leave-one-out sensitivity analysis confirmed the consistency of the findings (Supplementary Fig 4, B). Bayesian analysis showed a pooled RR of 0.96 (95% CrI, 0.51 to 1.62; Supplementary Fig 4, C). The posterior probability of any beneficial effect (RR < 1) was 56.4% in patients receiving propofol-supplemented cardioplegia (Supplementary Fig 4, D).

ICU Length of Stay

ICU length of stay was reported across 4 studies. One trial provided separate datasets for both the CABG and AVR groups,[10] resulting in a total of 5 distinct cohorts. The frequentist analysis found no significant differences between the propofol-supplemented cardioplegia and placebo groups (SMD, 0.07; 95% CI, −0.99 to 1.13; I^2 = 92.7%; p = 0.9030). Subgroup analyses based on type of procedure showed no significant reduction in ICU length of stay (in days) for CABG and AVR studies (p for interaction = 0.1199; Supplementary Fig 5, A). Sensitivity analysis remained stable across all iterations (Supplementary Fig 5, B). Bayesian analysis showed a pooled SMD of 0.06 days (95% CrI, −1.26 to 1.36; Supplementary Fig 5, C). The posterior probability of any beneficial effect (SMD < 0) was 46.2% in patients receiving propofol-supplemented cardioplegia (Supplementary Fig 5, D).

Hospital Length of Stay

Hospital length of stay was evaluated in 3 studies and showed no significant differences between groups in the frequentist analysis (MD, −0.31 days; 95% CI, −1.15 to 0.54 days; I^2 = 66.9%; p = 0.4769). Sensitivity analysis confirmed the robustness of the findings; however, the exclusion of the study by Attia et al.[11] showed a significant change in heterogeneity (from 66.9% to 0%; Supplementary Fig 6, A). Bayesian analysis showed a pooled MD of −0.28 days (95% CrI, −1.57 to 1.05 days; Supplementary Fig 6, B).

Quality Assessment

In the overall risk-of-bias assessment, based on the Cochrane risk-of-bias assessment tool (version 2), 4 RCTs

Table 1
Baseline and Operative Characteristics

Characteristics	Angelini et al.[12] (2026) (N = 162)		Attia et al.[11] (2023) (N = 100)		Mohamed et al.[22] (2022) (N = 40)		Reza et al.[23] (2021) (N = 120)		Rogers et al.[10] (2015) (N = 101)	
	Propofol (n = 80)	Control (n = 82)	Propofol (n = 50)	Control (n = 50)	Propofol (n = 20)	Control (n = 20)	Propofol (n = 60)	Control (n = 60)	Propofol (n = 51)	Control (n = 50)
Study design	RCT		RCT		RCT		RCT		RCT	
Country	United Kingdom		Egypt		Egypt		Iran		United Kingdom	
Age, y	64.7 ± 9.2	66.8 ± 7.6	53.88 ± 9.60	49.46 ± 9.09	39.15 ± 9.45	35.1 ± 7.97	63.23 ± 8.47	60.53 ± 11.13	66.5 (62.5-72.1)	70.6 (65.0-76.4)
Female sex, %	12	10	44	30	60	50	60	63.3	20	28
Diabetes mellitus, %	NA	NA	12	12	NA	NA	30	25	22	20
Hypertension, %	74	84	22	14	NA	NA	66.7	68.3	86	70
Smoking status, %										
No	54	43	82	88	NA	NA	68.3	73.3	33	48
Ex-smoker	34	44	6	6	NA	NA	NA	NA	57	42
Current smoker	12	13	12	1	NA	NA	31.7	26.7	10	10
Propofol dosage, μg/mL	6		10		9		4		6	
Placebo solution	Saline solution		NA		Saline solution		Saline solution		Intralipid	
NYHA class, %										
III	21	20	52	42	NA	NA	NA	NA	31	28
IV	4	4	0	0	NA	NA	NA	NA	2	6
Cross-clamp time, min	46 (36.0-60.0)	48 (37.0-59.0)	75.0 ± 21.47	79.58 ± 28.1	51.1 ± 15.38	53.15 ± 14.96	35.78 ± 11.99	35.53 ± 11.45	54.0 ± 19.7	53.4 ± 16.2
CPB duration, min	76 (62.0-94.0)	78 (63.0-93.0)	98.78 ± 34.16	100.42 ± 36.16	70.1 ± 16.72	70.95 ± 17.96	62.58 ± 19.07	61.86 ± 18.69	88.2 ± 22.0	88.8 ± 19.0
Anesthesia maintenance	Isoflurane or sevoflurane + propofol		NA		Sevoflurane + propofol		Propofol		Isoflurane + IV propofol	
Cardioplegia type	Warm blood cardioplegia (Calafiore)		Cold crystalloid cardioplegia		Cold blood cardioplegia		St. Thomas cardioplegia		Warm blood cardioplegia (Calafiore)	

NOTE. Data are presented as mean ± standard deviation, median (interquartile range), or percentage.
Abbreviations: CPB, cardiopulmonary bypass; IV, intravenous; NA, not available; NYHA, New York Heart Association; RCT, randomized controlled trial.

Table 2
Effects of Propofol Cardioplegic Supplementation on Primary and Secondary Outcomes

Outcome	No. of Studies	No. of Patients: Intervention/Control	Frequentist Model Effect (95% CI)	I^2	Bayesian Model Effect (95% CrI)	Certainty Level*
Postoperative troponin	5	260/260	SMD: −0.05 (−0.22 to 0.12)	0%	SMD: −0.05 (−0.33 to 0.24)	Moderate
Postoperative creatinine	3	190/192	SMD: −0.06 (−0.26 to 0.15)	14.3%	SMD: −0.06 (−0.71 to 0.46)	Moderate
Serious complications	4	210/196	RR: 0.84 (0.40 to 1.76)	73.6%	RR: 0.77 (0.18 to 2.28)	Low
Postoperative arrhythmias	5	257/269	RR: 0.96 (0.77 to 1.19)	52.9%	RR: 0.96 (0.51 to 1.62)	Low
ICU length of stay	4	201/202	SMD: 0.07 (−0.99 to 1.13)	92.7%	SMD: 0.06 (−1.23 to 1.36)	Low
Hospital length of stay	3	182/182	MD: −0.31 (−1.15 to 0.54)	66.9%	MD: −0.28 (−1.57 to 1.05)	Low

Abbreviations: CI, confidence interval; CrI, credible interval; ICU, intensive care unit; MD, mean difference; RR, risk ratio; SMD, standardized mean difference.
* Assessed with Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment tool.

were categorized as having low risk[10-12,23] and 1 RCT was categorized as having some concerns.[22] The primary contributors to the judgment of some concerns were issues related to the selection of the reported result process. A comprehensive visual summary is presented in Figure 3, A (domain-level judgments) and B (overall summary).

According to the GRADE assessment, postoperative troponin levels, postoperative creatinine levels, and serious complications were classified as moderate-quality evidence. Postoperative arrhythmias, ICU length of stay, and hospital length of stay were classified as low-quality evidence. The main reasons contributing to this assessment across endpoints were the heterogeneity among the included studies and CIs crossing the line of no effect. GRADE assessment is detailed in Supplementary Table 1.

Discussion

This systematic review and meta-analysis evaluated the effect of propofol supplementation of cardioplegic solution in both CABG and valve surgeries compared with placebo. This is, to the authors' knowledge, the first meta-analysis to assess propofol-supplemented cardioplegia and its impact on surgical outcomes using a dual statistical approach. The results demonstrate that adding propofol to cardioplegic solution does not provide any additional cardioprotection, with the pooled levels of cardiac troponins showing no significant statistical difference—a finding strongly corroborated by the authors' Bayesian models. There was also no significant benefit in terms of secondary outcomes, with low posterior probabilities of clinical benefit, as well as no increased risk of serious complications.

To reconcile the interpretive language of the authors' dual statistical frameworks, it is important to distinguish the underlying logic of these frameworks. The frequentist analysis relies on strict significance thresholds, leading to a binary conclusion of "no significant difference." In contrast, the Bayesian analysis evaluates treatment effects as a continuous probability distribution. Therefore, reporting a "moderate probability of benefit" indicates that, while the data mathematically lean toward a protective effect, this marginal benefit remains too uncertain to reach definitive significance or justify routine clinical adoption.

The theoretical rationale for incorporating propofol into cardioplegia is derived from its well-documented antioxidant properties and potential to mitigate ischemia-reperfusion injury through the scavenging of reactive oxygen species during CPB.[24] However, the present pooled analysis did not demonstrate the direct translation of this theoretical mechanism into a definitive clinical benefit. A critical methodological consideration in this analysis was the pooling of cardiac troponin T and cardiac troponin I to assess myocardial injury. Both cardiac troponin T and cardiac troponin I are highly specific, sensitive biomarkers released via the identical pathophysiological mechanism of myocyte membrane rupture following irreversible ischemic necrosis.[25,26] By using the SMDs in the present statistical model, the authors mathematically neutralized the

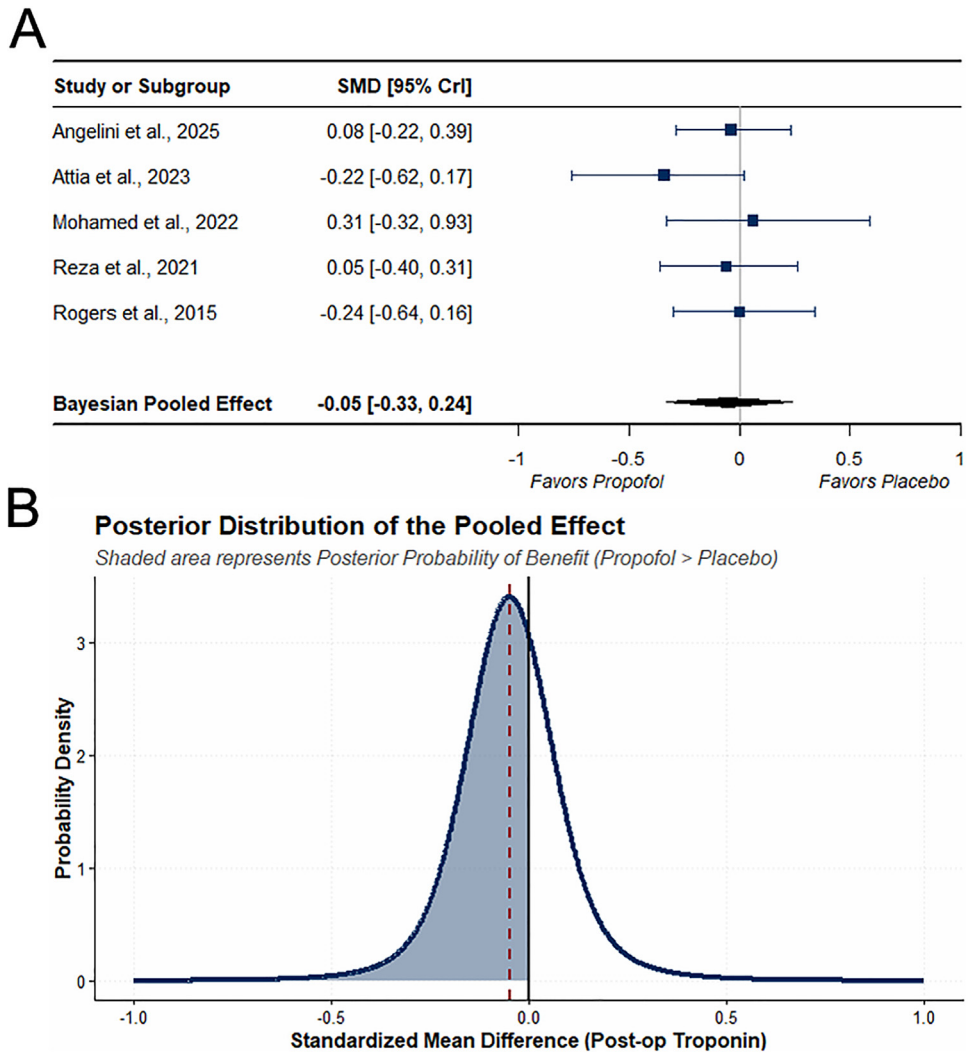

Fig 2. Postoperative troponin levels. (A) Forest plot showing standardized mean difference (SMD) in Bayesian meta-analysis of postoperative troponin between propofol and placebo groups. (B) Posterior density distribution of overall treatment effect for postoperative (Post-op) troponin. CrI, credible interval.

variances in absolute units and reference ranges inherent to the different assays. As established by the Cochrane Handbook, SMDs scale the results by their standard deviation, ensuring that continuous data remain directly comparable regardless of the specific troponin subtype or assay manufacturer used by the primary investigators.[16]

Pooled analysis of postoperative biomarker elevation and length of stay might reflect the mixed trends observed in each included trial.[10-12,22,23] However, the demonstration of no clinical benefit between propofol and standard cardioplegia in the present analysis highlights a significant translational gap within the broader literature. Extensive in vitro and animal models have historically demonstrated that propofol dramatically reduces infarct size and preserves ventricular function during ischemia-reperfusion.[27] However, the present meta-analysis confirms that this cellular-level protection does not readily translate into macroscopic clinical benefits for patients undergoing complex pump runs.

Furthermore, the present findings suggest that this lack of definitive cardioprotection persists even when propofol is delivered directly to the myocardium via cardioplegia. A key variable that may explain this neutral efficacy finding is the therapeutic overlap with background anesthesia protocols. Analysis of the included RCTs reveals that the majority of patients received systemic propofol or volatile anesthetics during maintenance. Because these agents independently exert cardioprotective effects through ischemic preconditioning and oxidative stress reduction, they may have established a protective threshold that overshadowed the localized effects of propofol-supplemented cardioplegia. This therapeutic overlap aligns with the broader debate regarding cardiac anesthesia maintenance, as existing studies evaluating total intravenous anesthesia versus volatile anesthetics have frequently suggested that agents such as sevoflurane may offer superior myocardial preconditioning compared with systemic propofol.[28] This may be due to pharmacokinetic limitations; the localized tissue concentration of propofol achieved during cardioplegic arrest may be too transient to sustain the necessary antioxidant effects upon cross-clamp release.[29,30]

Fig 3. Risk-of-bias assessment of included randomized controlled trials. (A) Domain-level judgments for individual studies evaluating randomization, deviations from intended interventions, missing outcome data, and measurement of outcome. (B) Overall risk-of-bias summary across all included studies.

In addition, the lack of definitive cardioprotection observed in the present analysis is particularly relevant when weighed against emerging concerns regarding propofol's broader safety profile. A recent large-scale meta-analysis encompassing more than 30,000 patients found that systemic propofol sedation was associated with a 10% increase in overall mortality compared with alternative agents—a risk that remained statistically significant in the cardiac surgery subgroup.[31] Furthermore, beyond known complications such as propofol infusion syndrome, contemporary evidence suggests that propofol may actively blunt the efficacy of other organ-protective interventions.[32] Given these systemic safety concerns, the present finding that propofol offers no clear benefit as a cardioplegic additive suggests that routine supplementation with propofol lacks a justifiable clinical rationale.

The present analysis showed moderate to high heterogeneity in multiple outcomes, a primary driver of which is the profound variance in cardioplegia delivery protocols among the included trials. The myocardial pharmacokinetics of propofol are highly dependent on both the temperature and the vehicle of the cardioplegic solution. Both Propofol for Myocardial Protection Trial (ProMPT) trials used warm blood cardioplegia, whereas the remaining trials used cold blood or cold crystalloid techniques.[10,12] The use of profound hypothermia in cold cardioplegia significantly depresses myocardial metabolic demand, which may induce a cardioprotective ceiling effect that masks any marginal antioxidant benefit provided by propofol.[33] Furthermore, the choice of vehicle significantly alters drug bioavailability: Propofol is highly lipophilic and heavily protein bound; therefore, its administration via blood cardioplegia likely reduces the active, unbound fraction of the drug compared with crystalloid solutions, in which 100% of the drug remains free.[34] These fundamental differences in delivery mechanics highlight the necessity for future trials to standardize cardioplegic protocols to isolate propofol's true effect.

This meta-analysis possesses several methodological strengths. A main strength is the utilization of both frequentist and Bayesian random-effects models; the perfect alignment between these two distinct statistical philosophies provides a highly robust validation of the neutral findings of this study. Crucially, the robustness of the present safety findings was confirmed via a leave-one-out sensitivity analysis, which demonstrated that no single study disproportionately drove the overall pooled estimates. Furthermore, the authors conducted rigorous subgroup analyses stratifying by surgical procedure to isolate procedure-specific effects. Finally, the application of the GRADE framework provides a transparent evaluation of the certainty of the present evidence.

Despite these strengths, this study has limitations that must be acknowledged. First, the total number of included trials and aggregate patient population remain relatively small, limiting the statistical power to detect subtle differences in rare adverse events. Second, clinical and statistical heterogeneity ($I^2 > 50\%$) was present in multiple outcomes. Third, while the authors evaluated serious perioperative complications, they were unable to extract and pool long-term mortality data as the included studies did not systematically report mortality outcomes at extended follow-up intervals. Fourth, although the subgroup analyses explored potential outcome differences based on surgical procedure (CABG *v* AVR), the overall tests for subgroup differences (interaction tests) were statistically nonsignificant. In strict adherence to Cochrane Handbook guidelines, the authors interpreted these findings as indicative of no true subgroup modifying effect, rigorously avoiding the misleading emphasis of isolated subgroup significance. Finally, several outcomes were downgraded for imprecision because their CIs crossed the clinical line of no effect.

Conclusions

Propofol supplementation of cardioplegic solutions during cardiac surgery does not provide a definitive cardioprotective benefit, nor does it improve secondary clinical outcomes such as ICU or hospital length of stay. While the addition of propofol appears to be safe and does not increase the risk of serious complications, its routine administration lacks evidence-based justification. Therefore, based on current methodological synthesis, the routine use of propofol-supplemented cardioplegia cannot be recommended and should remain at the discretion of the institutional heart surgery team.

Disclaimer

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2026.07.057.

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