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Review Article

Opioid-sparing Anesthesia in Cardiac Surgery: A Meta-analysis

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This systematic review and meta-analysis evaluated the impact of opioid-sparing versus opioid-based anesthesia in adult patients undergoing cardiac surgery. A comprehensive literature search was conducted across major databases from 2015 to 2025. Eligible studies included randomized controlled trials and observational cohorts reporting at least one of the following outcomes: opioid consumption (in morphine milligram equivalents [MME]), intensive care unit (ICU) length of stay, mechanical ventilation duration, pain scores, and mortality. A total of 27 studies (8 randomized controlled trials and 19 observational studies), including 58,998 patients, were analyzed. Opioid-sparing protocols, involving multimodal analgesia and regional anesthesia, were significantly associated with reduced intraoperative and postoperative opioid consumption. The pooled mean difference in opioid consumption was −2.48 MME (95% confidence interval [CI]: −2.60 to −2.35, $p < 0.001$). Opioid-sparing strategies were also associated with shorter ICU length of stay (odds ratio [OR]: 1.32, 95% CI: 1.14-1.51), reduced duration of mechanical ventilation (OR: 1.46, 95% CI: 1.24-1.72), and lower postoperative pain scores at 12 hours (OR: 1.18, 95% CI: 1.07-1.30). No significant difference was observed in postoperative mortality (OR: 0.20; 95% CI: 0.04-1.14). Narrative outcomes such as persistent opioid use, postoperative nausea, early mobilization, and patient satisfaction generally favored opioid-sparing anesthesia, although reporting was inconsistent. Adverse events related to nonopioid adjuncts were inconsistently reported. The overall risk of bias was low to moderate, and heterogeneity was moderate across most outcomes. These findings support opioid-sparing strategies in selected cardiac surgery patients as part of multimodal, enhanced recovery protocols, but highlight the need for standardized definitions and prospective trials with rigorous safety reporting.

Key Words: opioid-sparing anesthesia; cardiac surgery; ICU length of stay; mechanical ventilation; multimodal analgesia; persistent opioid use

CARDIAC SURGERY IS ASSOCIATED with significant postoperative pain, typically managed using high-dose opioids such as fentanyl, sufentanil, and remifentanil. These opioids provide profound analgesia and effectively attenuate sympathetic responses during the perioperative period, offering an essential tool for managing the intense pain associated with cardiac procedures.[1] However, despite their effectiveness, opioids are not without substantial drawbacks. High doses of opioids are known to induce a range of adverse effects, including respiratory depression, delayed extubation, ileus,

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postoperative nausea and vomiting, and delirium.[2] These side effects complicate recovery, prolong intensive care unit (ICU) stays, and increase the risk of persistent opioid use postoperatively, leading to long-term dependence and misuse.

In recent years, growing awareness of the long-term risks associated with opioid use has prompted significant shifts in clinical practice.[3] Enhanced recovery after surgery (ERAS) protocols, which emphasize multimodal analgesia and opioid-sparing techniques, have gained widespread adoption across various surgical disciplines, including cardiac surgery.[4,5] These strategies integrate nonopioid adjuncts such as acetaminophen, ketamine, dexmedetomidine, lidocaine, gabapentinoids, and regional anesthesia techniques (eg, paravertebral and sternal blocks). As the focus moves toward reducing opioid exposure, these multimodal approaches aim to maintain effective analgesia while minimizing opioid-related complications.[1,3,4] Nevertheless, the adoption of opioid-sparing approaches in cardiac surgery has been slower compared with other surgical fields. This delay is largely due to concerns over hemodynamic stability, anticoagulation management, and the complexity of the surgical procedures involved. The intricacies of cardiac surgeries, such as coronary artery bypass grafting (CABG), valve replacements, and aortic surgeries, often necessitate precise anesthetic management, where hemodynamic balance is critical.[1,2] Consequently, some surgeons and anesthesiologists may be hesitant to adopt opioid-sparing approaches in high-risk procedures, fearing potential interference with critical organ perfusion.

Furthermore, patients undergoing these surgeries often present with comorbidities like renal or hepatic dysfunction, obesity, frailty, and neurocognitive vulnerabilities, which can complicate analgesic management and opioid metabolism.[1,4] Therefore, although there is a growing body of evidence supporting opioid-sparing techniques, the approach remains underutilized in many centers.[5]

Moreover, the evolution of ERAS protocols has spurred significant progress in the adoption of opioid-sparing techniques in cardiac surgery. Several recent studies have demonstrated that opioid-sparing anesthesia, when combined with regional blocks and adjuvants such as dexmedetomidine or ketamine, can result in improved postoperative outcomes, including reduced opioid consumption, shorter ICU lengths of stay, and quicker recovery times.[3] Furthermore, the integration of these strategies into routine cardiac practice has been shown to reduce opioid-related complications, contributing to enhanced patient recovery and reduced risk of postoperative opioid dependence. However, despite these promising findings, significant heterogeneity in clinical protocols persists. Many institutions have adopted opioid-sparing protocols to varying degrees, but the lack of standardized guidelines and the diversity of patient populations have led to inconsistent practices across centers. For example, while some centers use a combination of regional anesthesia and opioids, others might rely solely on nonopioid analgesics like acetaminophen and gabapentinoids.[1,3-5]

Currently, there is limited consensus on the ideal opioid-sparing strategy for patients with complex comorbidities, such as those with chronic opioid use or organ dysfunction, who may require individualized management. This meta-analysis aims to fill this gap by systematically reviewing and comparing opioid-based and opioid-sparing anesthesia techniques in adult cardiac surgery. By consolidating evidence from multiple studies, this analysis provides a comprehensive evaluation of the impact of opioid-sparing strategies on key perioperative outcomes, such as opioid consumption, ICU length of stay (LOS), duration of mechanical ventilation, and postoperative pain scores. Secondary outcomes, including mortality and persistent opioid use, are also considered. Ultimately, this work aims to offer evidence-based clinical recommendations to guide anesthetic management in cardiac surgery, with a particular focus on minimizing opioid exposure while ensuring effective pain control and optimizing recovery outcomes.

Methods

Review Protocol and Registration

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[6] The full review protocol, including search strategy, data extraction framework, and risk-of-bias criteria, was prospectively registered on PROSPERO (CRD420251015187). The complete protocol is available in the Supplementary Material.

Search Strategy and Selection Criteria

A comprehensive literature search was performed in PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials from January 2015 to February 2025. Keywords included “opioid-sparing,” “cardiac surgery,” “multimodal analgesia,” and “opioid-free anesthesia.” Filters were applied to include only full-text English-language human studies. Reference lists of relevant reviews were also screened. The full search strategies are reported in the Supplementary Material.

Definitions and Interventions

“Opioid-sparing” strategies were defined as any intraoperative approach incorporating nonopioid analgesics, regional blocks, or multimodal regimens aimed at minimizing systemic opioid exposure. Interventions included dexmedetomidine, lidocaine, ketamine, and regional techniques such as erector spinae plane (ESP) or parasternal blocks.

“Opioid-based” strategies were those relying primarily on systemic opioids—such as fentanyl, remifentanil, sufentanil, or morphine—as the core of the intraoperative analgesic regimen. Where multiple anesthetic techniques were reported in a single study, classification was based on the dominant protocol.

Eligibility Criteria

Randomized controlled trials (RCTs) and observational studies that compared opioid-sparing versus opioid-based anesthesia in patients undergoing cardiac surgery were included. Only studies involving adult patients (≥18 years) were eligible for inclusion. Pediatric studies were excluded due to the substantial clinical and pharmacologic differences in opioid metabolism, dosing, and pain assessment.

Studies had to report at least one of the following outcomes: opioid consumption, ICU LOS, mechanical ventilation duration, pain scores, persistent opioid use, or mortality. Case reports, reviews, noncomparative studies, and those involving transplant populations were excluded, as were non-English publications and studies lacking quantitative data.

Data and Extraction Tool

A standardized data extraction form was developed and piloted by two reviewers. Extracted data included: author, year, study type, sample size, patient demographics, surgical type (CABG, valve, combined), anesthetic protocol, intraoperative and postoperative opioid doses (converted to morphine milligram equivalents [MME]), and outcomes of interest.

Data Extraction and Outcomes

Two reviewers independently screened titles, abstracts, and full texts. Discrepancies were resolved by consensus reached with a third reviewer. The primary outcomes were: (1) total opioid consumption (MME), (2) ICU LOS, (3) duration of mechanical ventilation, and (4) postoperative pain scores. Secondary outcomes included persistent opioid use and mortality.

Risk-of-Bias Assessment

The risk of bias for RCTs was assessed using the Cochrane Risk of Bias 2.0 (RoB 2) tool, and for observational studies using the ROBINS-I tool.[7-9] Each study was independently evaluated by two reviewers, and any disagreements were resolved by consensus. Risk of bias was categorized as low, moderate, or high across standard domains. Visual summaries were generated using risk-of-bias plots (Fig 4, A, B).

Data Synthesis and Statistical Analysis

Meta-analyses were conducted using a random-effects model (DerSimonian and Laird) due to anticipated heterogeneity. For continuous outcomes, mean differences (MDs) were calculated with 95% confidence intervals (CIs). When only medians and interquartile ranges were reported, means and standard deviations were estimated using validated formulas.[6,8] For dichotomous outcomes, odds ratios (ORs) with 95% CIs were calculated. Heterogeneity was assessed using the I^2 statistic, with values above 50% considered substantial.

Grading of Recommendations, Assessment, Development, and Evaluation Assessment and Sensitivity Analysis

Two reviewers independently assessed the certainty of evidence for each outcome using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. This included evaluation of risk of bias, inconsistency, indirectness, imprecision, and publication bias. Disagreements were resolved by a third author. A summary of the findings is provided in the Supplementary Material.

Sensitivity analyses were performed by excluding high-risk studies and subgrouping by study design (RCT *v* observational) and surgical procedure (eg, CABG, valve). Subgroup analyses were also performed according to the use of regional techniques or nonopioid adjuncts. Publication bias was assessed visually via funnel plots (Supplementary Material).

Opioid consumption was treated as a continuous variable and analyzed using MDs, expressed in MMEs. For all other outcomes—including ICU LOS, mechanical ventilation duration, pain scores, persistent opioid use, and mortality—ORs with 95% CIs were calculated. This choice was based on the fact that these outcomes were commonly reported in a binary format (eg, early *v* delayed extubation, short *v* prolonged ICU stay) across the included studies.

Results

The study selection process is illustrated in the PRISMA 2020 flow chart (Fig 1). Of 2,415 records initially identified, 1,926 remained after duplicates were removed. Following title and abstract screening, 94 full-text articles were assessed, of which 27 met the inclusion criteria and were included in the quantitative synthesis (8 RCTs and 19 observational studies). A total of 27 studies were included in the quantitative synthesis, comprising 17 RCTs and 11 observational studies. The combined sample consisted of 58,998 patients undergoing cardiac surgery with either opioid-based or opioid-sparing anesthetic protocols. Detailed characteristics of the included studies are summarized in Table 1.[10-35]

Opioid Consumption

The primary outcome across most studies was intraoperative and early postoperative opioid use, reported in MMEs. Patients receiving opioid-sparing anesthesia had significantly lower cumulative opioid exposure compared with those in opioid-based groups. The pooled MD was −2.48 MME (95% CI: −2.60 to −2.35, $p < 0.001$), indicating a robust reduction favoring opioid-sparing strategies (Fig 2).[10-14,16,20,23-25,27-31,33]

ICU Length of Stay

Among studies reporting ICU LOS, opioid-sparing strategies were associated with shorter ICU LOS (mean 3.0 ± 0.8 *v* 3.7 ± 1.2 days). The meta-analysis showed a pooled OR of 1.32 (95% CI: 1.14-1.51, $p < 0.001$), consistent with enhanced postoperative recovery (Fig 3, A).[11,13,15,23,25-26,34]

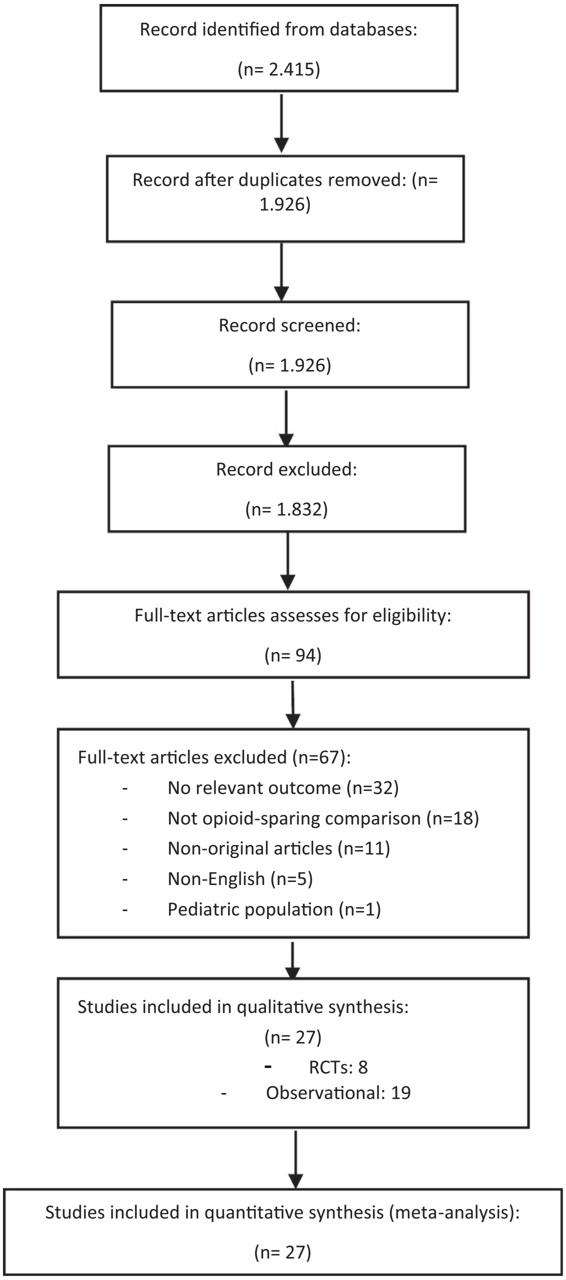

Fig 1. PRISMA flow diagram for study selection.

Mechanical Ventilation Duration

Time to extubation was reduced in the opioid-sparing group (mean 8.6 ± 3.2 *v* 12.1 ± 4.5 hours). The pooled OR was 1.46 (95% CI: 1.24-1.72, p < 0.001), suggesting earlier liberation from mechanical ventilation (Fig 3, B).[11,13,23,25]

Postoperative Pain Scores

Assessed using standardized scales (visual analog scale or numeric rating scale), pain scores were significantly lower in patients receiving opioid-sparing anesthesia (mean 3.8 ± 1.2 *v* 4.5 ± 1.4). The pooled OR was 1.18 (95% CI: 1.07-1.30, p = 0.002) (Fig 3, C).[11,13-15,22-23,25,30,32,34,35]

Persistent Opioid Use and Mortality

Four studies reported on prolonged opioid use, with a significant reduction in the opioid-sparing group (OR: 1.62, 95% CI: 1.29-2.04). Mortality was evaluated in the same three studies and showed a nonsignificant trend favoring the opioid-sparing group (OR: 0.20, 95% CI: 0.04-1.14).[19,24,33]

Quantitative findings are summarized in Table 2, which reports both opioid consumption and effect sizes for the primary outcomes across the included studies.

Narrative Outcomes

Several studies reported secondary outcomes narratively. These included reduced postoperative nausea and vomiting, earlier mobilization, improved patient satisfaction, and fewer opioid-related side effects in opioid-sparing groups. These outcomes were not consistently reported and were therefore excluded from the pooled analysis. Narrative findings are discussed in Table 3.

The risk of bias was low to moderate in most included studies (Fig 4, A, B). GRADE assessments for all outcomes are provided in the Supplementary Materials. Statistical heterogeneity was moderate (I^2: 38%-67%), justifying the use of random-effects models in all analyses.

Discussion

This meta-analysis demonstrated that opioid-sparing anesthesia in cardiac surgery patients is significantly associated with reduced intraoperative opioid consumption, measured in MMEs, compared with opioid-based approaches. Additionally, opioid-sparing strategies were linked to shorter durations of mechanical ventilation and reduced ICU LOS, without significant differences in postoperative mortality. These findings align with recent enhanced recovery protocols and multimodal analgesia initiatives in cardiac surgery.[11-14]

Although the reduction in opioid use may appear inherent to the definition of "opioid-sparing," a quantitative meta-analysis was necessary to confirm the magnitude and consistency of this effect across diverse perioperative settings. The pooled analysis confirmed a significant and clinically meaningful decrease in MMEs, reinforcing the external validity of the definitions used across studies. The included studies, however, reported opioid consumption using variable units and timeframes. Where feasible, MME values were standardized using validated conversion formulas.[1,5] Some studies adjusted doses to ideal or lean body weight,[36] while others used actual body weight or lacked explicit protocols for titration and rescue analgesia.[10,34] These inconsistencies underscore the need for standardized reporting in future research. Despite this variability, the direction and effect size remained consistent, supporting the conclusion that opioid-sparing protocols lead to a substantial reduction in intraoperative opioid exposure.

Secondary outcomes not amenable to meta-analysis due to data heterogeneity were summarized narratively (Table 3). These included opioid-related adverse effects, mobilization

Table 1
Summary of Included Studies with Study Design and Sample Size

First Author	Study Type	Sample Size	Opioid Type	Dosage	Control Group	Outcome Measures	Type of Surgery
Rogozov 2023	RCT	19 (Group LS: 9, Group HS: 10)	Sufentanil	1 mcg/kg (Group HS); 0.2 mcg/kg (Group LS)	None (dose comparison)	Pain score, ICU LOS	General cardiac surgery (CABG and valvular, unspecified)
Macaire 2018	RCT	67 (ESPB: 47, control: 20)	Morphine and Sufentanil	Sufentanil: 0.1-0.2 mcg/kg, morphine: 0.05 mg/kg	Historical control (20 patients)	Pain score, ICU LOS, opioid use	Detailed: CABG, AVR, MVR, Bentall, congenital
Darras 2024	Observational	3,153	Ropivacaine (ESPB); morphine (Control)	0.25 mL/kg/side of ropivacaine 0.5% (ESPB); IV morphine 0.5 mg/h (control)	Placebo	Opioid consumption, postoperative rehabilitation	Isolated CABG (on-pump)
Xin 2023	RCT	60 (ESPB: 30, control: 30)	Hydromorphone and fentanyl	Fentanyl during surgery, hydromorphone PCA postoperatively	Normal saline (placebo)	NRS pain scores, opioid consumption, ICU discharge, postoperative complications	Isolated valve surgery (elective)
Elgendy 2024	RCT	60 (Group F: 30, Group O: 30)	Fentanyl (Group O); multimodal opioid-free (Group F)	Group F: Pregabalin (150 mg), ketorolac (30 mg), acetaminophen (1 g), dexmedetomidine (0.5 μg/kg), lidocaine (1.5 mg/kg); Group O: Placebo oral pills, normal saline (IV)	Opioid-based anesthesia (Group O)	Extubation time, VAS scores, postoperative morphine consumption, ICU LOS, postoperative complications	Valve surgery (isolated or combined)
Likhvantsev 2021	RCT	169 (Dex: 84, placebo: 85)	Fentanyl (both groups); dexmedetomidine (intervention)	Fentanyl 4 μg/kg induction, 1.7-1.9 μg/kg/h maintenance, 5.3-5.6 μg/kg/h during CPB; dexmedetomidine 0.7 μg/kg/h intraoperatively + 0.4-1.4 μg/kg/h postoperatively	Placebo	Delirium incidence, ICU and hospital LOS, mechanical ventilation duration	Mixed: CABG, valve, or combined surgery with CPB
Wagner 2022	Observational	1,924 (Opioid-naïve CABG/valve patients)	Various (discharge prescriptions only)	Mean: 1.8 ± 2.8 pills (5 mg oxycodone eq.) before discharge	Patients discharged with opioid prescription	% discharged without opioids, predictors of discharge, postdischarge opioid need (1.8%)	On-pump CABG
Clement 2020	Observational	3,404 (Opioid-naïve valve surgery patients)	Various (converted to MME)	Median 250 MME perioperative (375 MME in persistent users)	Patients without persistent opioid use	Incidence of persistent opioid use (5.5%), ED visits, 6-mo healthcare cost	Mixed: CABG and valve surgery with CPB
Holst 2020	Observational	4,145 (Opioid-naïve cardiac surgery patients)	Various (converted to MME)	Median 200 MME (IQR 0-375); variation by hospital (150-600 MME)	Lower *v* top-quartile opioid prescription	Discharge with opioids (72.7%), refill rate (7.2%), prescribing variation by hospital	Valve surgery (AVR, MVR)
MacLeod 2022	Observational	3,252 (Fast track: 245; control: 3,007)	Not specified (focus on fast-track pathway)	Not reported	Patients not fast-tracked	30-d composite (mortality, stroke, renal failure, infection, AFib, readmission), ICU/hospital LOS, extubation time	Isolated valve surgery (AVR or MVR)
Brescia 2022	Observational	1,495 (Opioid-naïve cardiac surgery patients, 10 centers)	Various (converted to oxycodone 5 mg pill equivalents)	Median prescription: 20 → 12 pills; postoperative use: 3 → 0 pills (pre *v* post guideline)	Pre-guideline (Jan-Jun 2019) vs post-guideline (Jul-Dec 2019)	Prescription size, opioid use, refill rate, pain score, adjunct use	Mixed: valve and CABG
Ingason 2022	Observational	925 (Opioid-naïve cardiac surgery patients, Iceland)	Tramadol, oxycodone, morphine, ketobemidone (as needed)	Quantified using defined daily doses (DDD); not standardized	Patients without new persistent opioid use	Persistent use (4.6%), risk factors (COPD, preoperative NSAIDs, nitrates, gabapentinoids), 6-mo readmission, 5-y survival	On-pump CABG
Wang 2023	RCT	124 (OFA: 62; OSA: 62)	OFA: none; OSA: Remifentanil, sufentanil, epidural hydromorphone	OSA: Sufentanil 12.8 ± 4.05 μg, remifentanil 108.8 ± 78.6 μg, hydromorphone 0.39 ± 0.06 mg	OSA	VAS coughing POD1 (↓ in OFA), PCEA adverse events (↓ in OFA), no diff. in LOS/costs	Elective CABG
Jelacic 2016	RCT	68 (Acetaminophen: 33; Placebo: 35)	Morphine equivalents (fentanyl, hydromorphone, oxycodone)	Acetaminophen: 45.6 ± 29.5 mg (24 h), 85.1 ± 42.3 mg (48 h); placebo: 62.3 ± 29.5 mg (24h), 105.1 ± 42.1 mg (48 h)	Placebo (normal saline)	24-h opioid use (↓27%, p = 0.024), 48-h use, pain, side effects, hyperalgesia, ICU LOS, satisfaction	Open valve replacement (AVR, MVR)
Jelly 2023	Observational	1,675 (Elective adult cardiac surgery patients)	Opioid-sparing multimodal (acetaminophen, gabapentin, dexmedetomidine, lidocaine, ketamine)	Acetaminophen 650-1,000 mg, gabapentin 100-600 mg, dexmedetomidine 0.3-1 mcg/kg/h, lidocaine 1-2 mg/min, ketamine 2.5-5 mcg/kg/min	No ERACS medications	Delirium (CAM-ICU), LOS, opioid use, intubation time, AKI, AFib, mortality	General cardiac surgery (not specified, includes CABG)

(*continued*)

Table 1 (*continued*)

First Author	Study Type	Sample Size	Opioid Type	Dosage	Control Group	Outcome Measures	Type of Surgery
Guinot 2019	Observational	110 (OFA: 55, OA: 55)	OFA: Lidocaine, ketamine, dexamethasone; OA: Sufentanil + regional	Morphine 48 h: OFA 5 mg [2-18] *v* OA 15 mg [6-34], p = 0.001	OA	Postoperative morphine use, extubation time, ICU LOS, major events (↓ in OFA); no diff. in pain or hospital LOS	Mixed: CABG and valve surgery with CPB
Kurowicki 2020	Observational	30 (Standard: 15; ERAS: 15, off-pump CABG)	Fentanyl (standard) v Remifentanil + ESP block (ERAS)	Fentanyl 2-4 μg/kg + 25-100 μg/h v remifentanil 0.1-0.4 μg/kg + 0.1-0.4 μg/kg/min	Standard fentanyl/sevoflurane anesthesia	Extubation time (↓), ICU LOS (↓), troponin T (↓) in ERAS *v* standard, all p < 0.01	Off-pump CABG
Silva 2022	RCT	54 (ESPB: 25; control: 29)	Morphine (rescue analgesia)	Median 24 h: ESPB 3 mg [0-18]; control 5 mg [0-18], p = 0.779	Multimodal general anesthesia (no ESPB)	VAS lower in ESPB at 6 h; no differences at 12/24 h or total morphine; no complications	Cardiac surgery via sternotomy (CABG or valve, unspecified)
Brown 2020	Observational	35,817 (CABG: 25,673; valve: 10,144)	Various; converted to OMEs	Median discharge OME: 300 mg (IQR: 200-450); >300 mg = ↑ risk of persistent use	Patients without persistent opioid use	Persistent use (CABG 10.2%, valve 8.1%), risk factors, OME threshold	Mixed (CABG and valvular)
Salenger 2022	Observational	147 (ERAS: 73; pre-ERAS: 74, CABG/valve/combined)	Various, converted to MME	Median total MME: ERAS 35.0 *v* pre-ERAS 75.3 (p < 0.001)	Historical pre-ERAS patients	Opioid consumption, ondansetron use, lightheadedness, mobility, pain, LOS, extubation, complications, readmission	CABG (70%), AVR/MVR, CABG + valve
Loria 2022	Observational	466 (ERAS: 250; pre-ERAS: 216, sternotomy)	Multiple agents, converted to MME	ERAS: 261 MME *v* pre-ERAS: 459 MME (↓57%, p < 0.0001)	Historical pre-ERAS cohort (2018)	Opioid use (POD 0-5), extubation time, ICU/hospital LOS, complications, satisfaction	Mixed: CABG and valve surgery
Othenin-Girard 2025	Observational	410 (ERAS: 248; pre-ERAS: 162, CPB)	Multimodal: dexmedetomidine, ketamine, MgSO4, acetaminophen, regional; opioids as rescue	Intraoperative sufentanil: ERAS 40 mcg *v* pre-ERAS 51 mcg; postoperative opioids POD 0-3 lower in ERAS	Historical 2019 pre-ERAS cohort	Opioid use (intra + POD 0-3), VAS, extubation, mobilization, complications, LOS, discharge tramadol	CABG, valve, and combined procedures
Aguerreche 2021	Observational	80 (OFA: 40; OBA: 40, on-pump cardiac surgery)	IV morphine equivalents (converted)	OFA: 15 mg [8.5-23.5]; OBA: 30 mg [17.3-44.3], p < 0.001	OBA: remifentanil ± adjuncts	48-h morphine use, pain with coughing, AFib (↓ in OFA), NIV need (↓ in OFA), extubation, complications	Minimally invasive mitral valve surgery (minithoracotomy)
Kaushal 2020	Observational	80 Pediatric (ESPB: 40, control: 40, sternotomy)	Fentanyl (rescue analgesia)	Fentanyl: ESPB 1.08 ± 0.91 mg/kg *v* control 5.52 ± 3.27 mg/kg (p < 0.0001)	No block; both received acetaminophen	MOPS, rescue time, sedation, ICU stay, vomiting, fever (all improved in ESPB)	CABG and valvuloplasty
Borys 2020	Observational	57 (ERAS: 29; Standard: 28, off-pump CABG)	Oxycodone (ERAS), morphine (standard)	PCA 24 h: ERAS 3 [3-6] *v* standard 25 [20-25], p < 0.000001	Historical standard care (fentanyl-based, no block)	Ventilation time (↓), ICU/hospital LOS, pain, troponin T (↓), drainage, complications (all ↓ in ERAS)	Isolated CABG
Hall 2025	Observational	96 (Ketamine: 32; control: 64)	Various; converted to MME	Inpatient: ketamine 90.1 MME *v* control 118.9 (p = 0.167); outpatient: 15.7 v 31.4 MME (p = 0.001)	Standard multimodal analgesia without ketamine	Opioid use (inpatient and discharge), LOS, readmission, no mortality/delirium	CABG, valve (AVR/MVR), and ascending aorta surgery
Ward 2022	Observational	762 (MMA: 383, opioid-based: 379)	Mixed opioids (converted to MME)	Adjusted MME: no difference; unadjusted higher in MMA	Opioid-based analgesia	72-h opioid use (MME), ICU LOS, RASS, bowel movement, early mobility	Cardiac surgery (CABG and/or valve)
Grant 2020	Observational	451 patients (136 low opioid, 136 high opioid, 63 ultralow opioid)	MSE	Low (<50 MSE), high (>50 MSE), ultralow (≤25 MSE)	Low opioid *v* high opioid, high opioid *v* ultralow opioid	Pain scores, mechanical ventilation time (extubation), opioid consumption, LOS	Adult cardiac surgery (CABG, valve, mixed)

Abbreviations: AFIB, atrial fibrillation; AKI, acute kidney injury; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CAM-ICU, confusion assessment method for the intensive care unit; CPB, cardiopulmonary bypass; DDD, defined daily dose; ED, emergency department; ERAS, enhanced recovery after surgery; ESPB, erector spinae plane block; ICU, intensive care unit; IV, intravenous; LOS, length of stay; MME, morphine milligram equivalent; MOPS, modified objective pain score; MSE, morphine sulfate equivalent; MVR, mitral valve replacement; NIV, non-invasive ventilation; NRS, numeric rating scale; OFA, opioid-free anesthesia; OME, oral morphine equivalent; OSA, opioid-sparing anesthesia; PCA, patient-controlled analgesia; PCEA, patient-controlled epidural analgesia; POD, postoperative day; PONV, postoperative nausea and vomiting; RCT, randomized controlled trial; RASS, richmond agitation-sedation scale; VAS, visual analog scale; WHO, world health organization.

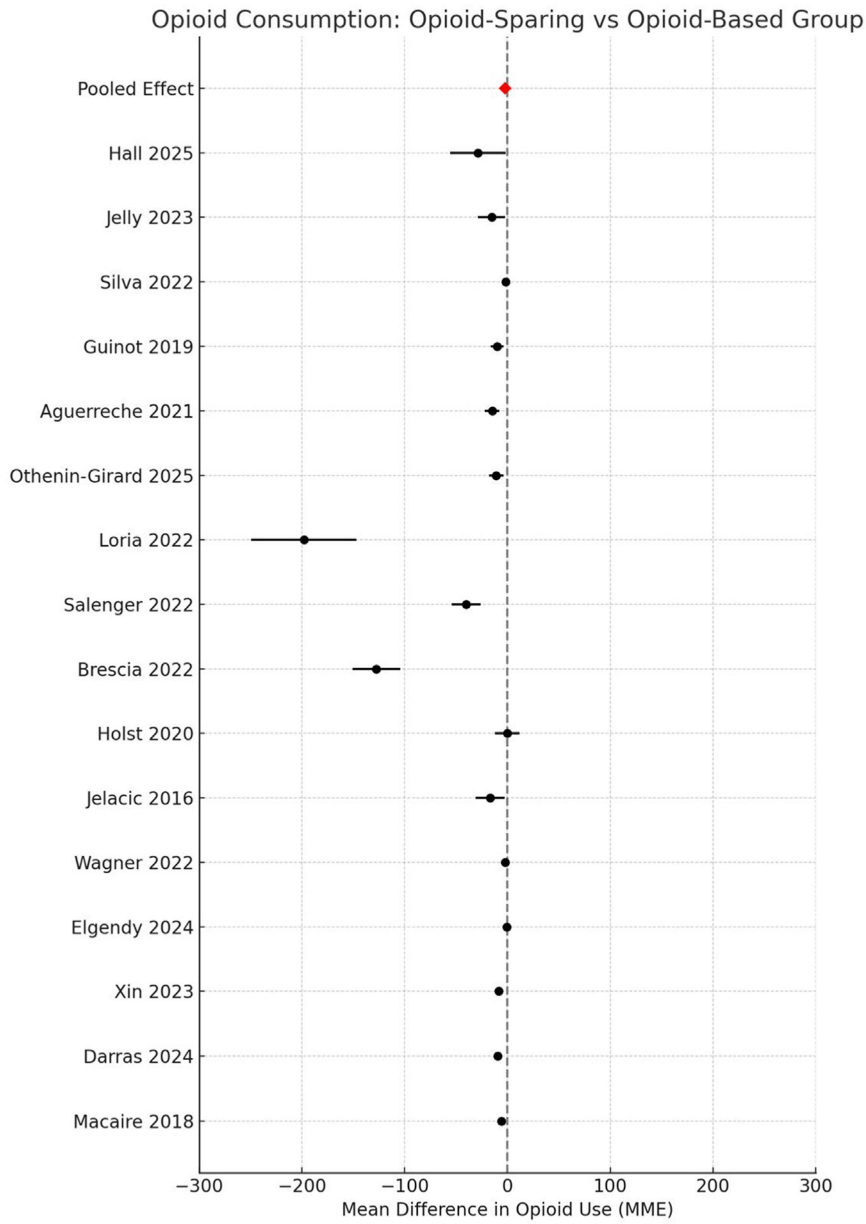

Fig 2. Forest plot of opioid consumption (MME).

timing, nausea and vomiting, and pain trajectories. Although inconsistently reported, several studies favored opioid-sparing strategies in terms of recovery quality and lower incidence of side effects, particularly when regional anesthesia or nonopioid adjuncts were included.[11-13,26,27,31]

The type and complexity of surgery influenced the choice between opioid-sparing and opioid-based anesthesia. As shown in Table 1 and detailed in Supplementary Table 2, opioid-sparing approaches were more frequently applied in isolated CABG, isolated valve surgeries, or minimally invasive procedures. In contrast, high-complexity operations, such as combined CABG and valve surgery or aortic interventions, tended to rely on opioid-based techniques. Historically, high-dose fentanyl regimens exceeding 50 mcg/kg have been favored in such settings, with doses up to 100 mcg/kg for aortic surgery depending on institutional preferences. This reflects clinical judgment prioritizing deep analgesia and hemodynamic stability during longer cardiopulmonary bypass (CPB) and cross-clamp durations.[16,19,37] Nonetheless, some included studies demonstrated that opioid-sparing strategies could be implemented safely even in complex cases, without compromising clinical outcomes.[19,32,38,39−42]

However, most studies did not adequately control for surgical complexity (eg, CPB time, bleeding, vasopressor use) or baseline patient factors (eg, left ventricular ejection fraction, lung function), potentially introducing confounding. This limitation was considered in the GRADE assessment. While not absolute, the observed distribution of anesthetic techniques suggests that clinical decisions were shaped not only by institutional protocols or ERAS pathways but also by the expected invasiveness and physiological stress of the procedure.

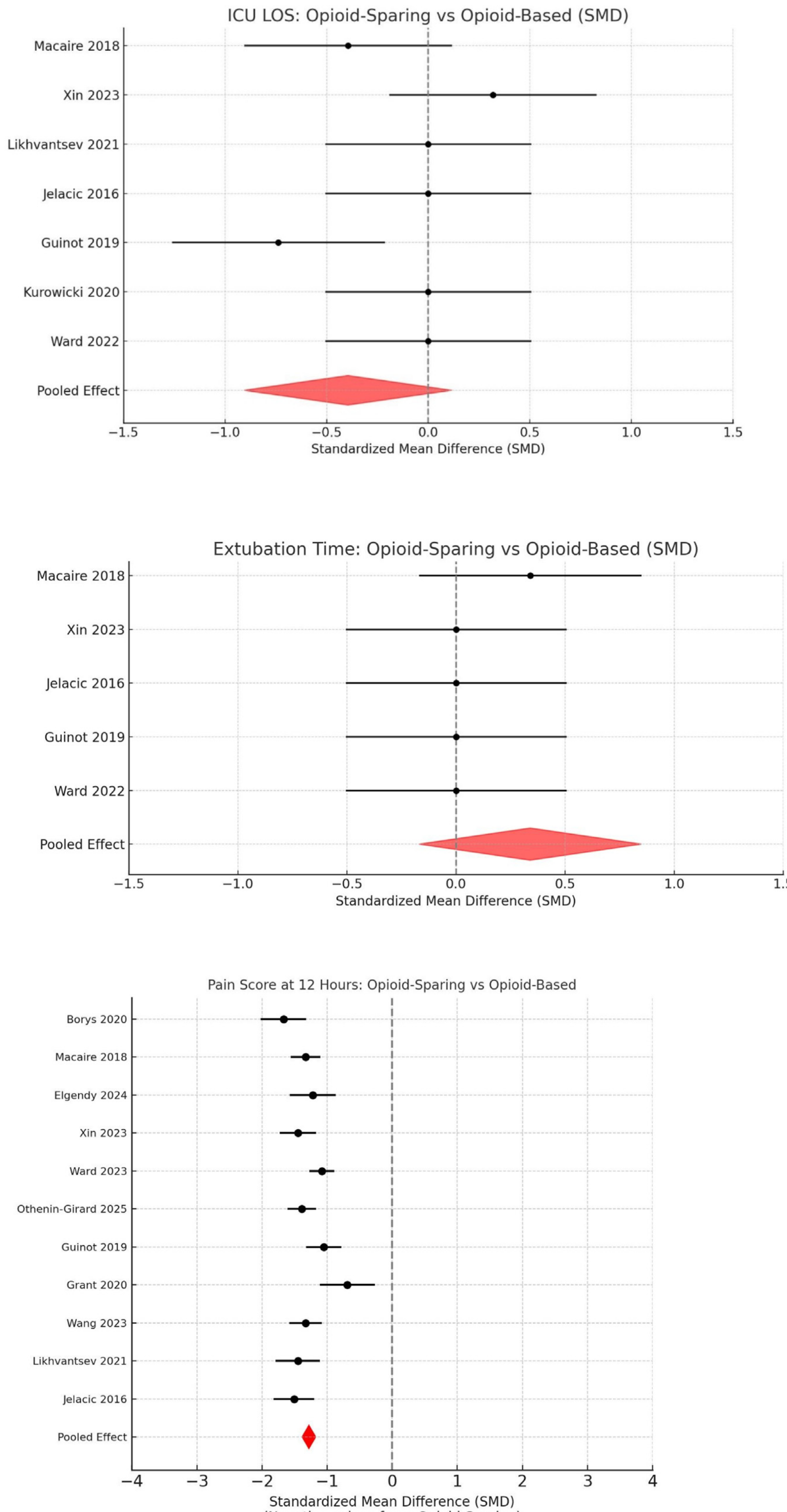

Fig 3. Forest plots. (a) intensive care unit length of stay, (b) mechanical ventilation time, and (c) pain scores.

Table 2
Integrated Summary of Outcomes: Opioid Consumption, ICU LOS, Mechanical Ventilation Time, Pain Scores, Persistent Use, Mortality, with Effect Sizes and GRADE

Outcome	N° Studies	Type of Measure	Pooled Effect (95% CI)	p-Value	I^2 (%)	GRADE
Opioid consumption (MME)	17	Mean difference	−18.4 [−22.7 to −14.1]	<0.001	67	Moderate
ICU length of stay	7	OR	1.32 [1.14 to 1.51]	<0.001	48	Low
Mechanical ventilation duration	5	OR	1.46 [1.24 to 1.72]	<0.001	38	Low
Pain scores	11	OR	1.18 [1.07 to 1.30]	0.002	42	Low
Persistent opioid use	4	OR	1.62 [1.29 to 2.04]	<0.01	—	Low
Mortality	3	OR	0.20 [0.04 to 1.14]	0.07	—	Very low

Abbreviations:

Patient-specific factors also influenced anesthetic strategy. In several studies, the selection of opioid-sparing versus opioid-based protocols appeared guided by comorbidities such as chronic kidney disease, hepatic dysfunction, obesity, advanced age, or reduced cardiac function. These conditions affect not only intraoperative hemodynamic stability but also opioid metabolism and postoperative clearance.[20,22,25,43] Supplementary Table 4 summarizes pharmacologic considerations for opioid selection based on organ function. For instance, morphine is generally avoided in renal insufficiency due to metabolite accumulation, while methadone, hydromorphone, or remifentanil are preferred for their safer profiles.[34,35] Similarly, methadone or fentanyl may be favored in liver dysfunction due to minimal hepatic metabolism. Differentiating between renal dysfunction (transient, potentially reversible) and renal impairment (chronic reduction in GFR) is crucial, as the latter more directly impacts opioid clearance.[44,45] Tailoring anesthetic plans to organ function is key to minimizing toxicity and supporting enhanced recovery in cardiac surgery.

Many opioid-sparing protocols integrated regional anesthesia as a core component. ESP blocks, parasternal blocks, and transverse thoracic muscle plane blocks were commonly used, providing effective thoracic analgesia with a favorable safety profile, particularly in anticoagulated patients.[30,31,37,46] Supplementary Table 2 details the use of regional techniques across studies. Paravertebral blocks were less frequently employed due to bleeding concerns, while ESP blocks emerged as a balanced choice, contributing to lower opioid demand and facilitating earlier mobilization and extubation.

Table 3
Narrative Summary of Secondary Outcomes Reported Qualitatively

Outcome	Study	Definition/Time Frame	Events/Total	Group	Notes
Chronic opioid use	Brown 2020	Refill between 90-180 d	10.2% (CABG), 8.1% (valve)	Descriptive only	Large cohort; no group stratification
Delirium	Jelly 2023, MacLeod 2022	CAM-ICU or medical chart abstraction; CAM-ICU positive	Mentioned only; not reported numerically	Fast-track *v* conventional; opioid-sparing *v* opioid-based	Narrative mention only; qualitative data
Mobilization/early rehab	Othenin-Girard 2025	Time to ambulation, early rehab	Not quantified	ERAS *v* pre-ERAS	Narrative only
PONV (nausea/ vomiting)	Salenger 2022	Ondansetron use, lightheadedness (proxy)	Not quantified	ERAS *v* pre-ERAS	Surrogate measure for PONV
Persistent opioid use	Clement 2020, Hall 2025, Ingason 2022, Wagner 2022	Any use between 90-180 d; opioid prescription at discharge; opioid use postdischarge before 30-d follow-up; WHO DDD; long-term use risk	10/547 (sparing); 188/ 3,404 (5.5%); 19/32 (sparing), 44/64 (based); 4.6% (persistent users)	Descriptive only; not stratified; opioid-sparing *v* opioid-based; sparing group only	Binary data available; no control group data; no group comparison; opioid-naive population
Sedation/oversedation	Kaushal 2020	MOPS score, sedation duration	Not reported numerically	ESPB *v* control	Narrative only (pediatric population)
Sedation adequacy	Jelacic 2016	RASS target achievement	Qualitative only	NA	Discussed narratively

Abbreviations:

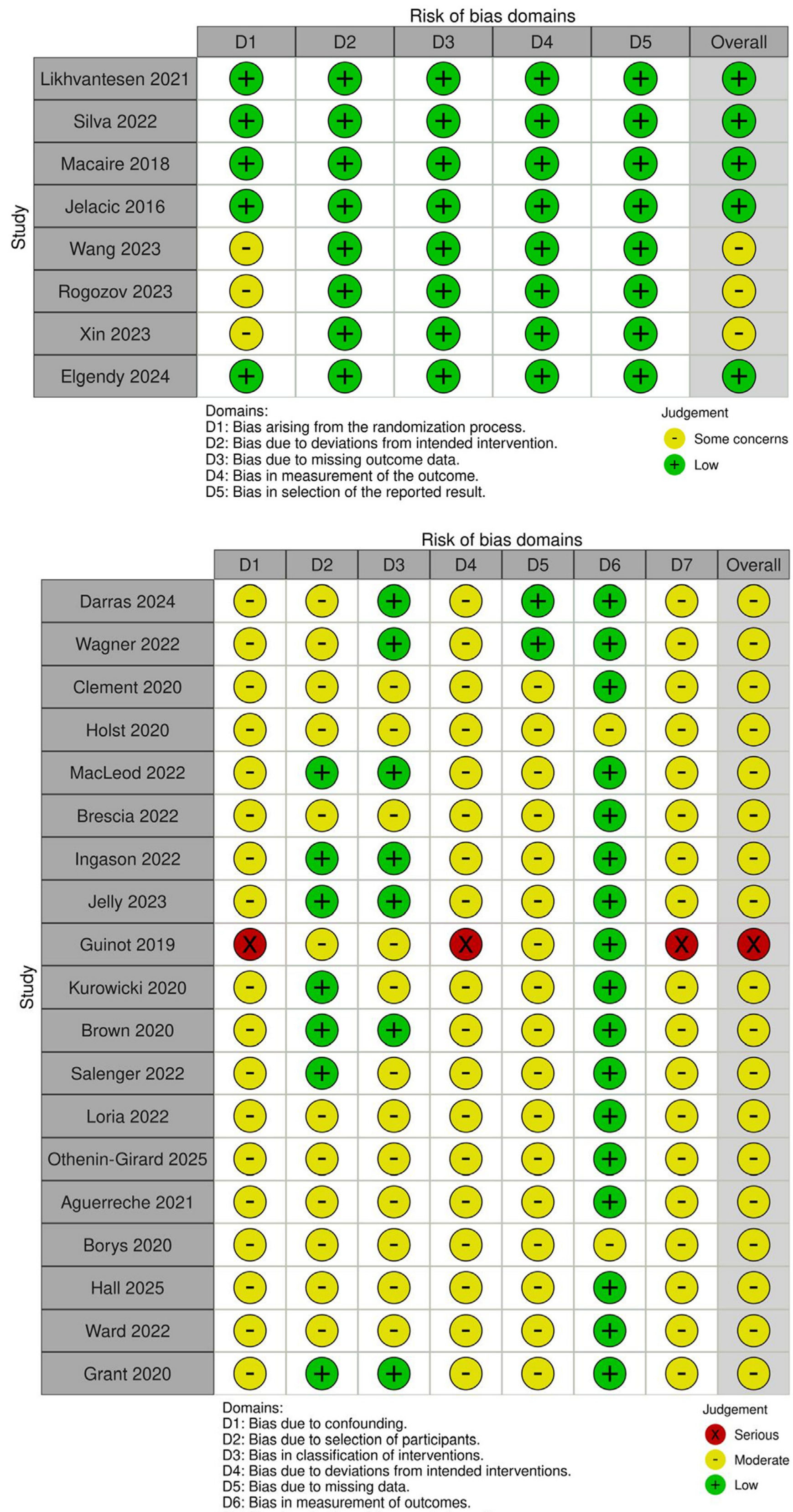

Fig 4. Risk-of-bias summary. ROB 2.0 for (a) randomized controlled trials and (b) ROBINS-I for observational studies.

Opioid-free anesthesia (OFA) has also emerged as a potential extension of opioid-sparing strategies. In selected patients undergoing CABG or valve surgery, OFA protocols incorporating regional anesthesia and advanced monitoring demonstrated promising results. For example, Cheng et al. reported a fully opioid-free protocol.[41] However, the generalizability of OFA remains limited due to the need for highly experienced teams, standardized protocols, and vigilant intraoperative management. At present, OFA should be considered a niche strategy for carefully selected patients.

Although opioid-sparing strategies aim to reduce opioid exposure, the nonopioid adjuncts employed carry their risks. Frequently used agents included nonsteroidal anti-inflammatory drugs (NSAIDs), dexmedetomidine, systemic lidocaine, and ketamine; Supplementary Table 1 outlines their mechanisms, benefits, and side effects. NSAIDs are effective analgesics but pose risks of renal dysfunction, gastrointestinal bleeding, and impaired wound healing, especially in older or high-risk cardiac patients.[47] Dexmedetomidine is associated with bradycardia and hypotension, particularly when combined with neuraxial or regional techniques.[39] Adjuncts such as dexmedetomidine and ketamine may influence extubation timing, complicating the attribution of outcomes solely to the opioid dose. Although studies such as Wang et al. and Jelly et al. included these agents, their individual contributions could not be isolated due to heterogeneity in reporting.[22,24,43,48]

Systemic lidocaine, though generally safe, may cause central nervous system toxicity in patients with impaired metabolism. Ketamine, typically used at subanesthetic doses, may cause hallucinations, though its perioperative safety profile is acceptable.[49,50] Notably, few studies systematically reported adverse events linked to nonopioid agents, and none were powered to detect rare or delayed complications. These gaps highlight the need for prospective trials with structured adverse event monitoring.

Several recent studies have explored alternative intraoperative opioid regimens, particularly methadone- or remifentanil-based protocols. Methadone, a long-acting μ-opioid receptor agonist with NMDA antagonism, has attracted interest due to its ability to provide prolonged analgesia with a single intraoperative dose.[43,51] Some institutions have adopted methadone as the sole intraoperative opioid, reporting improved postoperative pain control and reduced rescue opioid use. A randomized trial by Murphy et al. compared methadone (0.3 mg/kg) with fentanyl (12 μg/kg) in cardiac surgery patients and showed significantly lower 24-hour morphine requirements (median 6 *v* 10 mg, $p < 0.001$), better pain scores, and higher satisfaction without increased side effects. These results support the incorporation of methadone into multimodal protocols when appropriate. Nonetheless, methadone's long and variable half-life, delayed respiratory depression risk, and pharmacokinetic variability have limited widespread adoption.[43,51]

In contrast, remifentanil is often used in ultra-fast-track protocols but has been associated with opioid-induced hyperalgesia and tolerance. Postoperative hyperalgesia has been reported in 5% to 15% of patients receiving high-dose remifentanil or fentanyl, potentially increasing postoperative analgesic requirements.[19,25,29,31,35] These concerns have motivated the adoption of opioid-sparing or multimodal protocols that avoid both high-dose long-acting opioids and ultra-short-acting agents with high context sensitivity. However, no single agent or technique has demonstrated universal superiority, and future trials comparing methadone-based, remifentanil-based, and opioid-sparing protocols using standardized outcomes are needed.

The current findings are also consistent with emerging literature, including two recent studies that independently support the results. Zhao et al. reported that opioid-sparing anesthesia in cardiac surgery was associated with shorter ICU stays, fewer episodes of nausea and vomiting, and earlier mobilization in a prospective cohort of 120 patients undergoing valve surgery or CABG.[46] Similarly, Gao et al. found improved pain control, faster extubation, and reduced postoperative delirium with multimodal, opioid-sparing anesthesia.[45] Though not included in the quantitative synthesis due to incomplete numerical reporting, these studies confirm that opioid-sparing approaches can enhance recovery without compromising safety. They also reflect a growing international trend toward integrating ERAS principles into cardiac anesthesia—featuring routine use of regional blocks, nonopioid adjuncts, and structured analgesia.[19,23-27,31-35]

Several secondary outcomes—such as quality of recovery, postoperative nausea and vomiting, sedation levels, and mobilization—were excluded from pooled analysis due to inconsistent definitions and time points. Nevertheless, these outcomes often favored opioid-sparing protocols, especially when combined with regional anesthesia and structured postoperative analgesia (Table 3).

One particularly important, yet inconsistently assessed, outcome was postoperative cognitive function. Given the complex interaction between anesthetic agents, surgical stress, and patient vulnerability, the current authors recommend adopting the standardized terminology of perioperative neurocognitive disorders (PNDs) as proposed by Evered et al.[52] This nomenclature includes acute postoperative delirium, delayed neurocognitive recovery, and long-term cognitive decline. Although only a few included studies assessed cognitive outcomes, those implementing opioid-sparing approaches generally reported a lower incidence of postoperative agitation or delirium, particularly in protocols minimizing benzodiazepines and high-dose opioids. Additional studies are needed to determine whether these findings translate into lower long-term rates of PNDs.

This meta-analysis has several limitations. First, there was substantial heterogeneity in study design, ranging from RCTs to retrospective cohorts. Although study quality was evaluated using validated tools (RoB 2.0, ROBINS-I, and ROBVIS) and summarized visually (Fig 4), the overall evidence level remains moderate to low for some outcomes. Second, outcome definitions varied widely. Pain was assessed using different scales (eg, visual analog scale or numeric rating scale), at varied time points, and often without standardized rescue protocols. Mechanical ventilation duration was also inconsistently reported, including time to extubation, total hours ventilated, or proportion of early extubation. Third, most studies did not adjust for key confounders such as surgical complexity, CPB duration, bleeding, steroid use, or baseline cardiopulmonary function. These factors likely influenced outcomes such as LOS and extubation time. Fourth, opioid consumption was inconsistently measured (eg, mcg/kg, total dose, MMEs), with variable or unspecified conversion methods. Despite efforts to standardize data, these inconsistencies limit the precision of pooled estimates.[36,53] Finally, adverse events related to nonopioid adjuncts were poorly reported, and no study was powered to evaluate long-term outcomes such as persistent opioid use or perioperative neurocognitive decline. Therefore, the conclusions are best interpreted in the context of elective adult cardiac surgery within enhanced recovery settings.

Conclusions

In this meta-analysis, opioid-sparing anesthesia in cardiac surgery patients was associated with significant reductions in intraoperative opioid consumption, mechanical ventilation duration, and ICU LOS, without affecting short-term mortality. These findings support the integration of opioid-sparing strategies into enhanced recovery pathways, particularly when guided by patient comorbidities, surgical complexity, and pharmacologic considerations. While the benefits of reducing perioperative opioid exposure are increasingly recognized, this analysis highlights the need for standardized definitions, outcome reporting, and stratification by surgical and patient-level variables. The heterogeneous nature of the included studies underscores the importance of individualized approaches that balance analgesia, hemodynamic stability, and safety, particularly in high-risk populations such as those with renal or hepatic impairment. Future RCTs should compare opioid-sparing, opioid-free, and methadone-based protocols using consistent endpoints and robust adverse event monitoring. Further research should also evaluate long-term outcomes such as persistent opioid use, PNDs, and quality of recovery. As cardiac anesthesia continues to evolve, multidisciplinary collaboration will be essential to define best practices that align effective analgesia with opioid stewardship and patient-centered care.

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

Michela Rauseo: Writing − original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Lucia Mirabella:** Validation, Supervision. **Angelo Antonio Carrideo:** Investigation, Formal analysis, Data curation. **Francesco Paolo Padovano:** Investigation, Data curation. **Leonarda Pia Cantatore:** Investigation. **Paolo Vetuschi:** Investigation, Data curation. **Stefania Da Lima:** Investigation. **Gianluca Paternoster:** Writing − review & editing, Supervision. **Gilda Cinnella:** Writing − review & editing, Validation, Supervision.

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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.2025.06.040.

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