Review Article

Bivalirudin Versus Heparin and Protamine in Adult Patients Undergoing Cardiac Surgery: A Systematic Review and Meta-Analysis

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ABSTRACT

Objectives: To summarize the evidence on the morbidity, mortality, and transfusion requirements of adult patients undergoing cardiac surgery using bivalirudin for anticoagulation compared to unfractionated heparin (UFH).

Measurements and Main Results: A total of 407 patients in three randomized controlled trial (RCTs) were included for pooled analysis. There was no significant difference in the primary outcome; reexploration for hemorrhage between groups (risk ratio: 1.38, 95% confidence interval: 0.42 to 4.48). There were no observable differences in any of the secondary outcomes; thromboembolic events (myocardial infarction, stroke, pulmonary embolism), mortality, or postoperative transfusion requirements (packed red cells (PRC), platelets, cryoprecipitate, fresh frozen plasma (FFP)). All studies included were assessed to have some concern for risk of bias. Interstudy heterogeneity was low across all comparisons.

Conclusion: Bivalirudin has not been shown to have any significant difference to UFH on clinical outcomes in patients undergoing cardiac surgery, and as per current international guidelines, can be considered for safe use in those patients for whom UFH is contraindicated. The study is limited by the bias of the included studies and the variability of bivalirudin drug dosage and its therapeutic monitoring; further, well-powered RCTs are required.

Keywords: Anticoagulation, bivalirudin, cardiac surgery, cardiopulmonary bypass, heparin, heparin-induced thrombocytopenia, heparin resistance, HIT, off-pump cardiac surgery, unfractionated heparin

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Submitted: 23-Jan-2026 **Revised:** 14-Mar-2026 **Accepted:** 04-Apr-2026 **Published:** 12-Oct-2026

INTRODUCTION

Unfractionated heparin (UFH) has been a cornerstone of cardiac surgery since the first procedure requiring cardiopulmonary bypass (CPB) in 1953.[1] UFH has been the mainstay anticoagulant for cardiac surgery due to its rapid onset, reliable reversibility with protamine, and extensive clinical experience. The use of UFH may be limited in some patients, notably by heparin-induced thrombocytopenia (HIT) and heparin resistance. With HIT seen more frequently in surgical patients and those receiving higher doses of UFH as is typical in cardiac surgery, its incidence is reported between 1% and 2%.[2,3] Heparin resistance leads to increased morbidity and mortality and is seen in 17.5% of patients undergoing procedures requiring CPB.[4]

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Quick Response Code:	Website: https://www.ovid.com/jnls/aoca
	DOI: 10.4103/aca.aca_28_26

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How to cite this article: Cadd M, Green S, Puntis D, Huellen HV, Seavill M, Bullard S. Bivalirudin versus heparin and protamine in adult patients undergoing cardiac surgery: A systematic review and meta-analysis. Ann Card Anaesth 2026;29:494-502.

Where there are contraindications to UFH use, a number of other therapies, including bivalirudin, argatroban, danaparoid, or plasmapheresis, can be used,[5,6] with the latest European guidelines recommending bivalirudin as the first-choice alternative to heparin.[6] Since its discovery in the early 1990s, bivalirudin has been widely used in acute myocardial infarction and shown to improve coronary blood flow without increasing bleeding risk.[7,8] Over the subsequent three decades, a number of RCTs and observational studies using bivalirudin have been carried out in cardiac surgery with varying results with regard to bleeding complications, transfusion requirements, thrombotic events, and mortality.

This meta-analysis and systematic review aims to compare the clinical outcomes of adult patients undergoing cardiac surgery requiring bivalirudin or UFH.

METHODS

The literature search and subsequent meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[9] The study protocol was submitted to and subsequently published by PROSPERO (reference: CRD420251274233).

Search strategy

The following electronic databases from January 1990 up to January 2026 were searched for articles without language restriction: Embase, Medline, Cochrane Database of Systematic Reviews, Cochrane Central Register Controlled Trials, ISI, CINAHL, Scopus, and Web of Knowledge. All included studies' reference lists were manually screened to identify additional studies. A further search of the "grey" literature was also undertaken, including Google Scholar (URL: https://scholar.google.com/) and thesis databases, ProQuest, British Library EThOS, and OATD (Open Access Thesis and Dissertation). Where full text was not available, colleagues unable to translate accurately into English, results were ambiguous, or insufficient data was provided, the named corresponding author was contacted and additional information or English-translated versions were requested. Searches were carried out independently by two authors systematically using keyword and phrases: bivalirudin, heparin, unfractionated-heparin, anticoagulation, cardiopulmonary bypass, coronary artery bypass grafts, cardiac surgery. Disagreement about study inclusion was adjudicated by a third study author.

Eligibility criteria and study selection

The primary outcome of the study was the incidence of postoperative hemorrhage and return to the operating theatre. Secondary outcomes included thromboembolic events (myocardial infarction, stroke, pulmonary embolism), mortality, postoperative transfusion requirements (PRC, platelets, cryoprecipitate, FFP), intensive care unit (ICU), and hospital length of stay.

Randomized controlled trials (RCTs) on adult patients (≥18 years) receiving bivalirudin or UFH and undergoing cardiac surgery ("on-pump" or "off-pump") were included.

Published studies, including crossover trials, parallel-designed trials, prospective cohort studies and retrospective cohort studies, case series, case reports, letters to the editor, conference abstracts, abstract data, preclinical studies, and nonhuman studies, were excluded. Any study that included nonadults (<18 years), patients not undergoing cardiac surgery, or receiving a placebo was excluded.

Data extraction

Data was extracted independently by two authors using a standardized data collection form. Any discrepancies were resolved by a third author. For all included studies, the following were extracted:

1. Study author, publication year, and patient demographics.
2. Underlying pathology requiring surgery, surgical procedure, and CPB time.
3. Bivalirudin, UFH, and protamine dosing regimes.
4. Postoperative hemorrhage and return to the operating theatre.
5. Thromboembolic events (myocardial infarction, stroke, pulmonary embolism).
6. Postoperative blood loss and transfusion requirements (PRC, platelets, cryoprecipitate, fibrinogen concentrate).
7. ICU and hospital length of stay and mortality.

If further data was required for clarification about specific aspects of a study or its results, the relevant study author was contacted using details provided to request this.

Quality assessment

For all RCTs, risk of bias assessment was carried out using the Revised Cochrane RoB-2 tool and the risk of bias was classified as low, some concerns, or high across five domains: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results.[10] Assessments were carried out independently by two authors. Discrepancies between the initial reviewers were adjudicated and the final risk of bias was determined by a third reviewer.

The influence of each study on the overall effect size of the primary meta-analysis was conducted using the leave-one-out method of sensitivity analysis (i.e., removing each individual study and repeating the analysis). Further sensitivity analysis was carried out removing all studies assessed as being at high or serious risk of bias.

To explore potential sources of heterogeneity, we conducted *a priori* subgroup analyses of surgery requiring CPB and surgery not requiring CPB.

Statistical analysis

Collected study information was entered into tables, and subsequent statistical analyses were completed using Review Manager Software version 5.4.[11]

For all continuous outcomes, mean and standard deviation were pooled and presented as forest plots using mean difference with 95% confidence intervals (CI). For dichotomous outcomes, risk ratios (RR) were pooled for analysis. Data was presented as forest plots using RR with 95% CI.

Interstudy heterogeneity was assessed using the Higgins I^2 test; low, moderate, and high interstudy heterogeneity was denoted by I^2 values of 25, 50, and 75 percent, respectively.[12,13] For all meta-analyses performed, a random effects model was used.[14] A *P* value of <0.1 was used to identify the statistical significance of heterogeneity.[15] Sources of large heterogeneity were assessed through subgroup analysis where able.

RESULTS

Study selection

Following the completion of electronic searches, a total of 380 studies were identified. Eliminating duplicates and excluding studies following title/abstract review left a total of seven full-text articles to be retrieved; of these, three met the inclusion criteria. Full-text articles were excluded for either including patients aged under 18 years or having noncardiac surgery procedures. The full search and details for study exclusion are displayed as a PRISMA flow diagram [Figure 1].

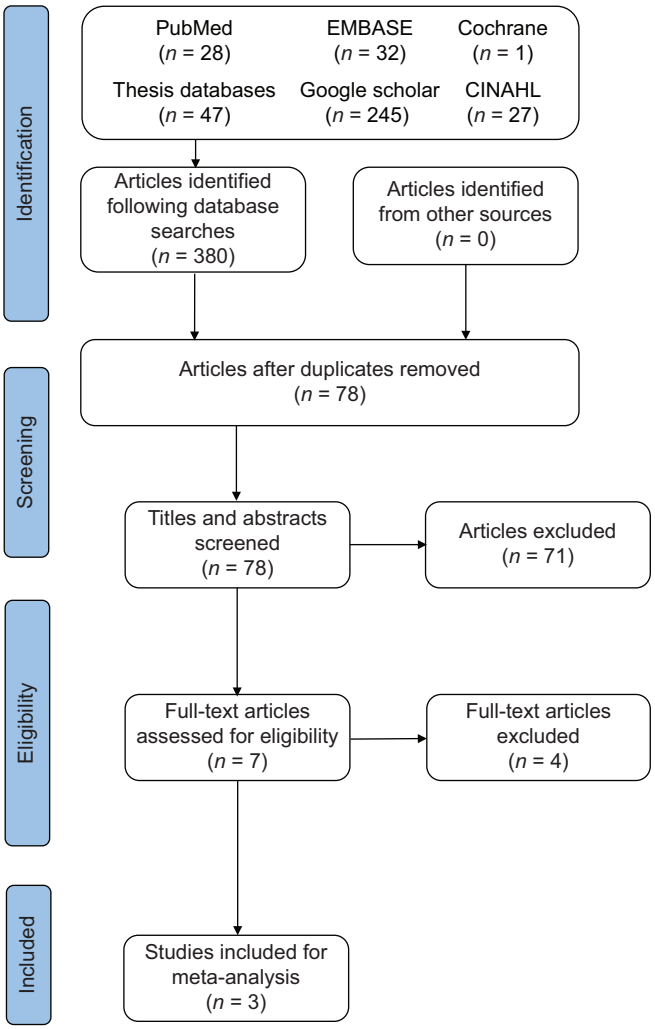


Figure 1: PRISMA flow diagram for study screening and selection. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Study characteristics

A total of 407 patients were included from three RCTs[16-18]; the characteristics of these are shown in Table 1. All studies compared the use of bivalirudin to heparin. Two studies included only elective off-pump coronary artery bypass grafts (OPCAB) and the other a mix of CABG and valve procedures. Mean age across studies was from 63.9 to 65.1 years, and 79.1% of the total patients were male.

All three studies reported reexploration for hemorrhage, myocardial infarction (7 days), mortality (7 days), total transfusion, PRC, platelets, and FFP transfusion. Both OPCAB studies used a bivalirudin bolus of 0.75 mg/kg and marginal variation between infusion dose,[16,18] with the study using CPB having a higher mean bolus of 1 mg/kg and higher infusion dose.

The studies were carried out in the USA, Germany, and New Zealand, and all were published in English. Three participants dropped out of the bivalirudin group after randomization in one study (reason not recorded) and instead received heparin.[17] In addition, four patients in another study swapped arms after randomization due to surgeon preference or exclusion criteria being identified.[18]

Primary outcome

All three studies reported on the primary outcome of interest,[16-18] reexploration for hemorrhage (REF ALL).

Table 1: Summary of studies included for pooled analysis

Study	Location, study period	Groups (no. of patients)	Dose	Age, sex, weight	Procedures and CPB time	Primary outcome	Inclusion and exclusion criteria	Follow-up
Merry *et al.*[16] (Multicenter RCT)	3 sites, Auckland, New Zealand (November 00–May 02)	Bivalirudin (50)	Bolus (mean) 0.77 mg/kg. Infusion 1.57 mg/kg/h	64±11 years 90% Male Weight (kg) 83.1±14.2	OPCAB (50) CPB NA	Total blood loss from the time of chest incision to 12 hours after study drug initiation	Inclusion Patients suitable for OPCAB Exclusion Stroke<2 years Intracranial neoplasm, AVM or aneurysm RRT or Creat<30 mL/min Warfarin therapy, LMWH<24 h Abciximab<48 h APTT>50 s	24 h, 4 days, hospital discharge, 3 months
		UFH and Protamine (50)	Heparin bolus (mean) 285 units/kg. Target ACT 300–350 s Protamine 198 mg	65±9.9 years 84% Male weight (kg) 84.0±13.3	OPCAB (50) CPB NA			
Dyke *et al.*[17] (Multicenter RCT)	21 sites USA and Germany (not recorded)	Bivalirudin (98)	Bolus (mean) 1.0±0 mg/kg bolus. Infusion 2.5±0.2 mg/kg/h	63.9.5±11.0 years 79.6% Male Weight (kg) 87.8±15.0	CABG (70), CABG + Valve (10), AVR (10), MVR (2), Other (6) 85.3±37.4 min	In-hospital procedural success, defined as the absence of death, Q-wave MI, stroke, or repeat coronary revascularization	Inclusion Patients undergoing cardiac surgery with planned CPB Exclusion Severe renal failure Preoperative glycoprotein IIb/IIa antagonists, adenosine diphosphate antagonists, LMWH, or thrombolytics	7, 30 days and 12 weeks
		UFH and protamine (52)	Heparin bolus (mean) 344.2±101.3 units/kg. Protamine 3.7±1.5 mg/kg	65.1±9.8 years 69.2% Male Weight (kg) 85.5±20.4	CABG (35), CABG + Valve (8), AVR (3), MVR (3), Other (3) 89.0±51.2 min			
Smedira *et al.*[18] (Multicenter RCT)	21 sites USA, New Zealand, and Germany (not recorded)	Bivalirudin (101)	Bolus 0.75 mg/kg. Infusion 1.75 mg/kg/h	63 years (IQR 56–73) 76.2% Male Weight NR	OPCAB (101) CPB NA	Procedural success is defined as freedom from a composite of death, myocardial infarction, stroke, and repeat revascularization	Inclusion Cardiothoracic surgery patients Received B_{12} or MB in the OR or ICU up to 24 hours after CPB separation Exclusion Patients with HIT Previous sternotomy, RRT Stroke<6 months Preoperative warfarin, clopidogrel (<5 d), lepirudin, or argatroban (<24 h). Known allergy to bivalirudin or hirudin-type drugs.	7, 30 days and 12 weeks
		UFH and protamine (56)	Weight-adjusted for an ACT>300 s. Protamine 205 mg (range 15–450 mg)	67 years (IQR 60–73) 80.4% Male	OPCAB (56) CPB NA			

ACT – Activated clotting time, AVM – Arteriovenous malformation, AVR – Aortic valve replacement, CABG – Coronary artery bypass graft, CPB – Cardiopulmonary bypass, HIT – Heparin-induced thrombocytopenia, LMWH – Low molecular weight heparin, MI – Myocardial infarction, MVR – Mitral valve replacement, OPCAB – Off-pump coronary artery bypass, RRT – Renal replacement therapy, UFH – Unfractionated heparin

Of the 407 included patients, 249 received bivalirudin and 158 UFH. There was no observable difference of reexploration for hemorrhage between groups (RR: 1.38, 95% CI 0.42 to 4.48, $P = 0.60$, $I^2 = 25\%$) [Figure 2a].

Secondary outcomes

Myocardial infarction

All three studies (407 patients) reported the incidence of MI.[16-18] There was no observable difference of MI between groups (RR: 0.81, 95% CI 0.43 to 1.52, $P = 0.51$, $I^2 = 0\%$) [Figure 2b].

Stroke

Two studies (307 patients) reported incidence of stroke.[17,18] There was no observable difference of stroke between groups (RR: 0.22, 95% CI 0.22 to 1.64, $P = 0.14$, $I^2 = 0\%$) [Figure 2c].

Mortality

All three studies (407 patients) reported on mortality.[16-18] There was no observable difference of mortality between groups (RR: 1.59, 95% CI 0.37 to 6.77, $P = 0.53$, $I^2 = 0\%$) [Figure 2d].

All transfusion

All three studies (407 patients) reported total transfusion requirements.[16-18] There was no observable difference of total transfusion products received between groups (RR: 0.90, 95% CI 0.73 to 1.09, $P = 0.28$, $I^2 = 0\%$) [Figure 3a].

Packed red cells

All three studies (407 patients) reported on PRC transfusion.[16-18] There was no observable difference of total PRCs received between groups (RR: 0.96, 95% CI 0.73 to 1.25, $P = 0.76$, $I^2 = 34\%$) [Figure 3b].

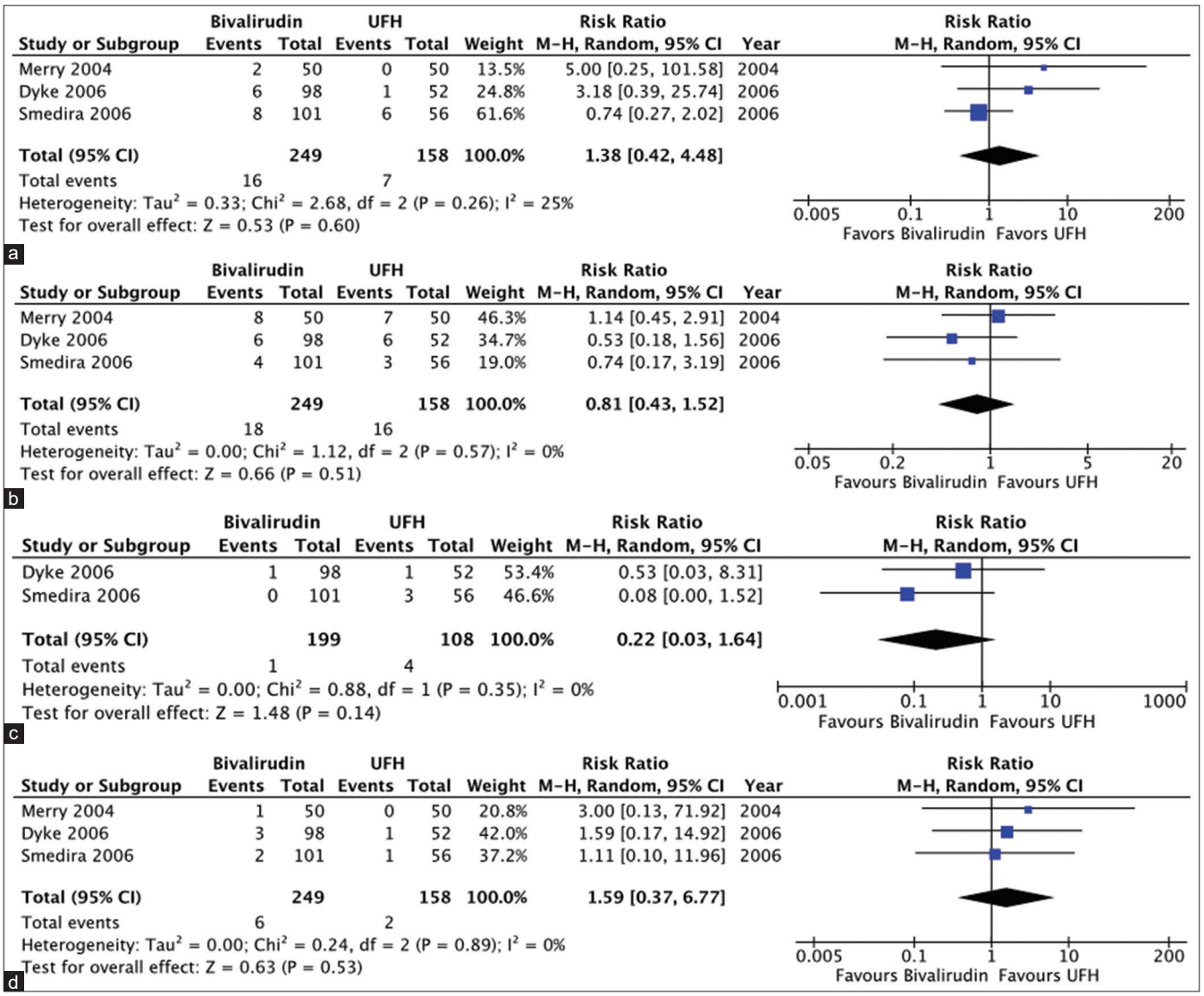


Figure 2: Forest plots of pooled analysis for (a) Reexploration for hemorrhage, (b) myocardial infarction, (c) stroke, and (d) mortality

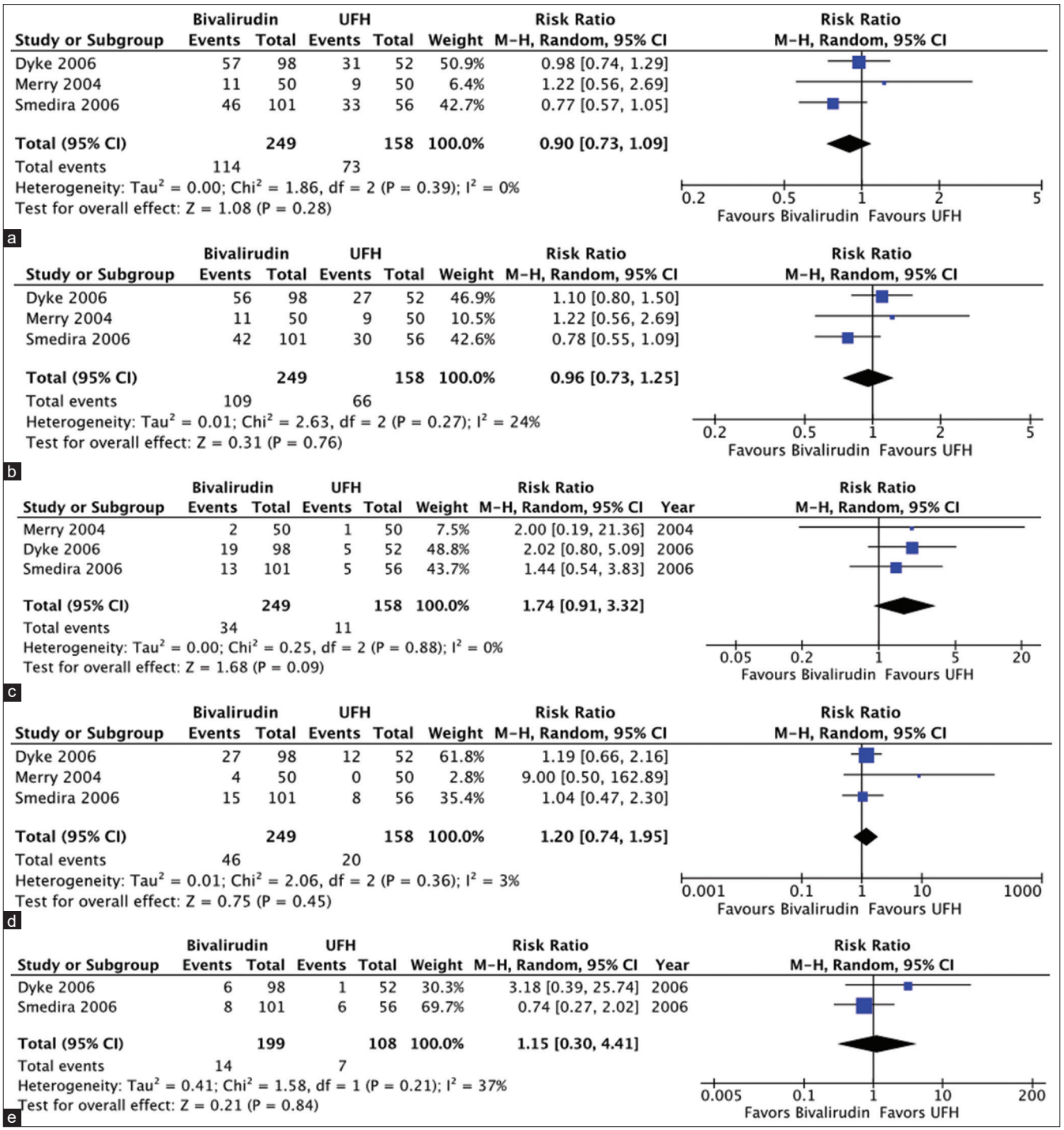


Figure 3: Forest plots of pooled analysis for (a) All transfusions, (b) PRC, (c) platelets, (d) FFP, and (e) subgroup OPCAB reexploration. FFP = Fresh frozen plasma; OPCAB = Off-pump coronary artery bypass grafts; PRC = Packed red cell

Platelets

All three studies (407 patients) reported on platelets transfusion.[16-18] There was no observable difference of total platelets received between groups (RR: 1.74, 95% CI 0.91 to 3.32, $P = 0.88$, $I^2 = 0\%$) [Figure 3c].

Fresh frozen plasma

All three studies (407 patients) reported on FFP transfusion.[16-18] There was no observable difference of total FFP received between groups (RR: 1.20, 95% CI 0.74 to 1.95, $P = 0.45$, $I^2 = 3\%$) [Figure 3d].

Postoperative blood loss

All included studies reported postoperative blood loss as median and interquartile range (IQR) and were not suitable for meta-analysis.[16-18] Merry *et al*.[16] reported no significant difference in blood loss at 12 hours: 793 mLs (IQR 532–1214 mLs) and 805 (IQR 517–1117 mLs) for bivalirudin

and UFH, respectively. Dyke *et al*.[17] also reported no significant difference at 24 hours between groups but showed a significant increase in blood loss in the bivalirudin group at 2 hours (238 mL vs. 160 mL; $P = 0.0009$). Smedira *et al*.[18] reported blood loss as 717 mL (IQR 475–1190) and 783 (IQR 528–1032) for bivalirudin and UFH, respectively, although this was at an unknown time postoperatively and without statistical test for significance (REF SMED).

Subgroup analysis

Two studies (307 patients) included only patients undergoing OPCAB and reported on the primary outcome of reexploration for hemorrhage.[17,18] There was no observable difference between groups (RR: 1.15, 95% CI 0.30 to 4.41, $P = 0.84$, $I^2 = 37\%$) [Figure 3e].

Risk of bias

A risk-of-bias summary plot has been produced to show risk of bias in individual studies using ROBVIS software [Figure 4].[19] All studies were assessed as having "some concerns" with respect to overall risk of bias. Merry *et al*.[16] blinded the surgeon intraoperatively and additionally the radiographer assessing coronary blood flow at 12 weeks. Both other studies were open label, although no deviations from intended measures were declared based on this lack of blinding. Both the Dyke *et al*.[17] and Smedira *et al*.[18] studies had patients swap study arms after randomization from bivalirudin to UFH and were deemed to have some concerns with regard to the randomization process.

As only three studies were included, Egger's test for publication bias and leave-one-of-sensitivity analysis were not carried out.

DISCUSSION

This systematic review and meta-analysis of three RCTs (407 patients) is the first to directly compare bivalirudin and UFH in patients undergoing cardiac surgery. The use of bivalirudin was not associated with any significant difference in patient outcomes or blood transfusion requirements. All trials had some concerns for risk of bias.

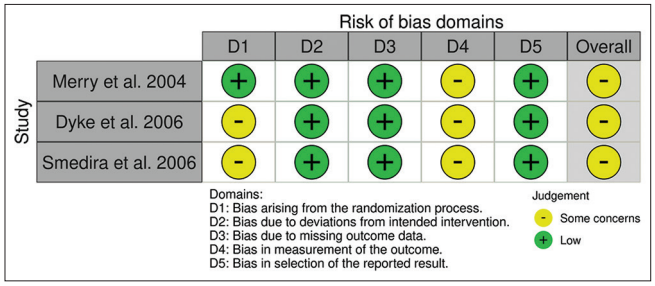


Figure 4: RoB2 (Risk of Bias 2 tool for randomized trials) summary table

Despite there being a range of therapeutic options available for anticoagulation in patients for whom UFH is less favorable or contraindicated, a recent survey of anesthesiologists and perfusionists found 75% would opt for bivalirudin in patients with HIT.[20] A 2009 prospective study of 49 HIT patients requiring CPB found that day 30 procedural success (absence of death, MI, revascularization, stroke) was achieved in 42 of the patients.[21] Furthermore, the study assessed patients with moderately impaired renal function (CrCl 30–60 mL/min) and found no significant difference in postoperative blood loss (24 h) or rates of blood product transfusion. A further retrospective study examined 72 patients with confirmed HIT who underwent procedures requiring CPB[22]; 13 received a direct thrombin inhibitor (DTI) (10 bivalirudin and three argatroban) and the rest UFH. They found a significant reduction in moderate and severe hemorrhage favoring DTIs (8% vs. 51%, $P < 0.01$).

A notable limitation of bivalirudin is the lack of reversal agent. It is approximately 80% cleared through proteolytic cleavage with the remainder renally excreted unchanged.[23] With a half-life of 25 minutes, excretion can be significantly longer in patients with renal failure and even longer in patients with profound hypothermia following CPB. A recent systematic review found that ultrafiltration was commonly used at the end of CPB cases using bivalirudin and can reduce ACT by up to 35%.[24,25]

Bivalirudin is currently only licensed for use in patients undergoing percutaneous coronary intervention (PCI).[26] One of the earlier large RCTs comparing bivalirudin to UFH in patients undergoing PCI used a dosing regimen of 1 mg/kg bolus, followed by 2.5 mg/kg/h to target an ACT >350 s.[27] Current manufacturer's dosing guidelines are 0.75 mg/kg bolus dose followed by 1.75 mg/kg/h plus a further 0.3 mg/kg bolus if ACT is not in the target range 5 minutes after the bolus dose. Dosing of bivalirudin between the three included studies was noted to be relatively consistent; however, a recent systematic review (of mostly case studies requiring CPB) highlighted the wide range of dosing of bivalirudin in cardiac surgery.[25] Nearly all cases used 50 mg in the CPB priming solution, with bolus dose ranging from 1.0 to 3.0 mg/kg and infusion 1.25–4.0 mg/kg/h. There was notable variability in ACT target from >400 s up to 550–600 s or more frequently x2.5 the baseline.

The effect of bivalirudin can be monitored using a number of point-of-care and formal assays.[28] At the lower doses of bivalirudin used for PCI, the ecarin clotting time (ECT) has shown the strongest correlation coefficient with bivalirudin

concentration at therapeutic levels (R^2 = 0.96), although ACT was also strongly correlated (R^2 = 0.90).[29] While ECT is not yet commercially available, ACT remains the most frequently used test for anticoagulation with a recent survey showing 83% of anesthesiologists and perfusionists opting to use it when bivalirudin is being used during CPB.[20]

Although not amenable to meta-analysis, Merry *et al*.[16] notably assessed graft flow in 79% of their patients at three months postoperatively. They found significantly more grafts in the bivalirudin group had complete flow compared to the UFH group: 101 of 123 (82%) versus 83 of 123 (67%), respectively (X^2 test, P = 0.03)

The primary use of bivalirudin over UFH has been in patients with confirmed HIT or allergy to UFH or protamine. McNair *et al*.[30] reported on two cases of patients with clot formation in the CPB circuit despite receiving 957 and 1125 units/kg of UFH, respectively. Both patients were administered bivalirudin with subsequent reduction in clot formation in the circuit; both were antithrombin deficient and made an uncomplicated recovery.

Limitations

Although this meta-analysis provides more robust evidence than previous systematic reviews, it has a number of limitations. Merry *et al*. kept the operating surgeon blinded to the study arm only until chest closure, with the other two trials conducting open-label studies, leading to an increased risk of bias. Smedira reported a notable increase of aminocaproic acid or aprotinin use in the bivalirudin group (47.5% vs. 32.1%, respectively). Both Smedira *et al*.[18] and Dyke *et al*.[17] did not report other intra-operative blood product use, and postoperative transfusion triggers were not standardized and left to the discretion of the surgeon, anesthesiologist, and intensivist.

CONCLUSION

Bivalirudin has not been shown to have any significant differences in patient morbidity and mortality, nor blood product requirements when compared to UFH, and as per current guidelines, should be considered as a suitable alternative in those patients in whom UFH is contraindicated.[6] Future well-powered RCTs should focus on establishing an optimum dose of bivalirudin in cardiac surgery (both on and off pump) along with further development of a suitable test for monitoring coagulation during its use.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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