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The efficacy and safety of bivalirudin and heparin in patients with acute coronary syndrome: a systematic review and meta-analysis

You Zhai[1,2*], Hongcai Shang[1*], Yan Li[2], Nan Zhang[2], Jisi Zhang[2] and Shangwen Wu[3]

Abstract

Background Patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) are at high risk of thrombosis. However, bleeding-related complications during antithrombotic therapy remain a major barrier to effective treatment and can often lead to adverse outcomes. This meta-analysis aimed to determine the efficacy and safety of bivalirudin and heparin in patients with ACS after PCI.

Methods Randomized controlled trials (RCTs) on the efficacy and safety of bivalirudin versus heparin in patients with ACS after PCI were identified from the PubMed, Embase, Cochrane Library, CBM, CNKI, WanFang, and VIP database until August 2024. The outcomes included all-cause mortality, major adverse cardiovascular events (MACEs), incidence of recurrent myocardial infarction, stent thrombosis, short-term bleeding, revascularization, and retransfusion. Meta-analysis was performed using RevMan 5.3 and Stata 12.0 softwares. The included studies were assessed for risk of bias using the Cochrane risk-of-bias assessment tool.

Results A total of 70,199 patients from 27 randomized controlled trials (RCTs) were analyzed in this review. There were no significant differences between the bivalirudin and heparin groups in terms of all-cause mortality, major adverse cardiovascular events (MACEs), recurrent myocardial infarction, stent thrombosis within 30 days, or subacute stent thrombosis. Specifically, the incidence of short-term bleeding ($P=0.001$) and retransfusion ($P=0.001$) was significantly lower in the bivalirudin group compared to the heparin group. Conversely, the incidence of acute stent thrombosis ($P<0.0001$) and revascularization ($P=0.009$) was significantly higher in the bivalirudin group.

Conclusions Compared with heparin, bivalirudin has definite anticoagulant effect in patients with acute myocardial infarction after PCI, and the risk of bleeding and the incidence of retransfusion were lower in the bivalirudin group. This review helps doctors in PCI management choose bivalirudin or heparin more precisely based on patients' conditions for better treatment and fewer adverse events.

Keywords Bivalirudin, Heparin, Acute coronary syndrome, Percutaneous coronary artery, Meta-analysis

*Correspondence:
You Zhai
zhaiyou036@163.com
Hongcai Shang
shanghongcai@foxmail.com
Full list of author information is available at the end of the article

Introduction

The incidence of severe cardiovascular ischemic events remains high worldwide and is increasing with the aging of the population [1]. Coronary artery disease (CAD) is a common cardiovascular disease that refers to heart disease caused by coronary atherosclerosis that narrows or blocks the lumen, or functional changes in the coronary arteries, leading to myocardial ischemia and hypoxia. CAD is one of the main causes of human death [2, 3]. The disease is more common in men over 40 years old than in women, and most of them are mental workers [4]. The incidence of acute coronary syndrome (ACS) is increasing rapidly, and the use of antithrombotic drugs is critical in its clinical management. However, bleeding-related complications during antithrombotic therapy remain a major barrier to effective treatment and can often lead to adverse outcomes [5]. Therefore, it is important to carefully weigh the benefits versus risks of antithrombotic therapy to optimize its overall therapeutic efficacy.

In addition to drug treatment of CAD, interventional treatment of CAD has made great progress. Interventional treatment of CAD in China began in 1984 and has a history of more than 40 years. In the past 10 years, the number of people receiving interventional treatment has increased by 20% per year [6]. The use of coronary stenting can significantly improve patient symptoms, reduce rehospitalization rates, preserve heart function, and improve prognosis. However, it is important to note that in-stent thrombosis and in-stent restenosis may also occur as potential complications. Additionally, bleeding events and other complications can exacerbate the overall risk profile associated with the procedure [7]. Therefore, a careful assessment of the risks and benefits of coronary stenting should be made for each individual patient to optimize clinical outcomes. To improve the therapeutic effect of percutaneous coronary intervention (PCI), traditional antiplatelet and anticoagulant drugs, such as aspirin, heparin, and platelet membrane glycoprotein IIb/IIIa receptor antagonist (GPI), have been used for the prevention of complications after PCI. Their effectiveness and safety were also studied [8, 9].

Heparin has long been a prominent drug in the antithrombotic treatment of thromboembolic diseases, distinguished by its rapid onset and potent anticoagulant action. It is routinely administered during percutaneous coronary intervention (PCI) to mitigate ischemic complications stemming from thrombosis [10, 11]. Bivalirudin, on the other hand, represents a direct thrombin inhibitor that exerts a reversible, specific, and direct inhibitory effect on thrombin. It has gained widespread adoption in the perioperative management of CAD patients undergoing PCI [12]. Nevertheless, comparisons between bivalirudin and unfractionated heparin have been hampered by inconsistent or flawed research designs both domestically and internationally. Consequently, the pertinent conclusions remain contentious [13, 14], and there is a scarcity of reports comparing the safety profiles of these two agents, as highlighted in [15].

The objective of this review is to conduct a comprehensive meta-analysis to evaluate the efficacy and safety of bivalirudin versus heparin in emergency PCI for patients with acute coronary syndrome. This evaluation is prompted by ongoing clinical debates concerning their anticoagulant effects, bleeding risks, and other potential complications. By comparing of the anticoagulant efficacy, bleeding risks, and incidence of other adverse events between these two anticoagulants in patients with diverse clinical characteristics, we hope to offer a more scientific rationale for clinicians to select appropriate anticoagulant drugs in PCI treatment, thereby resolving existing clinical controversies and optimizing patient treatment plans.

Methods

This meta-analysis was conducted with reference to methods set out in the *Cochrane Handbook for Systematic Reviews of Interventions* [16]. This study was not registered.

Search strategy

The reporting of this meta-analysis closely followed the guidelines of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [17]. The PRISMA completed checklist was listed in Additional file 1. A comprehensive search of the PubMed, Embase, Cochrane Library, China Biology Medicine disc (CBM), Chinese National Knowledge Infrastructure (CNKI), WanFang database, and VIP database was conducted to collect randomized controlled trials (RCTs) comparing the efficacy and safety of bivalirudin and heparin in patients with ACS after PCI. The retrieval time is from database establishment to August 2024. The retrieval keywords were "randomized trial", "randomized controlled trial", "bivalirudin", "hirulog", "anticoagulation", "unfractionated heparin", "acute coronary syndrome", "myocardial infarction", "reperfusion", "primary angioplasty", "coronary angioplasty", and "percutaneous coronary intervention". An example query was as follows: (Bivalirudin OR Hirudin) AND (Unfractionated Heparin OR Heparin OR Heparin Sodium OR Alpha-Heparin) AND (Percutaneous Coronary Intervention OR Coronary Intervention Percutaneous OR Percutaneous Coronary Revascularization).

Review inclusion criteria

(1) RCTs, complete data, and language limited to Chinese and English
(2) People clinically diagnosed with ACS, including ST-elevated myocardial infarction (STEMI), non-ST elevated myocardial infarction (NSTEMI), and unstable angina (UA), and undergoing PCI treatment
(3) Comparison of interventions between bivalirudin and heparin
(4) Outcome indicators include all-cause mortality, major adverse cardiovascular events (MACEs), incidence of recurrent myocardial infarction, stent thrombosis, short-term bleeding, revascularization, and retransfusion
(5) Follow-up time ≥ 1 month

Review exclusion criteria

(1) The data are unclear or wrong.
(2) Repeatedly published records
(3) Non-RCT or experimental design is not rigorous.
(4) Special samples that cannot represent the general population, such as all enrolled patients, are heparin-resistant patients.
(5) Cases, reviews, lectures, abstracts, or research on the same material

Data extraction and risk-of-bias assessment

Two researchers independently screened the records, extracted information according to the records inclusion and exclusion criteria, and cross-checked. Disagreements were discussed and resolved. According to the purpose of the review, the data extraction form was self-made, including the first author, publication time, number of cases, age, intervention measures, follow-up time, and main outcome indicators.

The quality of the included records was evaluated using the Cochrane risk-of-bias assessment tool (RoB-1). The main evaluation indicators included the following: random sequence generation, allocation concealment, blinding of subjects, researchers and outcome evaluators, and completeness of outcome data. In sex, selective outcome reporting, and other sources of bias, for the included records evaluation, choose "yes" (low risk of bias), "no" (high risk of bias), or "unclear" (unclear risk of bias).

Statistical analysis

RevMan 5.3 software was used to carry out meta-analysis and draw forest diagrams. The Q-test and I^2 values were used to test the heterogeneity. If it was found that $I^2 < 50\%$ or $P \geq 0.1$, it indicated that the studies were homogeneous, and the fixed effect model was used. Otherwise, the random effect model was used. For count data, the risk ratio (*RR*) and its 95% CI were used as analysis statistics. $P < 0.05$ was considered statistically significant. Stata 12.0 software was used to conduct Egger linear regression to determine whether there was publication bias, and a sensitivity analysis was performed to exclude a single study.

Results

Basic information about records

A total of 1035 records were retrieved. Among them, 674 duplicates were excluded, and 361 were initially obtained. After reading titles and abstracts, 265 irrelevant records were excluded. Finally, by screening the inclusion and exclusion criteria, 27 studies [18–44] were included with a total of 70,199 patients (Additional file 2: Supplementary Fig. 1). The characteristics of all the included studies were shown in Table 1.

Quality evaluation

According to the Cochrane risk-of-bias assessment tool (RoB-1), the quality of the included records was high (Fig. 1).

Meta-analysis results

All-cause mortality

A total of 21 studies reported all-cause mortality. A fixed effect model was used with no statistical heterogeneity among studies ($I^2 = 0\%$, $P = 0.46$). The results of the meta-analysis showed that there was no significant difference in all-cause mortality between the bivalirudin group and the heparin group [*RR* = 0.94; 95% *CI* (0.85–1.04); $P = 0.24$] (Fig. 2). The Egger's linear regression test showed that there may be no publication bias ($t = -3.07$, $P = 0.169$, Table 2).

Incidence of major cardiovascular adverse events

A total of 13 studies reported the incidence of MACEs. The statistical heterogeneity among the studies was small ($I^2 = 40\%$, $P = 0.06$), and the fixed effect model was used. The results showed that there was no significant difference in the incidence of MACEs between the bivalirudin group and the heparin group [*RR* = 1.05; 95% *CI* (0.93–1.18); $P = 0.41$] (Fig. 3A). The Egger's linear regression test showed that there may be no publication bias ($t = 2.24$, $P = 0.134$, Table 2).

Incidence of recurrent myocardial infarction

A total of 13 studies reported the incidence of myocardial infarction. A random effect model was used with moderate heterogeneity ($I^2 = 50\%$, $P = 0.02$). There was no significant difference in the incidence of myocardial

Table 1 The characteristics of all the included studies

First author	Years	Number of cases (B/H)	Age (B/H)	Men ratio (B/H)	Intervention		Dose		Outcome
					Bivalirudin	Heparin	Bivalirudin	Heparin	
Omerovic [18]	2024	3004/3002	72.6/73.3	70.1/72.9	Single use B/B + GPIIb/IIIa antagonist	H or enoxaparin + GPIIb/IIIa antagonist	0.75 mg/kg bolus injection + 1.75 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ upkeep	60 IU/kg bolus	①⑤⑥
Song [19]	2023	30/30	73.5/73.6	53/57	B + aspirin + clopidogrel bisulfate tablets	H + aspirin + clopidogrel bisulfate tablets	0.75 mg/kg bolus injection + 1.75 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ maintenance	100 IU/kg	③⑤
Li Y. [20]	2022	3009/3007	71/73	67/71	Single use	H + temporarily given GPIIb /IIIa antagonist	0.75 mg/kg bolus injection + 1.75 $mg{\cdot}kg^{--1}{\cdot}h^{-1}$ upkeep	60 IU/kg bolus	⑤
James [21]	2021	1501/1504	68/70	70.1/73.6	Single use	Single use	0.75 mg/kg bolus injection + 1.75 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ upkeep	60 IU/kg bolus injection, 12 $IU{\cdot}kg^{-1}{\cdot}h^{-1}$ dimension hold	①⑦
Wester [22]	2020	799/793	73/71	71/70	Single use	H or enoxaparin + GPIIb/IIIa antagonist	0.75 mg/kg bolus injection + 1.75 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ upkeep	100 IU/kg	①④⑤
Li Y. Z. [23]	2020	34/34	57.5/58.2	62/53	B + clopidogrel + aspirin	H + clopidogrel + aspirin	0.75 mg/kg bolus injection + 1.75 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ maintenance	100 IU/kg	③⑤
Erlinge [24]	2019	1503/1498	68/70	64/68	B + GPIIb/IIIa antagonist	H or enoxaparin + GPIIb/IIIa antagonist	0.75 mg/kg bolus injection + 1.75 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ upkeep	100 IU/kg bolus	①⑤
Li C. [25]	2018	42/42	71.2/72.9	74/76	B + GPIIb/IIIa antagonist	H + heparin	0.75 mg/kg bolus injection + 1.75 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ upkeep	60 IU/kg bolus	③⑤
Czarny [26]	2017	3380/4553	69/71	68.8/69.3	Single use	Single use	0.75 mg/kg bolus injection + 1.75 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ upkeep	60 IU/kg bolus injection, 12 $IU{\cdot}kg^{-1}{\cdot}h^{-1}$ dimension hold	①④⑦
Lima [27]	2018	123/137	70.3/69.5	65.3/66.8	Single use	Single use	1. 0 mg/kg static push, then 2.5 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ for 4 h, and finally 0.2 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ for 14–20 h	60 IU/kg bolus	③⑤
Wang [28]	2017	576/576	66/68	70/68	B + clopidogrel + aspirin	H + temporarily given GPIIb/IIIa antagonist	0.75 mg/kg bolus injection + 1.75 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ upkeep	60 IU/kg bolus injection, 12 $IU{\cdot}kg^{-1}{\cdot}h^{-1}$ dimension hold	③⑤
Erlinge [29]	2016	3004/3006	69/70	65/68	B + GPIIb/IIIa antagonist	H or enoxaparin + GPIIb/IIIa antagonist	0.75 mg/kg bolus injection + 1.75 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ upkeep	60 IU/kg bolus injection, 12 $IU{\cdot}kg^{-1}{\cdot}h^{-1}$ dimension hold	①④⑤
Briguori [30]	2015	3610/3603	67.5/69.1	71.6/72.8	B + clopidogrel + aspirin	H + temporarily given GPIIb/IIIa antagonist	0.75 mg/kg bolus injection + 1.75 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ upkeep	60 IU/kg bolus	①⑤⑦
Han [31]	2015	655/629	57.3/58.2	82.7/81.9	Single use	Single use	0.75 mg/kg bolus injection + 1.75 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ for 4 h	100 IU/kg bolus injection, dose adjusted to ACT < 200 s	①②③④⑤⑥

Table 1 (continued)

First author	Years	Number of cases (B/H)	Age (B/H)	Men ratio (B/H)	Intervention		Dose		Outcome
					Bivalirudin	Heparin	Bivalirudin	Heparin	
Feldman [32]	2014	50/50	-	78/60	Single use	Single use	0.75 mg/kg bolus injection + 1.75 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ maintenance	-	①⑤
Schulz [33]	2014	269 / 275	61.4/61.4	76/79	B + prasugrel	H + heparin	0.75 mg/kg bolus injection + 1.75 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ maintenance	70 ~ 100 IU/kg bolus injection, adjust the dose to make ACT 200 ~ 250 s	①②③④⑤⑥
Shahzad [34]	2014	905 / 907	62.9/63.6	64.7/66.3	Single use	Heparin	0.75 mg/kg bolus injection + 1.75 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ maintenance	70 IU/kg bolus	①②③④⑤⑥
Steg [35]	2013	1089/1109	61/62	73.7/77.6	Single use	H ± GPI or enoxaparin	0.75 mg/kg bolus injection + 1.75 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ maintenance	100 IU/kg or 60 IU/kg + GPIIb/IIIa or enoxaparin (0.5 mg/kg)	①②③④⑤⑥
Waksman [36]	2013	51/49	63.3/62.2	72.5/63.3	Single use	H + temporarily given GPIIb/IIIa antagonist	0.75 mg/kg bolus injection + 1.75 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ upkeep	60 IU/kg bolus injection, adjust the dose to make ACT < 200 s	①⑤
Xiang [37]	2013	105/102	63/65	84/82	Single use	H + GPIIb/IIIa antagonist	0.75 mg/kg bolus injection + 1.75 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ maintenance	60 IU/kg bolus	①⑤
Patti [38]	2012	198/203	70 /70	71/73	Single use	Single use	1. 0 mg/kg static push, then 2.5 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ for 4 h, and finally 0.2 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ for 14–20 h	100 IU/kg bolus	①③④⑤
Kastrati [39]	2011	2289/2281	67.5/67.5	76.9/76.8	Single use	H + GPIIb/IIIa antagonist	0.75 mg/kg bolus injection + 1.75 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ maintenance	70 IU/kg bolus	①③④⑤⑦
Moliterno [40]	2011	185/198	-	-	B + GPIIb/IIIa antagonist	H + GPIIb/IIIa antagonist	0.75 mg/kg bolus injection + 1.75 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ maintenance	50 IU/kg	①⑤
Parodi [41]	2010	363/308	69/69	77/75	Single use	H + heparin	0.75 mg/kg bolus injection + 1.75 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ maintenance	70 IU/kg bolus injection, adjust dose to ACT 200 ~ 250 s	①④⑤⑦
Mehran [42]	2009	1800/1802	59.8/60.7	59.8/60.7	Single use	H + GPI	0.75 mg/kg bolus injection + 1.75 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ maintenance	60 IU/kg bolus injection, adjust the dose to make ACT 200 ~ 250 s	①②③④⑤⑥
Stone [43]	2007	5228/2561	63/62	74/73	Single use B/B + GPIIb/IIIa antagonist	H or enoxaparin + GPIIb/IIIa antagonist	0.75 mg/kg bolus injection + 1.75 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ maintenance	60 IU/kg bolus injection, 12 $IU{\cdot}kg^{-1}{\cdot}h^{--1}$ dimension hold	①⑤
Gurm [44]	2005	864/801	66/66	70/73	Single use	H + heparin	0.75 mg/kg bolus injection + 1.75 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ maintenance	70 ~ 100 IU/kg bolus injection, adjust the dose to make ACT 200 ~ 250 s	①③④⑦

B Bivalirudin, *H* Heparin ①, all-cause mortality; ②, incidence of thrombosis; ③, incidence of major adverse events; ④, rate of recurrent myocardial infarction; ⑤, incidence of short-term bleeding events; ⑥, incidence of revascularization; ⑦, incidence of retransfusion

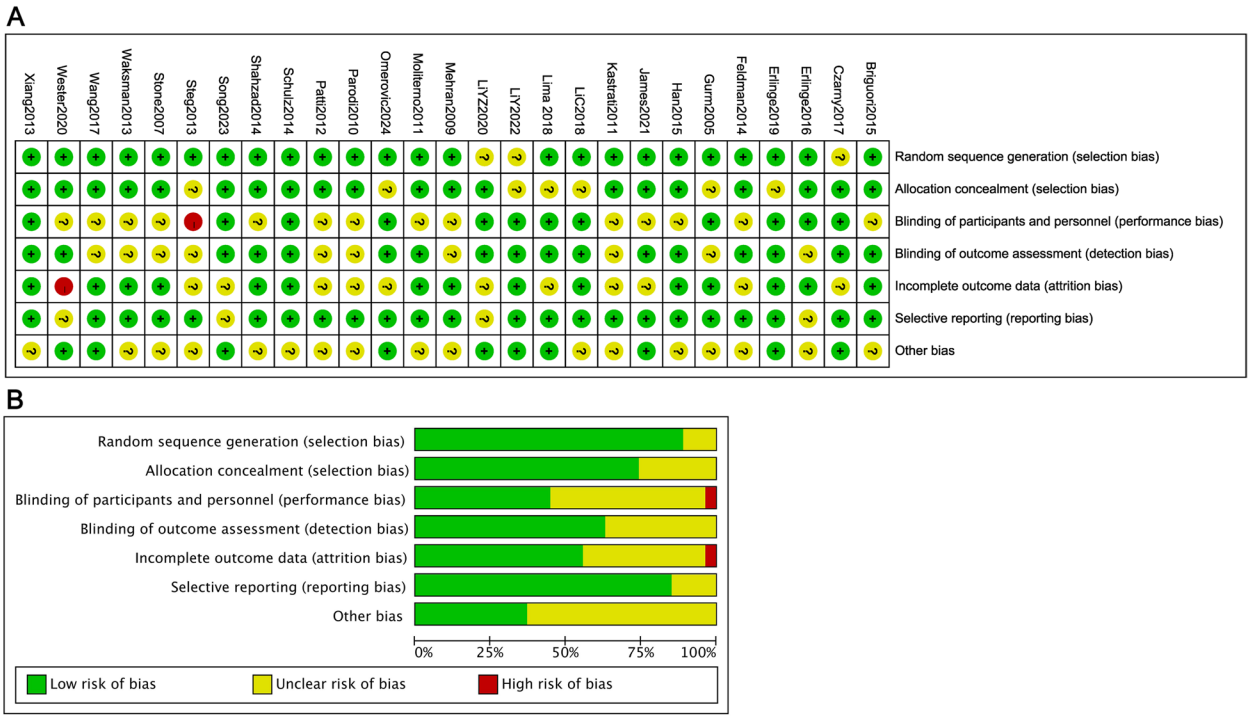

Fig. 1 The quality of the included records. **A** Risk-of-bias graph: review authors' judgments about each risk-of-bias item presented as percentages across all included studies. **B** Risk-of-bias summary: review authors' judgments about each risk-of-bias item for each included study

infarction [$RR=1.16$; 95% CI (0.95–1.41); $P=0.15$] between the bivalirudin group and the heparin group (Fig. 3B). The Egger's linear regression test showed that there may be no publication bias ($t=-0.87$, $P=0.456$, Table 2).

Incidence of stent thrombosis

- Thirty-day (≤30-day) incidence of stent thrombosis: A total of five studies reported the 30-day incidence of stent thrombosis. There was statistical heterogeneity among the studies ($I^2=58\%$, $P=0.12$), and a random effect model was used. The results showed that there was no significant difference in the 30-day incidence of stent thrombosis between the bivalirudin group and the heparin group [$RR=1.65$; 95% CI (0.87 ~ 3.10); $P=0.12$] (Fig. 4). The Egger's linear regression test showed that there may be no publication bias ($t=2.42$, $P=0.339$, Table 2).
- Incidence of subacute (24 h to 30 days) stent thrombosis: A total of four studies reported the incidence of subacute stent thrombosis. The statistical heterogeneity among the studies was small ($I^2=17\%$, $P=0.70$), and the fixed effect model was adopted. The results showed that there was no significant difference in the incidence of subacute stent thrombosis between the bivalirudin group and the heparin group [$RR=0.88$; 95% CI (0.45 ~ 1.70); $P=0.70$] (Fig. 4). Egger's linear regression test showed that there may be no publication bias ($t=-0.12$, $P=0.441$, Table 2).
- Incidence of acute (≤24 h) stent thrombosis: A total of four studies reported the incidence of acute stent thrombosis. There was statistical heterogeneity among the studies ($I^2=0\%$, $P=0.43$), and a random effect model was used. The results showed that there was a statistically significant difference in the incidence of stent thrombosis between the bivalirudin group and the heparin group [$RR=3.78$; 95% CI (2.08 ~ 6.86); $P<0.0001$] (Fig. 4). The Egger's linear regression test showed that there may be no publication bias ($t=-0.30$, $P=0.794$, Table 2).

Incidence of short-term bleeding events

A total of 24 studies reported the incidence of short-term bleeding events. A random effect model was used with moderate heterogeneity ($I^2=60\%$, $P=0.0001$). The results showed that there was a statistically significant difference in the incidence of bleeding between the bivalirudin group and the heparin group [$RR=0.80$; 95% CI (0.71–0.92); $P=0.001$] (Fig. 5). The Egger's linear regression test showed that there may be no publication bias ($t=0.38$, $P=0.819$, Table 2).

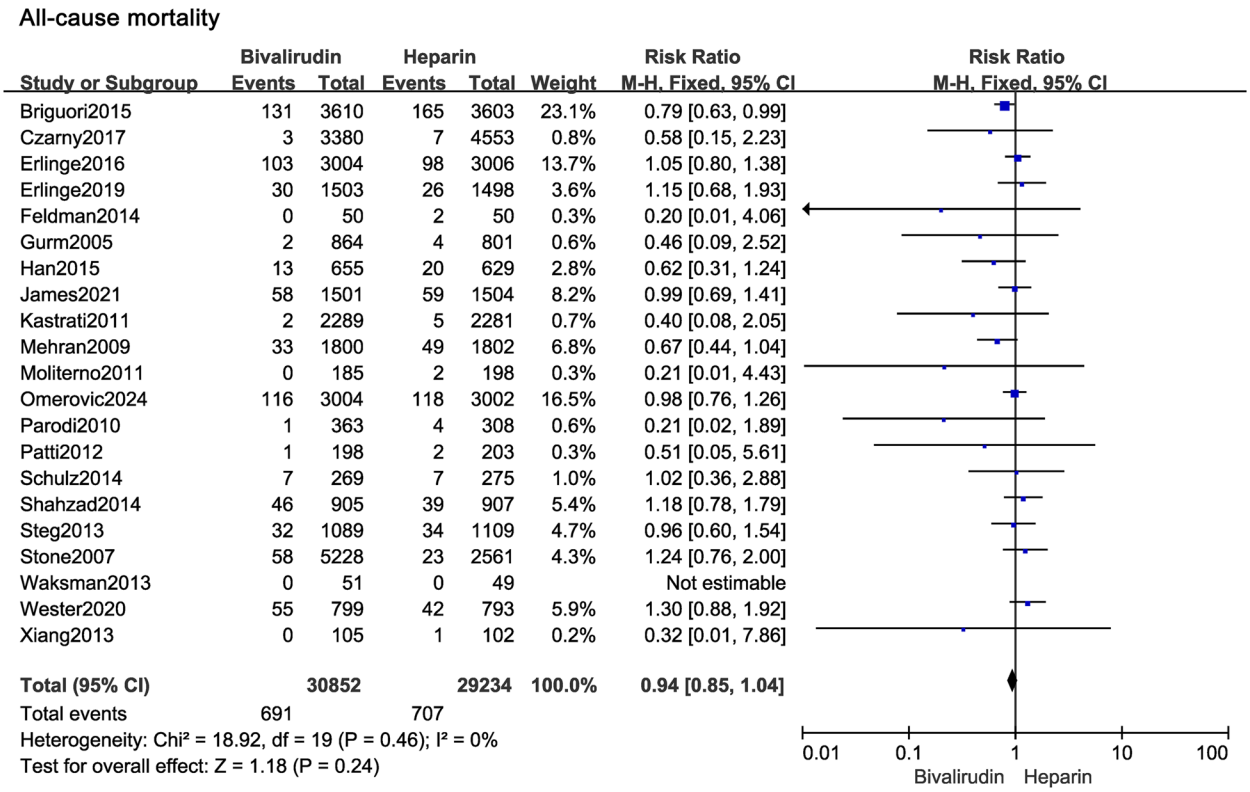

Fig. 2 The forest plot of the effect of bivalirudin and heparin on all-cause mortality in patients with ACS

Table 2 The incidence of all-cause mortality, major cardiovascular adverse events, recurrent myocardial infarction, stent thrombosis, short-term bleeding events, revascularization, and retransfusioncalculated by the Egger's method

	Std_Eff	Coef	Std. err	*t*	*p* >|t|	95% conf. interval	
All-cause mortality	Slope	6.7465	1.3173	5.12	0.023	3.8763	9.6167
	Bias	−4.037	1.3441	−3.07	0.169	−6.9012	−1.1734
Major cardiovascular adverse events	Slope	6.5584	1.4123	7.30	0.000	1.9903	3.8294
	Bias	1.0227	1.3917	2.42	0.134	0.1456	2.4913
Recurrent myocardial infarction	Slope	4.7574	1.6265	2.92	0.019	0.6229	8.4368
	Bias	−1.6139	1.8549	−0.87	0.456	−6.2366	2.5831
Stent thrombosis in 30 days	Slope	3.1175	0.3462	0.23	0.834	−19.1951	22.1624
	Bias	1.0227	0.4223	2.42	0.339	−16.8959	18.4912
Subacute stent thrombosis	Slope	8.2450	5.2901	1.56	0.363	−58.9723	75.4624
	Bias	−5.1163	4.2493	−1.20	0.441	−59.1098	48.8771
Acute stent thrombosis	Slope	4.5230	7.3765	0.61	0.602	−27.2157	36.2618
	Bias	−1.5006	5.0404	−0.30	0.794	−23.1880	20.1867
Short-term bleeding events	Slope	3.3284	0.7321	5.43	0.000	1.1564	4.4187
	Bias	0.2967	0.8822	0.38	0.819	−1.5423	2.3893
Revascularization	Slope	0.2545	4.0988	0.07	0.694	−12.7673	13.3211
	Bias	2.3470	4.0307	0.61	0.747	−10.3813	15.2735
Retransfusion	Slope	7.5548	2.9110	1.67	0.015	3.1010	12.0086
	Bias	−4.5410	2.7337	−2.86	0.062	−9.6001	0.5185

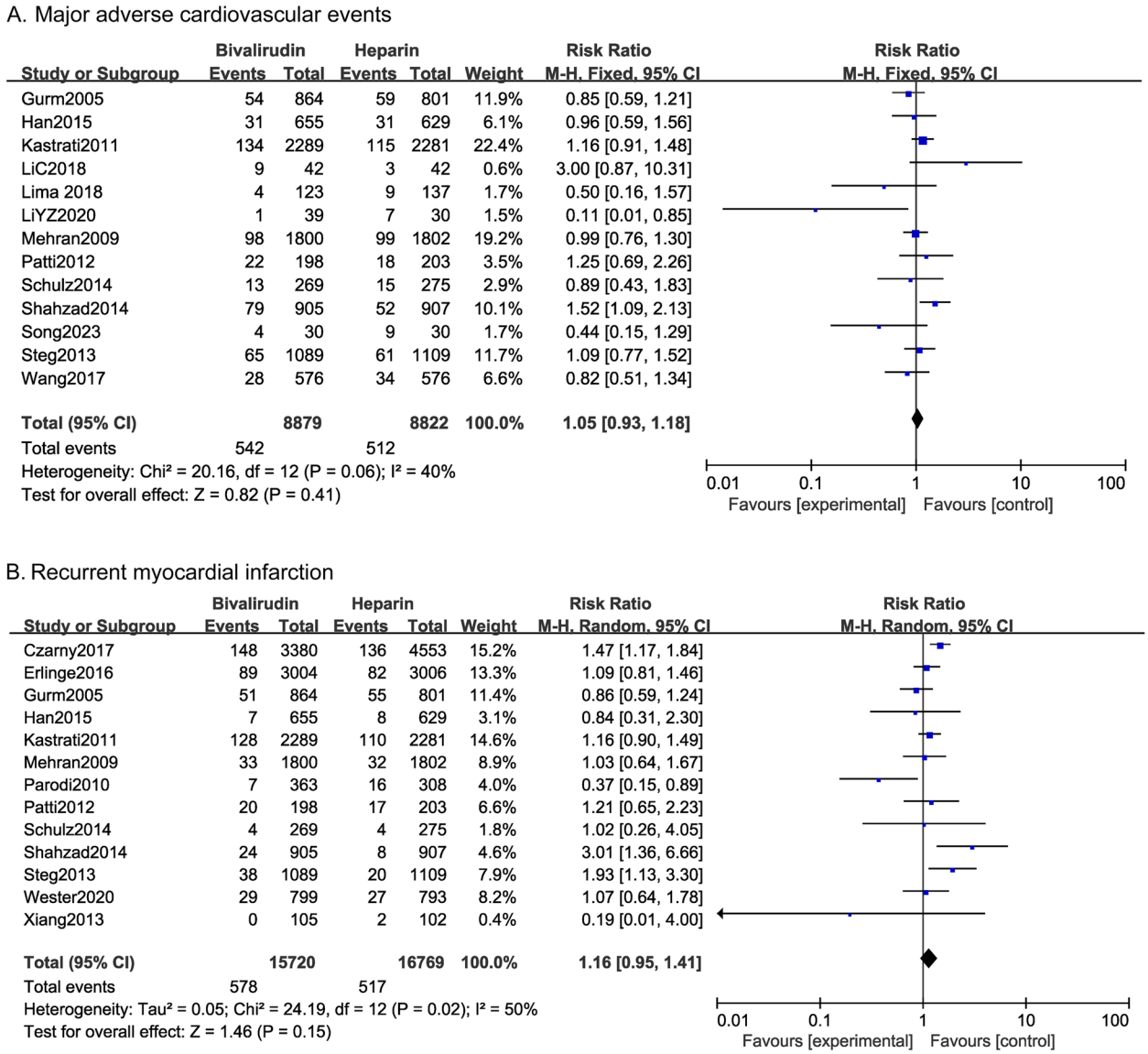

Fig. 3 The forest plot of the effect of bivalirudin and heparin on major adverse cardiovascular events and recurrent myocardial infarction in patients with ACS. **A** Major adverse cardiovascular events. **B** Recurrent myocardial infarction

Incidence of revascularization

Six studies reported the incidence of revascularization. A fixed effect model was used with moderate heterogeneity ($I^2=41\%$, $P=0.13$). The results showed that there was a statistically significant difference in the incidence of revascularization between the bivalirudin group and the heparin group [$RR=1.44$; 95% CI (1.10–1.89); $P=0.009$] (Fig. 6A). The Egger's linear regression test showed that there may be no publication bias ($t=0.61$, $P=0.747$, Table 2).

Incidence of retransfusion

A total of six studies reported the incidence of retransfusion. A random effect model was used with moderate heterogeneity ($I^2=63\%$, $P=0.02$). The results showed that there was a statistically significant difference in the incidence of retransfusion between the bivalirudin group and the heparin group [$RR=0.77$; 95% CI (0.66–0.90); $P=0.001$] (Fig. 6B). The Egger's linear regression test showed that there may be no publication bias ($t=-2.86$, $P=0.062$, Table 2).

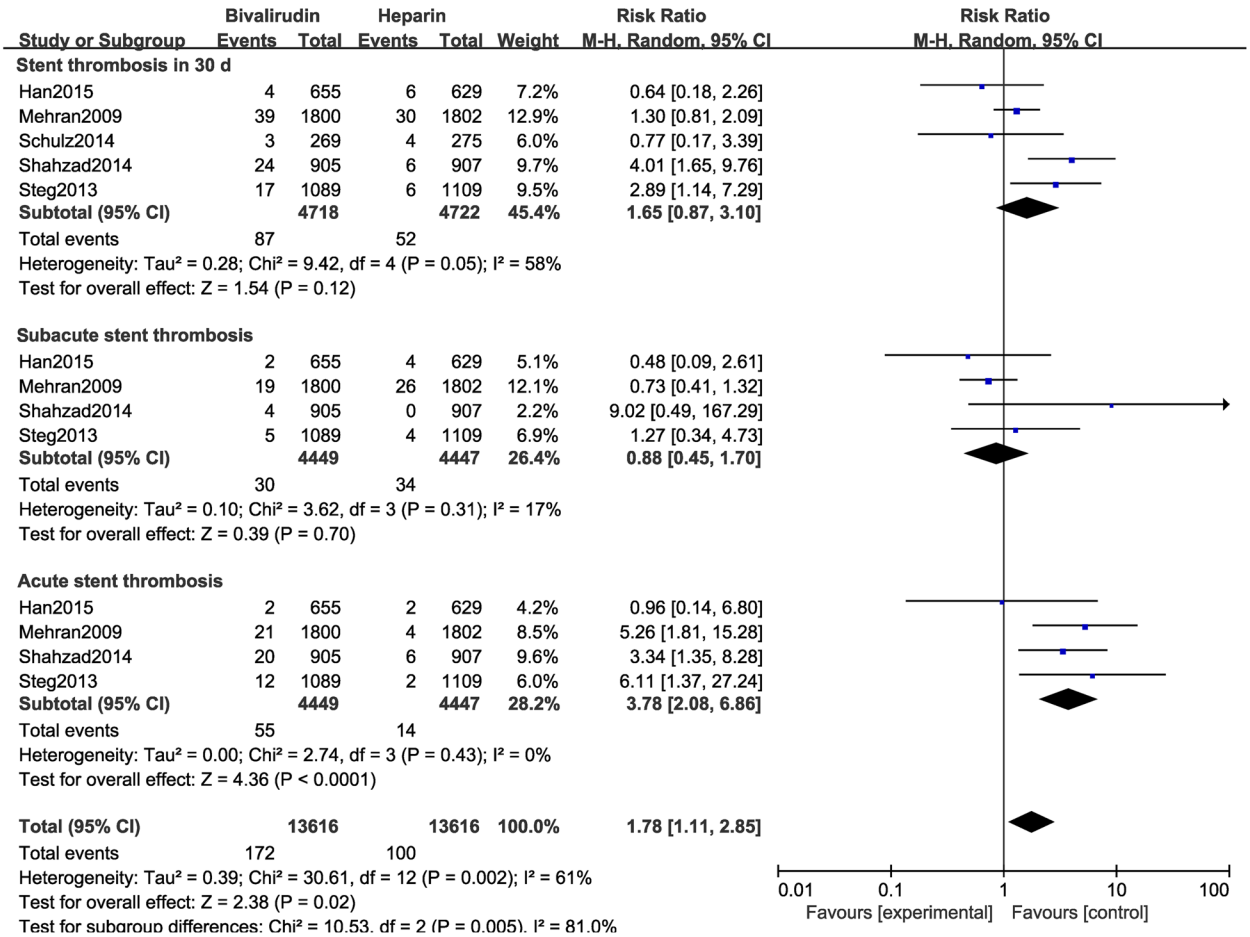

Fig. 4 The forest plot of the effect of bivalirudin and heparin on the incidence of stent thrombosis in patients with ACS

Sensitivity analysis

Because "incidence of short-term bleeding events" was the outcome measured with the largest number of included studies, sensitivity analysis was conducted using Stata 12.0 software. The results showed that the elimination of any study had no effect on the overall stability, and the results of all measures were not reversed, indicating that the results of the meta-analysis were robust and credible (Fig. 7).

Discussion

Patients with ACS undergoing PCI are at high risk of thrombosis, emphasizing the importance of selecting appropriate anticoagulants to mitigate such risks [45]. But at the same time, for patients with high bleeding risk, how to effectively take antithrombotics has become a difficult problem [46]. At present, PCI-related research emerges in an endless stream, and the selection of antithrombotic drugs in the perioperative period of PCI is still a research hotspot [47].

Bivalirudin is a new type of direct thrombin inhibitor. Its anticoagulant component is a hirudin derivative. The anticoagulant effect has the advantages of directness, specificity, and reversibility, and the anticoagulant effect is more sufficient [48]. In recent years, the clinical application of bivalirudin has become increasingly widespread, including percutaneous coronary angioplasty (PTCA), UA, ACS, myocardial infarction (MI), peripheral arterial interventional therapy, and anticoagulant therapy in major cardiac surgery and heart–lung transplantation [49].

According to the 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation [50], the 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation [51], and the 2021 ACC/AHA/SCAI Guideline for coronary artery revascularization [52], unfractionated heparin is primarily recommended as an anticoagulant for PCI. Bivalirudin may be considered as an alternative to unfractionated heparin. In patients with

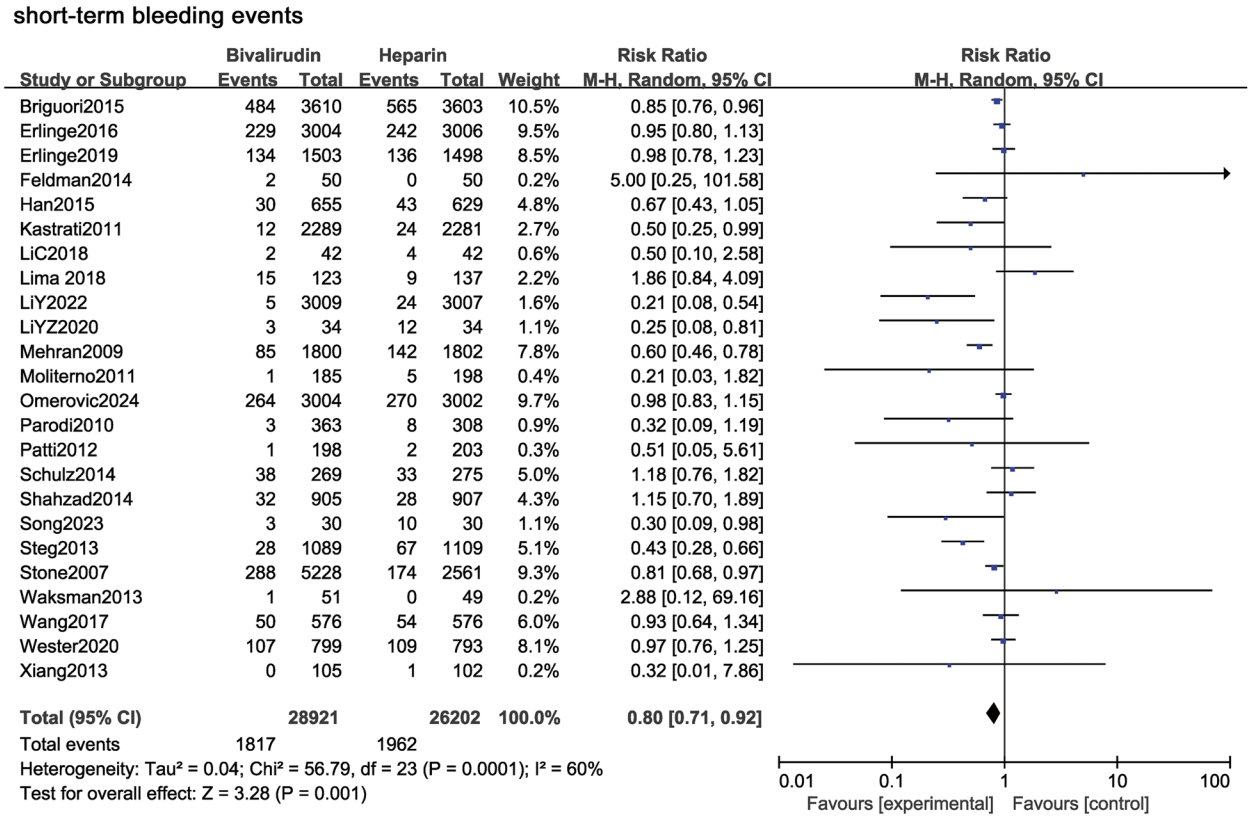

Fig. 5 The forest plots of the effect of bivalirudin and heparin on the incidence of short-term bleeding events

heparin-induced thrombocytopenia undergoing PCI, bivalirudin should be used to replace unfractionated heparin to avoid thrombotic complications.

It is undeniable that unfractionated heparin has the advantages of easy detection, convenient use, and low price, and it still plays a pivotal role in the anticoagulant treatment of PCI [53]. In recent years, with the advent of bivalirudin and compared with the various advantages of unfractionated heparin, people are still exploring the clinical evidence of its application in PCI [54, 55]. At present, it is not yet clear which of the two drugs can reap greater clinical benefits [56]. So, it is necessary to objectively and dialectically analyze the results of each study and seriously consider whether this study objectively reflects the true anticoagulant clinical benefits of two anticoagulants.

This meta-analysis systematically assessed the efficacy and safety of bivalirudin and heparin in emergency PCI for individuals with acute coronary syndrome. An exhaustive database search for randomized controlled trials, each with clear inclusion and exclusion criteria, was undertaken. Intention-to-treat analyses were appropriate for statistical analysis, effectively discounting any possibility of bias. However, some studies' baseline similarity analyses may have had a slight likelihood of potential bias. To ensure consistency with the overall conclusion, a sensitivity analysis was conducted, thereby considerably enhancing the conclusion's dependability and reliability.

In the present review, it was found that there was no statistically significant difference in the incidence of all-cause mortality, 30-day stent thrombosis, subacute (24 h to 30 days) stent thrombosis, MACEs, and recurrent myocardial infarction between the heparin group and the bivalirudin group during the follow-up period. The incidences of short-term bleeding and retransfusion in the bivalirudin group were significantly lower than those in the heparin group. It is noteworthy that the incidences of acute ($\leq$24 h) stent thrombosis and revascularization in the bivalirudin group were higher than those in the heparin group.

In this review, MACEs mainly manifested as nonfatal myocardial infarction, recurrent angina pectoris, in-stent restenosis, in-stent thrombosis, cardiac death, etc., including common MACEs after PCI with clinical symptoms. Some researchers [57] reported MACEs risk factors in the short term following PCI for acute myocardial infarction. The greater the platelet aggregation rate, the greater the risk of MACEs. Other scholars

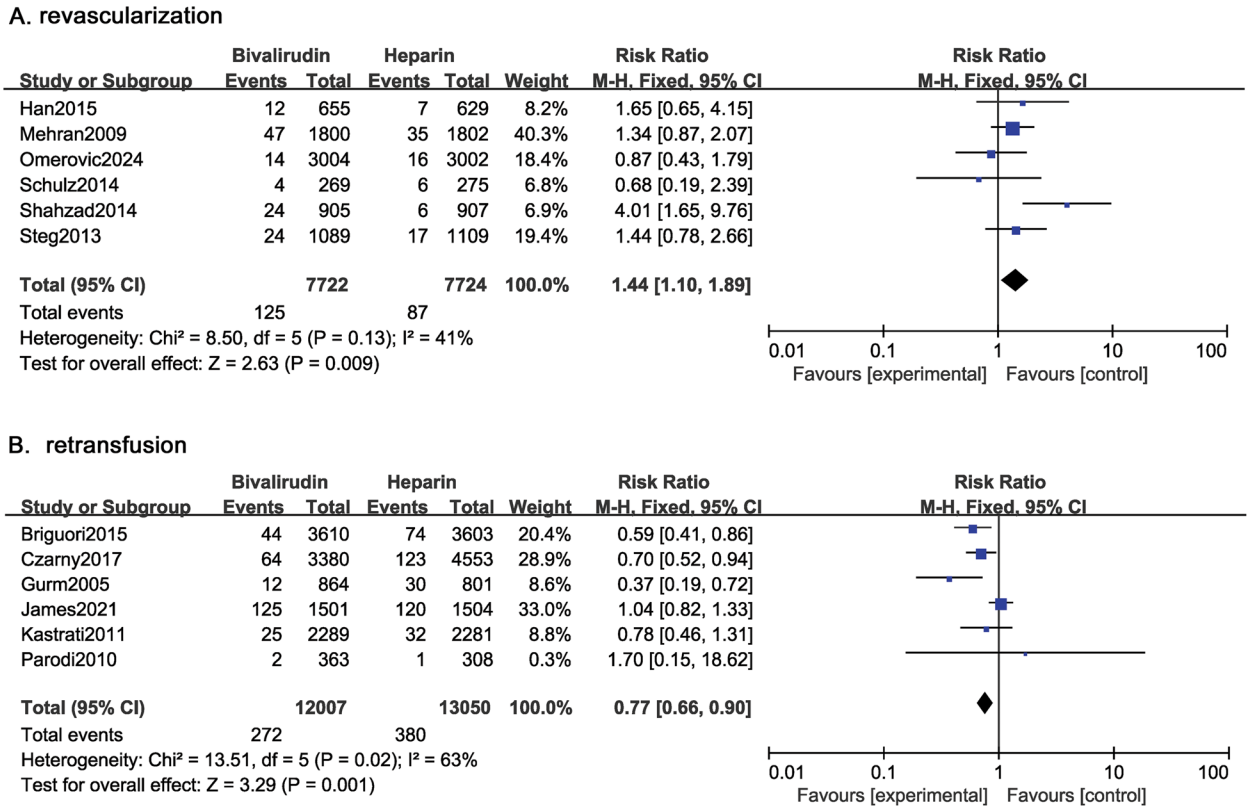

Fig. 6 The forest plots of the effect of bivalirudin and heparin on the incidence of revascularization and retransfusion in patients with ACS. **A** Revascularization. **B** Retransfusion

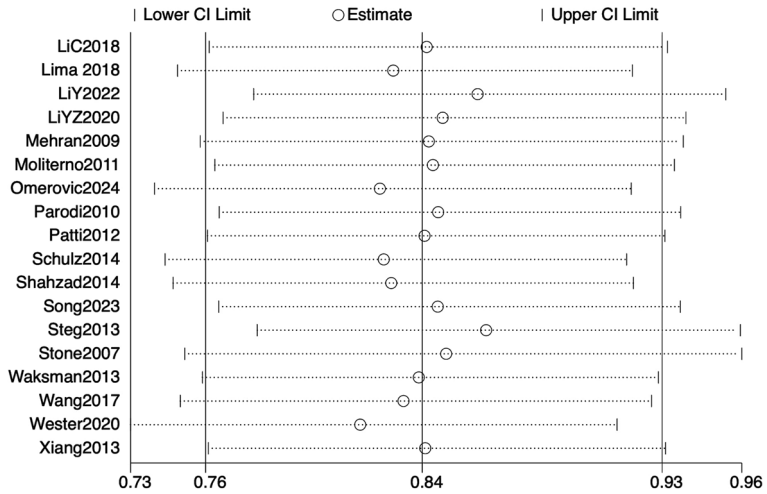

Fig. 7 The sensitivity analysis of included documents

[58, 59] found that in patients with ACS who underwent PCI, compared with unfractionated heparin, bivalirudin treatment could not reduce the incidence of MACEs and 30-day stent thrombosis, but bivalirudin could reduce short-term bleeding events and the incidence of retransfusion. The bivalirudin group demonstrated a significantly lower incidence of severe bleeding events and blood transfusion compared to the heparin group, and the higher incidence of severe bleeding events in the heparin group may be caused

by the application of high-dose heparin. This review shows that there is a significant difference in the incidence of ischemic complications between bivalirudin and high-dose heparin in the prevention of coronary revascularization, and the incidence of severe bleeding events in the bivalirudin group also has a downward trend. Thus, bivalirudin in transit was associated with a reduced risk of major bleeding events and an increased risk of acute stent thrombosis in patients undergoing PCI. Bivalirudin is comparable to heparin in preventing PCI ischemic events, but it has a better safety profile, a lower incidence of serious bleeding events, and can also reduce the incidence of thrombocytopenia.

Bivalirudin demonstrates certain advantages in reducing bleeding, which is a highly significant benefit for patients at high risk of bleeding. Studies have shown that the incidence of postoperative bleeding events in patients using bivalirudin is lower than that in the heparin group, which helps to reduce adverse consequences such as blood transfusion demand and prolonged hospital stay caused by bleeding [20, 60–62]. However, bivalirudin is associated with a higher risk of stent thrombosis. This risk has been confirmed in several studies [63, 64], which may be related to the mechanism of action of bivalirudin. It may disrupt the normal coagulation environment on the surface of the stent during the process of inhibiting coagulation, thereby increasing the likelihood of stent thrombosis. In clinical practice, this risk must be carefully balanced against the benefits of reduced bleeding. Future research should focus on determining the optimal dose of bivalirudin for patients with acute coronary syndrome undergoing PCI. The findings of this review align with guidelines from the ESC (European Society of Cardiology) [50] or AHA (American Heart Association) [65]. For instance, these guidelines emphasize the importance of weighing the risks of bleeding and thrombosis when selecting anticoagulant drugs, which is consistent with the risk–benefit analysis of this review comparing bivalirudin and heparin. Additionally, the guidelines highlight the varying responses of different patient groups to medications, which aligns with our emphasis on the need to explore the benefit subgroups of bivalirudin in future research.

There are some limitations in this review:

1) Only studies in Chinese and English languages were included, which may lead to retrieval bias.
2) There were variations in the doses of bivalirudin and heparin administered, with bivalirudin doses ranging from 0.75 to 1.0 mg/kg and heparin doses ranging from 50 to 100 IU/kg.
3) Subgroup analysis based on doses was not performed, and the evaluation of specific organ system safety was conducted.
4) Many of the studies incorporated into the research lacked precision in terms of detailed dose stratification.

Various factors, including dose-related ones, were intricately intertwined, and the subgroup sample sizes following grouping were potentially too small, increasing the risk of bias. Consequently, a subgroup analysis based on dose was not conducted, and future research will delve deeper into this aspect. Hence, future high-quality, large-scale randomized controlled trials are imperative to furnish additional evidence.

Conclusion

Bivalirudin can replace heparin for anticoagulant therapy in PCI, and it is safe and effective and has a good clinical application prospect in coronary interventional therapy. Due to the control of the quantity and quality of the included studies, this review needs to include more RCTs from different countries and regions, with a large sample size and high quality for further verification.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-025-02782-7.

Additional file 1. The PRISMA completed checklist.

Additional file 2. Supplementary Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for studies included in and excluded from the meta-analysis.

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None.

Authors' contributions
YZ was the main investigator, designed the study, and wrote the first draft. YL provided key information and contributed to writing process. NZ and JZ contributed to methodology and writing process. SW was the study advisor and critically reviewed the manuscript. HS supervised the study and contributed to the final manuscript. All authors read and approved the manuscript.

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Data availability
The datasets supporting the conclusions of this article are included within the article and its additional files.

Declarations

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Key Laboratory of Chinese Internal Medicine of Ministry of Education and Beijing, Dongzhimen Hospital, Beijing University of Chinese Medicine, Haiyuncang Lane 5, Dongcheng District, Beijing 100700, China. [2]Henan University of Chinese Medicine, No. 156 Jinshui Road, Zhengzhou, Henan 450046, China. [3]The First Affiliated Hospital of Henan University of Chinese Medicine, No. 19 Renmin Road, Zhengzhou, Henan 450000, China.

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