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ORIGINAL ARTICLE

A meta-analysis and cost-minimization analysis of bivalirudin versus heparin in high-risk patients for percutaneous coronary intervention

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Abstract

This meta-analysis was performed to compare the safety, efficacy, and pharmacoeconomic of bivalirudin versus heparin in high-risk patients for percutaneous coronary interventions (PCI). Earlier meta-analysis comparing bivalirudin and heparin during PCI demonstrated that bivalirudin caused less bleeding with more stent thrombosis. However, little data were available on the safety of bivalirudin versus heparin in high-risk patients for PCI. Thus, we performed a meta-analysis to evaluate the efficacy and safety in the "high-risk" patients. A systematic search of electronic databases was conducted up to July 30, 2020. The Cochrane Risk of Bias assessment tool was used to assess the quality of included studies. The primary outcomes were all-cause death and major adverse cardiac events (MACE); secondary outcomes were major and minor bleeding, followed by a cost-minimization analysis comparing bivalirudin and heparin using a local drug and medical costs reported in China. Subgroup analysis was based on the type of disease of the high-risk population. Finally, a total of 10 randomized controlled trials involved 42,699 patients were collected. The Cochrane Risk of Bias Tool was employed to appraise the research quality. No significant difference was noted between bivalirudin and heparin regarding all-cause death and MACE. However, subgroup analysis showed that bivalirudin caused less major bleeding in female (OR:0.65, 95% CI:0.53–0.79), diabetes (OR:0.55, 95%CI:0.42–0.73), and CKD (OR:0.59, 95%CI:0.63–1.65). The scatterers of the included literature were approximately symmetrical, and no research was outside the funnel plot. Additionally, cost-minimization analysis showed that heparin was likely to represent a cost-effective option compared with bivalirudin in China, with potential savings of 2129.53 Chinese Yuan (CNY) per patient for one PCI. Overall, the meta-analysis showed that although bivalirudin appeared to have a lower risk of major bleeding rate, the overall effectiveness and safety

Abbreviations: ACS, acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarctions; PCI, percutaneous coronary interventions; RCTs, randomized controlled trials.

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between the two groups showed no significant difference in high-risk patients for PCI. But the results of the cost-minimization analysis showed that heparin could be a potential cost-saving drug than bivalirudin in patients for PCI in China.

KEYWORDS
bivalirudin, economic evaluation, heparin, meta-analysis, PCI

What is already known about this subject

- Heparin and bivalirudin are currently the most commonly used antithrombotic agents in patients with the acute coronary syndrome (ACS).
- The meta-analysis and economic evaluation of high-risk patients for percutaneous coronary intervention (PCI) are still controversial.
- There is no economic evaluation of the Chinese population based on meta-analysis.

What this study adds

- This meta-analysis evaluated the safety and efficacy reported in randomized controlled trials (RCTs) on the use of bivalirudin versus heparin in high-risk patients for PCI.
- Heparin has better economic benefits than bivalirudin in Chinese patients for PCI.

1 | INTRODUCTION

Percutaneous coronary intervention (PCI) refers to recanalization of stenosed or occluded coronary arteries by cardiac catheterization to improve myocardial perfusion.[1] As compared with fibrinolytic therapy and medical treatment measures, PCI has substantially improved the prognosis of patients presenting with acute coronary syndrome (ACS).[2] Data show that the total number of PCI treatments for coronary heart disease in mainland China in 2018 was 915,256. Compared with 2017, it increased by 21.5%.[3] The early characteristics of ACS are the increased risk of thrombotic complications, emphasizing the need for fast, safe, and effective antithrombotic therapy, especially in patients undergoing PCI.[4,5] Patients for PCI are bound to receive antithrombotic therapy to prevent thromboembolic events.

Bivalirudin and heparin are the two adjunctive antithrombotic therapies used during primary PCI.[6] Heparin is currently the most commonly used antithrombotic agent in patients with ACS.[7] Bivalirudin is a direct intravenous thrombin inhibitor. ESC/EACTS guidelines recommend it as an alternative to heparin in patients with ACS, in particular non-ST-segment elevation myocardial infarctions (NSTEMI). Unfractionated heparin is traditionally regarded as the mainstay anticoagulant strategy in PCI. A study published by Steg et al.[8] indicated that bivalirudin was equally efficacious with less bleeding than heparin, despite its predilection for stent thrombosis. Although several meta-analyses[9–11] have been performed comparing the safety and efficiency of bivalirudin versus heparin, there are few studies for high-risk patients.

In this meta-analysis, women, patients with anemia, CKD, and diabetes were regarded as high-risk groups to explore the effectiveness and safety of bivalirudin and heparin. In the REPLACE-2 experiment, patients with diabetes, women, and CKD were considered as high-risk patients for subgroup analysis to observe the effectiveness and safety of bivalirudin and heparin. Chinese PCI interventional treatment guidelines point out that for some special ACS patients, those with diabetes and CKD, the risk of thrombosis or bleeding is relatively high. Antithrombotic drugs should be used to fully weigh their efficacy and safety. The American AHA/ACC guidelines also indicated that the characteristics of the diseases could affect the effectiveness of PCI, such as diabetes, CKD, anemia, and female patients. Reducing bleeding rates in patients with high-risk features can be clinically more relevant and have a higher impact on prognosis. For patients in high-risk, for example, compared with men, women undergoing PCI have a higher probability of suffering from comorbidities, such as hypertension and chronic kidney disease.[12,13] Patients with kidney dysfunction often have impaired coagulation and abnormal platelet function that increase the tendency of bleeding events when anticoagulants are used.[14] Therefore, the weighted risk versus benefit of the type of anticoagulation used is extremely important and deserves careful evaluation.

At present, bivalirudin is considered to have a similar effect as heparin in clinical application.[15] Several clinical studies have shown that bivalirudin has significant advantages in reducing perioperative complications, improving medical quality, and reducing medical cost. There have been some cost-effect clinical trials that compare the difference of economic evaluation.[16–18] One study in China based on a randomized, double-blind, multicenter phase III clinical trial, BRIGHT trial, showed that under the current economic conditions in China, bivalirudin is proved to have higher significant cost-effectiveness compared with heparin. It is recommended to use bivalirudin instead of heparin in ACS patients for PCI. Other studies draw a similar conclusion mostly that bivalirudin saves clinical cost. At this stage, China has gradually begun to further promote the use of bivalirudin in clinical treatment.[19]

To ensure the rational promotion of the clinical use of bivalirudin, more clinical staff, researchers, and payment policymakers are required to formulate relevant policies according to clinical evidence and health economics evidence.

Thus, the objectives of this meta-analysis were to (1) compare the efficacy and safety reported in randomized controlled trials (RCTs) on the use of bivalirudin versus heparin for high-risk patients for PCI; (2) use the meta-analysis result to compare the economic benefits in heparin and bivalirudin (from a healthcare system perspective) for patients planned for PCI in China.

2 | MATERIALS AND METHODS

This meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis[20,21]) statement for conducting systematic reviews and meta-analyses in health care interventions.

2.1 | Data sources and searches

Two reviewers (K.X. and B.C.) did a computerized literature search of PubMed, Cochrane Library, MEDLINE, Web of Science, EMBASE, Clinical Trials.gov. databases from inception until July 30, 2020, for relevant studies. Two researchers independently read the abstract and full text of the literature according to the specified inclusion and exclusion criteria and evaluated the quality of the literature and data extraction. If there is any disagreement, negotiated with the third researcher to resolve it. The following search terms were used: "bivalirudin," "Angiomax," "Hirulog," "percutaneous coronary intervention (PCI)," "acute coronary syndrome (ACS)," "ST-elevation myocardial infarction (STEMI)," "non-ST-elevation myocardial infarction (NSTEMI)," "unstable angina," "clinical trial," "women," "female," "sex," "gender," "diabetes mellitus," "anemia," "CAD," and "CKD." We searched all potentially eligible literature for review, a manual search of the bibliographies and related articles of all retrieved studies was also done to complete the search.

2.2 | Selection criteria

We searched for studies reporting data on the safety and efficacy in patients for PCI in the following specific subgroups of "high-risk" patients according to the AHA/ACC Guideline: female, anemia patients, diabetes patients, and chronic kidney disease.

Inclusion criteria were (a) RCTs including further analyses, (b) individuals with planned PCI were randomly assigned to two groups, one group was treated with bivalirudin and the other with heparin plus either routine or provisional GPI, (c) studies reporting clinical outcomes in both groups, d) a subgroup analysis of a certain high-risk population included in the RCT experiment.

Studies with any of the following conditions were excluded: (a) lack of data for detailed analysis results; (b) reviews, editors, observational studies, and small sample trials ($n < 50$).

2.3 | Data extraction and quality assessment

The following data from each study were extracted by two independent authors: baseline characteristics of study patients, countries, interventions, diseases, drug dose, mean age, and outcomes. The quality evaluation and risk of bias of each RCT study were separately assessed by two reviewers with application of Cochrane Collaboration's risk of bias assessment tool. The evaluation contents mainly included: (1) generation of random sequence (selection bias); (2) concealment of distribution sequence (selection bias); (3) blind method for research object and implementer (implementation bias); (4) blind method for result evaluation (measurement bias); (5) incomplete result (loss of follow-up bias); (6) selective report (report bias); (7) other bias. The quality analyses were performed with Review Manager software (RevMan Version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

2.4 | Outcome measures

The primary endpoints were all-cause mortality and MACE. MACE rate included myocardial reinfarction and stroke and thrombosis rate. Secondary outcomes included major bleeding rate and minor bleeding rate. Major bleeding was defined as Bleeding Academic Research Consortium (BARC) type 3 or 5. The minor bleeding rate was defined as BARC type 1 or 2. According to the definition of the World Health Organization (WHO), the baseline hemoglobin value of anemia males is <130 g/L, and of females <120 g/L.

2.5 | Statistical analysis

The data were calculated by random-effects models and expressed as odds ratios (ORs) and 95% confidence intervals (CI). Heterogeneity across trials was evaluated using the Cochran Q test and the Higgins I^2 test. $I^2 < 25\%$ was considered low heterogeneity, and $I^2 > 75\%$ high between studies. Publication bias was assessed using a funnel plot and the Egger test. All statistical analyses were made by using STATA statistical software version 12.0 (Stata Corp).

2.6 | Cost analysis

According to the results of the meta-analysis, the appropriate economic evaluation method was selected. If there was no significant difference in the efficacy and safety of bivalirudin and heparin, the "cost-minimization analysis" is selected to analyze the economy of the two schemes; if there was a significant difference in the efficacy

or safety of the two drugs, the "cost-effectiveness analysis" is selected to compare the economy of the two schemes.

This study only focused on the direct medical cost. Assuming that the source, basic information, and main symptoms of patients were similar in baseline characteristics. The inspection costs and registration costs generated during the treatment process were the same, so the cost of this study only included the drug cost. The drug price data were from the average bid winning price of domestic drugs published on the MENET (www.menet.com) in 2019. As heparin was commonly used in combination with tirofiban in clinical trials, therefore, the cost of tirofiban was included in the cost of the heparin group in the economic evaluation. The specifications, unit prices, and average daily clinical dosage for commonly used heparin and bivalirudin were collected. The winning bid price of the drug in China was used as the estimated cost to compare the cost difference between the two groups. The cost of tirofiban was included in the heparin group.

3 | RESULTS

Subsequently, 2380 related articles were searched, and 10 RCTs satisfied our predefined inclusion criteria after screening (Figure 1). Table 1 detailed the primary features of the included trials. Outcomes of the included studies were given in Table 2. In detail, we identified seven studies[4,17,19–23] stratifying bleeding according to gender (898 female use bivalirudin vs. 1086 use heparin), three studies[4,19,22] in which stratification was made according to anemia (1251/1243), five studies[16,19,21,22,24] stratifying according to diabetes (2657/2585), and five studies[16–19,21] stratifying according to chronic kidney diseases (1745/1888).

3.1 | Female patients

As shown in Figure 2, women receiving bivalirudin during PCI demonstrated reduced risk of major bleeding (OR = 0.65; 95%CI: 0.53–0.79; p = .73; I^2 = 0.0%) compared with those receiving heparin. There was no difference in the risk of MACE (OR = 0.81; 95%CI: 0.63–1.04; p = .59; I^2 = 0.0%), all-cause mortality (OR = 0.90; 95%CI: 0.57–1.43; p = .06; I^2 = 56.8%), minor bleeding (OR = 0.67; 95%CI: 0.43–1.06; p = .22; I^2 = 34.5%) between both groups.

3.2 | Anemia patients

No significant results were obtained overall and in the analysis of all-cause death (OR 1.61; 95%CI: 0.92–2.83; p = .13; I^2 = 51.5%) and major bleeding (OR = 0.82; 95%CI: 0.58–1.16; p = .23; I^2 = 31.8%) as shown in Figure 3.

3.3 | Diabetes patients

In the overall analysis, no significant difference was detected between the risk of death in the bivalirudin and heparin group (OR = 0.76; 95%CI: 0.55–1.04; p = .68; I^2 = 0.0) as shown in Figure 4. On a pooled analysis, major bleeding was significantly lower in the

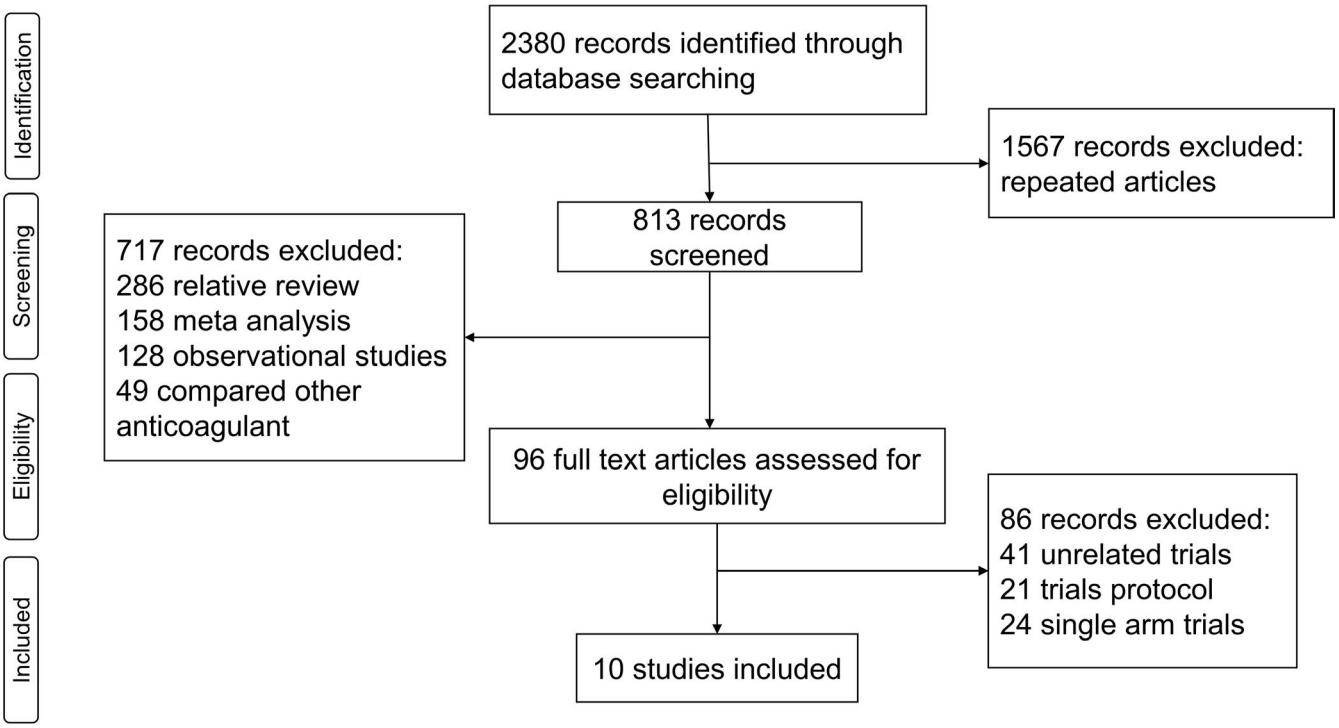


FIGURE 1 Flow chart showing the progress through the stages of the meta-analysis

TABLE 1 Characteristics of the included studies

Study	Country	Follow-up	Diseases	Dose		BIV (n)	UFH (n)	Mean age	
				UFH	BIV			BIV	UFH
ACUITY[25]	17 countries	1 year	ACS	60 U/kg	1.75 mg/kg	4612	4603	62.5	62.7
BRIGHT[26]	China	30 days	ACS	100 U/kg	0.75 mg/kg; 1.75 mg/kg/h at least 30 min	735	729	57.3	58.1
EUROMAX[27]	9 countries	30 days	STEMI	100 U/kg	0.75 mg/kg; 1.75 mg/kg/h at least 30 min	1089	1109	61	62
HORIZON-AMI[28]	11 countries	30 days	STEMI	60 U/kg	0.75 mg/kg; 1.75 mg/kg/h at least 30 min	1800	1802	62.3 ± 10.1	62.4 ± 9.6
ISAR-REACT[29]	Germany	1 year	ACS	140 U/kg	0.75 mg/kg; 1.75 mg/kg/h at least 30 min	2289	2281	67.5	67.5
MATRIX[30]	4 countries	1 year	ACS	50–70 U/kg	0.75 mg/kg; 1.75 mg/kg/h at least 30 min	3610	3603	65.4	65.4
NAPLES[31]	Italy	30 days	ACS	70 U/kg	0.75 mg/kg; 1.75 mg/kg/h at least 30 min	418	419	78	78
REPLACE[32]	USA	1 year	ACS	70 U/kg	0.75 mg/kg; 1.75 mg/kg/h at least 30 min	532	524	64.3	64.4
VALIDATE SWEDEHEART[7]	Sweden	30 days	ACS	70–100 U/kg	0.75 mg/kg; 1.75 mg/kg/h at least 30 min	3004	3002	68	68
Wester[33]	Sweden	180 days	MI	70–100 U/kg	0.75 mg/kg; 1.75 mg/kg/h at least 30 min	799	793	80±4.3	81±4.44

Abbreviations: ACS, acute coronary syndrome; BIV, Bivalirudin; MI, myocardial Infarction; NA, not available; STEMI, ST-segment elevation myocardial infarction; UFH, heparin.

TABLE 2 High-risk groups of the included studies

Study	Chronic kidney disease	Anemia	Male sex	Diabetes
ACUITY	819/826	N/A	3195/3249	1287/1298
BRIGHT	66/155	43/29	608/595	168/137
EUROMAX	147/165	129/148	814/961	127/169
HORIZON-AMI	262/292	175/181	1388/1372	281/312
ISAR-REACT	N/A	N/A	1744/1751	618/636
MATRIX	146/147	N/A	2731/2764	824/793
NAPLES	N/A	227/231	208/233	189/181
REPLACE	452/468	N/A	2236/2229	840/784
VALIDATE SWEDEHEART	N/A	N/A	2229/2177	491/508
Wester	N/A	203/181	495/456	N/A

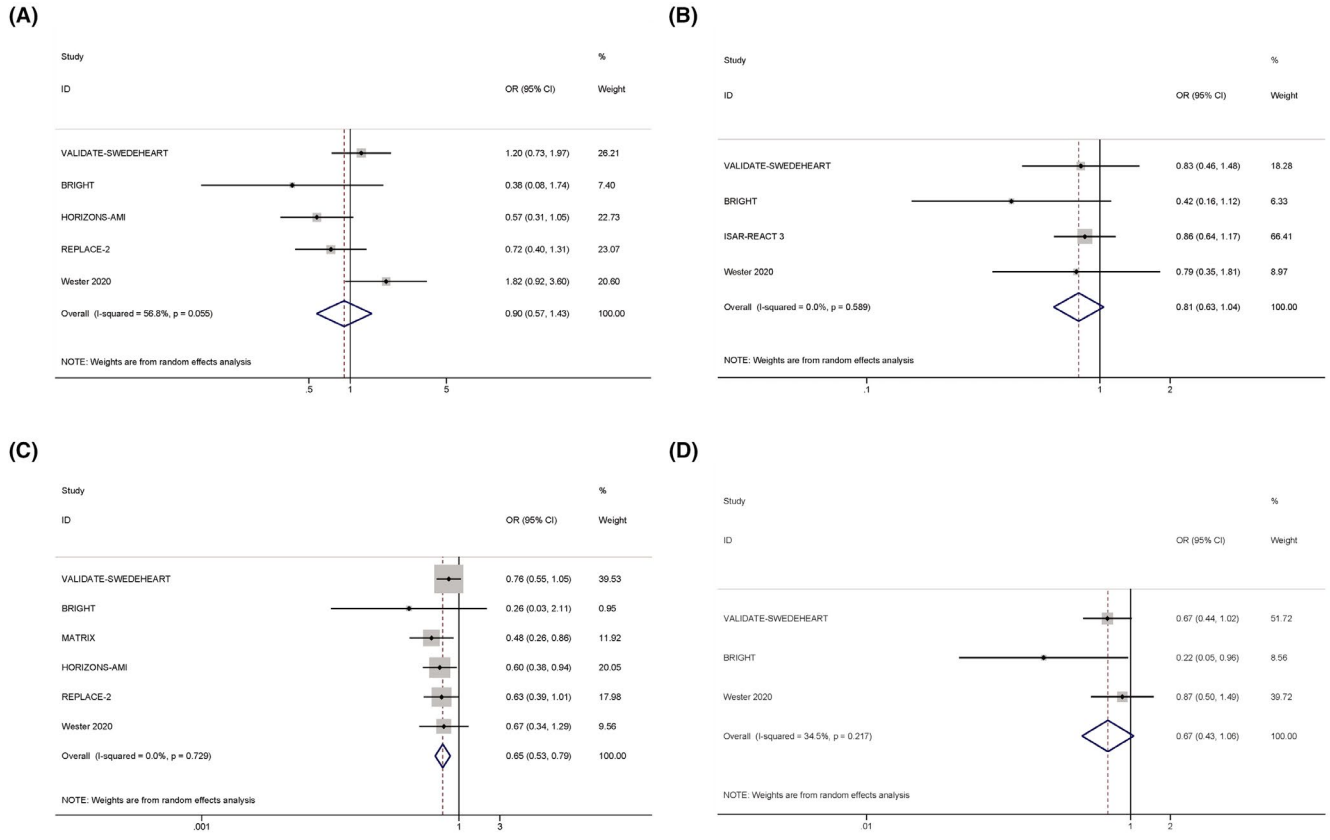


FIGURE 2 Forest plots of the all-cause death (A), MACE (B), major bleeding, (C) minor bleeding, (D) stratified according to gender

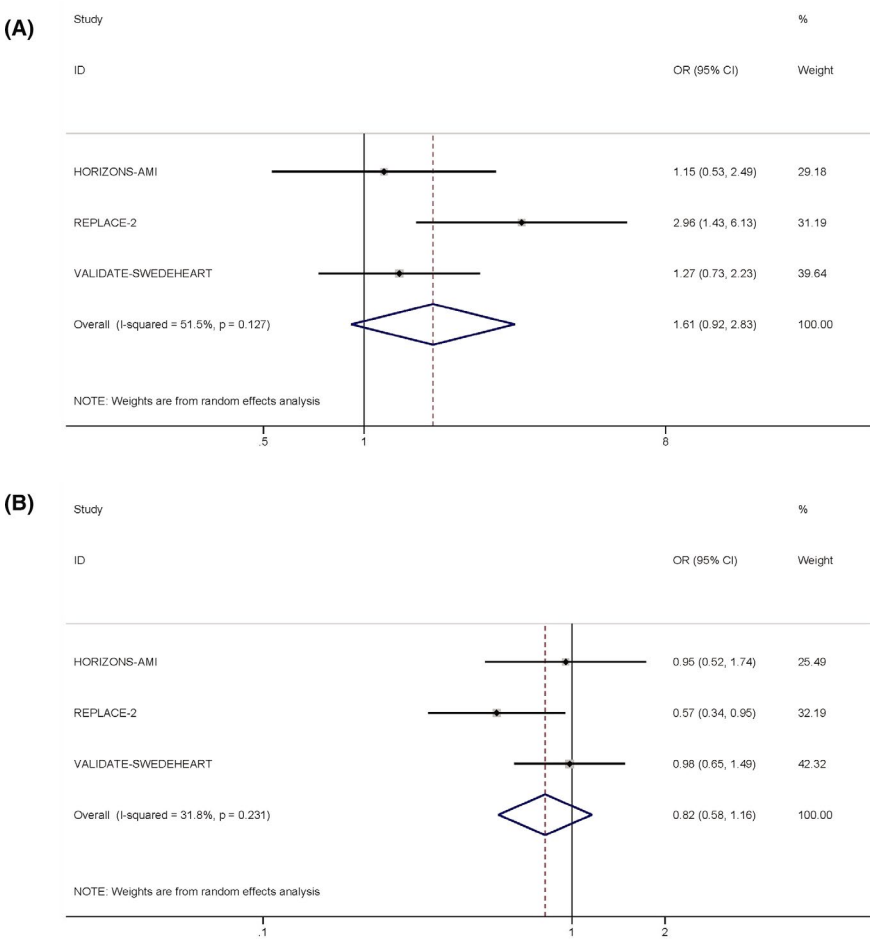
bivalirudin group compared with the heparin group (OR = 0.55, 95%CI: 0.42–0.73; p = .54, I^2 = 0.0). There was no statistically significant difference between the two groups with respect to MACE (OR = 0.85; 95%CI: 0.71–1.01; p = .40, I^2 = 13%).

3.4 | Chronic kidney disease

Pooled results failed to show statistically significant differences between MACE treated with bivalirudin and heparin (OR = 1.04; 95%CI: 0.63–1.05; I^2 = 48.1%; p = .15), as shown in Figure 5. Major bleeding was significantly lower in bivalirudin group compared with heparin group (OR = 0.59, 95%CI 0.45–0.78; p = .84, I^2 = 0.0).

3.5 | Quality accesses and publication bias

The results of 10 RCT studies were analyzed by the Cochrane evaluation system as shown in Figure 6. In six studies stratifying



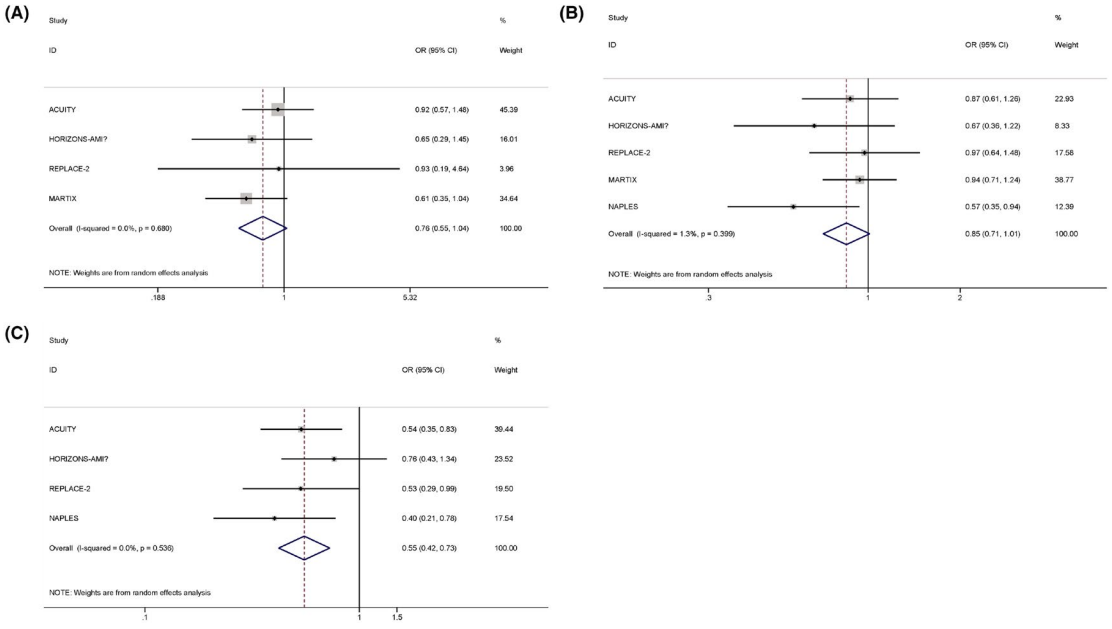


FIGURE 3 Forest plots of the all-cause death (A) and major bleeding (B) stratified according to anemia

FIGURE 4 Forest plots of the all-cause death (A), MACE (B), major bleeding (C) stratified according to diabetes

episodes according to gender reported mortality, a funnel plot was used to assess publication bias. Figure 7 showed that the scatterers of the included literature were approximately symmetrical, and no research was outside the funnel plot. There was a certain bias, but combined with I^2 < 50%, the publication bias was not considered.

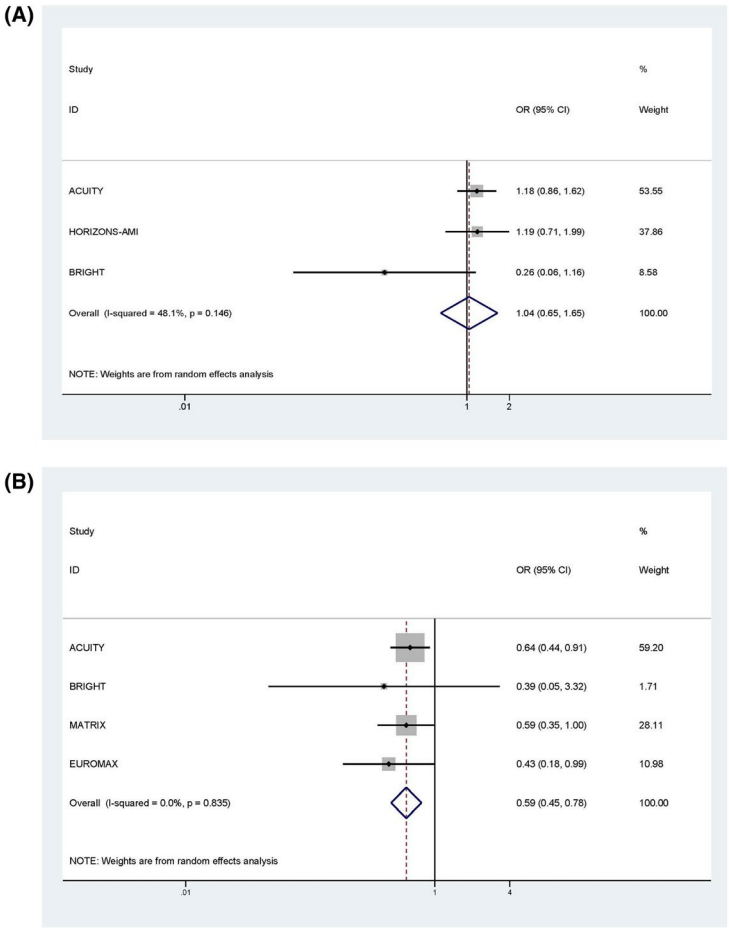


FIGURE 5 Forest plots of the MACE (A) and major bleeding (B) stratified according to CKD

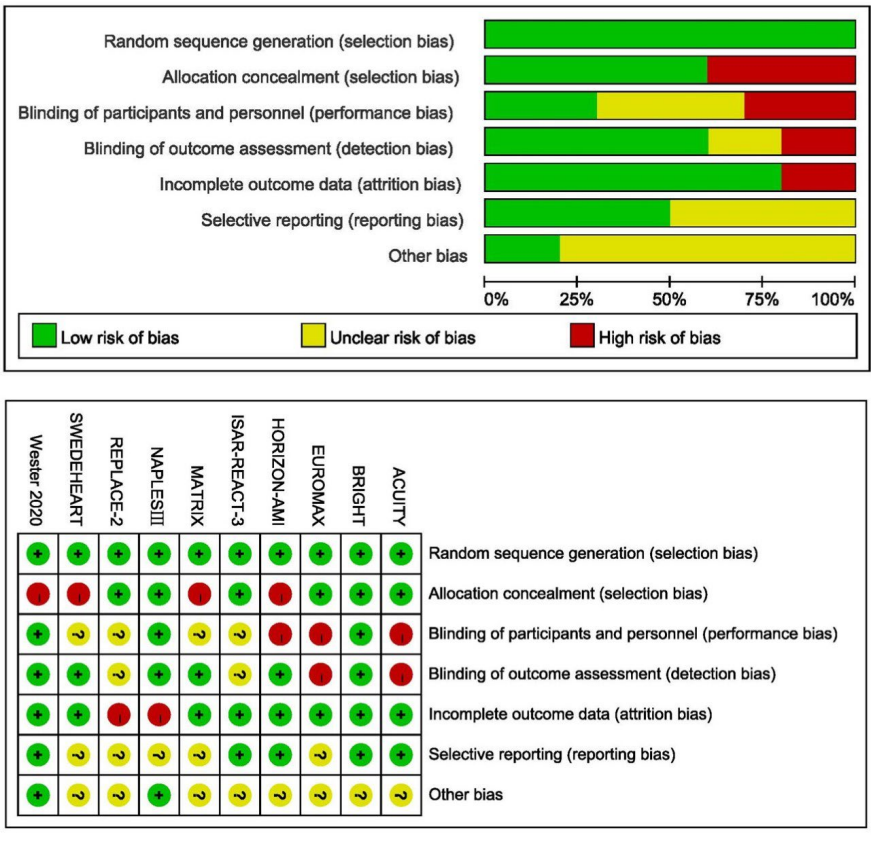


FIGURE 6 Quality accesses of bias of the included studies

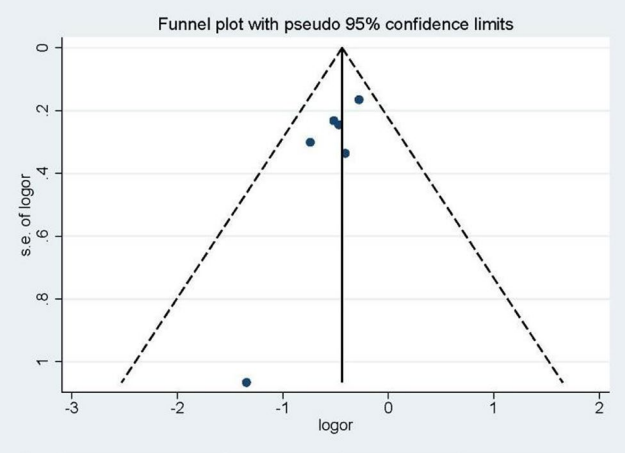


FIGURE 7 Funnel plot of the mortality stratified according to gender

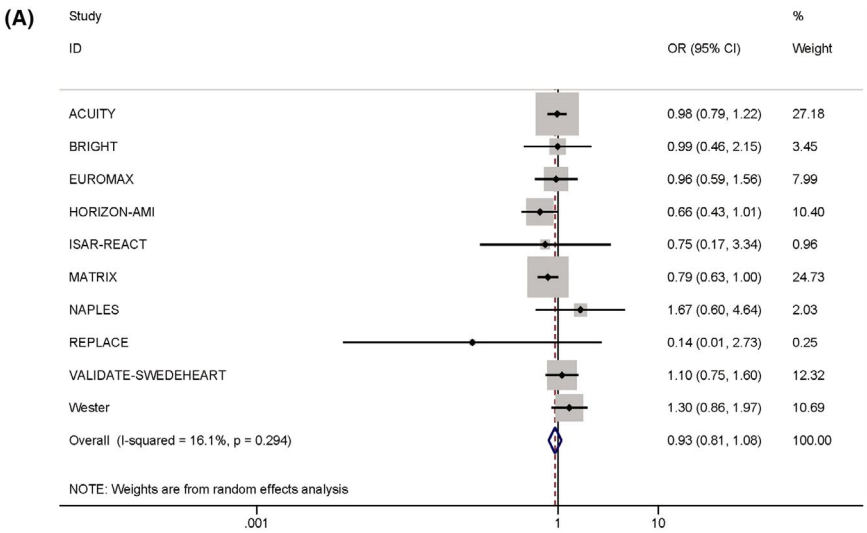
3.6 | Cost analysis

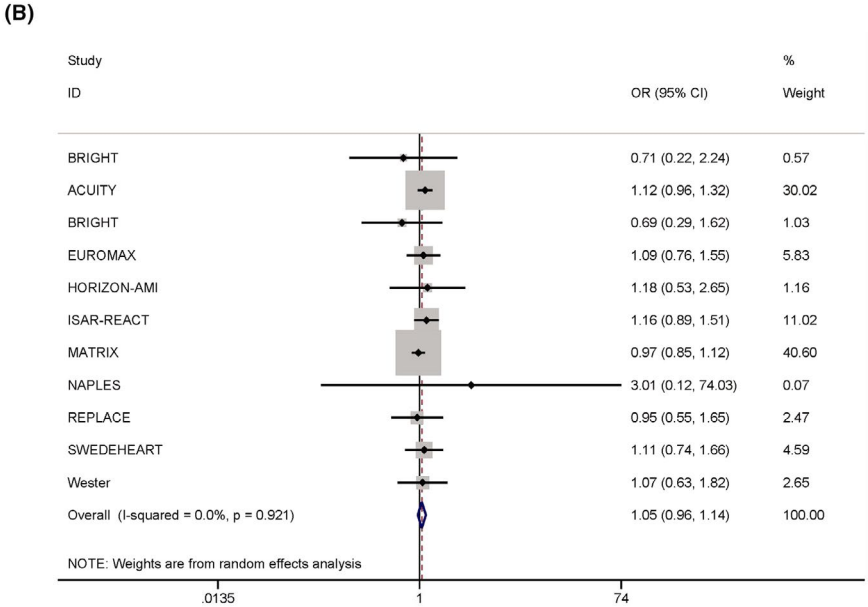
According to the comprehensive evaluation of 10 included RCTs, there was no significant difference between the mortality and MACE of bivalirudin and heparin in high-risk groups. The forest plots were shown in Figure 8. The cost difference results between the two groups in China was presented in Table 3.

TABLE 3 Drug cost information and cost-minimization analysis

Data input	BIV	UFH + Tirofiban
Specifications	25 g	2 ml
Weight average daily dosage	75 U/kg	0.75 mg/kg;1.75 mg/kg/h at least 30 min
Total cost	2613.59	484.06
Cost difference	2129.53	

FIGURE 8 Forest plots for the death (A) and MACE (B) of all including trial





The sensitivity results for drugs and adverse reactions showed that the minimum cost analysis results of bivalirudin and heparin did not change when the price was within the range of changes. The sensitivity analysis results, as given in Table 4, were consistent with the cost-benefit analysis results, indicating that the pharmacoeconomic analysis of this study is stable and reliable.

4 | DISCUSSION

To the best of our knowledge, this is the first meta-analysis focusing on high-risk patients for PCI to compare the efficacy and safety of bivalirudin versus heparin. Using high information from 10 RCTs, we provided, for the first time, high-quality data including 1984 women, 2494 anemia patients, 5242 diabetes patients, and 3633 CKD patients on the relative risk of bleeding events in these specific subgroups of patients receiving PCI. In this study, we found that bivalirudin is associated with a lower risk of major bleeding more significantly compared with heparin in high-risk patients.

Our results indicated that among female high-risk patients, bivalirudin was associated with reduced risk of major bleeding and no difference in MACE, death, and minor bleeding. Prior studies of female patients have shown conflicting results: one clinical trial showed that female patients in the bivalirudin group had a lower MACE rate and significantly lower incidences of bleeding rate.[24] Vivian found that bivalirudin had similar safety benefits in reducing bleeding complications of men and women (HR: 0.53 vs. 0.56).[22] Differences in the definition of major bleeding and MACE used in these studies may contribute to these considerable variations. Alternatively, they may reflect the heterogeneity inevitably in the populations studied. A study published by Hamon et al. has suggested that statins may influence as an independent protective factor in the treatment of female patients with early PCI.[23,34] Despite this, the proportion of women in large-scale randomized trials is still insufficient and requires further investigation using large-sample, randomized trials.

The NAPLES trial showed that the influence of bivalirudin on MI and major bleeding in DM patients for elective PCI is similar to that of heparin. The MARTIX trial and the latest published meta-analysis by Juan[35] indicated that bivalirudin use was associated with a lower risk of death and major bleeding. A meta-analysis published in 2015 by Nairooz et al.[36] reported that the application of bivalirudin significantly lower levels of major bleeding and mortality compared with that resulting from heparin and GPI use in diabetes patients for PCI.

This systematic study confirmed that compared with the combination treatment of the heparin group, CKD patients receiving bivalirudin treatment were associated with a 41% relative risk reduction of major bleeding. There was one meta-analysis published that assesses CKD patients; this study extends previous studies and includes more recent trials. Several factors might explain the safety benefits of bivalirudin: (1) In patients with CKD, the elimination half-life of bivalirudin is prolonged from 25 min to 3.5 h.[37] (2) In PCI patients receiving heparin, chronic kidney disease is associated with a prolonged period of severe, continuously activated partial thromboplastin.[38]

There was no significant difference in all-cause death and major bleeding between bivalirudin and heparin in patients with anemia. Nearly 25% of patients who underwent elective PCI and 40% of patients who underwent PCI due to acute myocardial infarction have been proved to have baseline anemia.[39] Anemia is a common disease in PCI patients and is associated with significant increases in post-procedural death rate, reinfarction, and bleeding.[40] The prognostic importance of anemia in relation to bleeding events among patients treated exclusively with bivalirudin versus heparin has not been studied. HORIZONS-AMI trial in anemia patients indicated that bivalirudin compared with unfractionated heparin resulted in two-fold lower rates of all-cause death and cardiac mortality, and major bleeding in patients without baseline anemia. McKechnie et al.[41] found that anemic patients who had greater major bleeding were not statistically different between bivalirudin and heparin groups. This may be because patients with baseline anemia are more likely to discontinue antithrombotic medications if they suffer a major bleed due to the perceived risks of extremely low hemoglobin levels in patients with coronary artery disease.

Cost minimization analysis showed that heparin might act as a cost-saving alternative to bivalirudin in the local Chinese setting, and further potential savings in the maintenance phase. Most of the related studies abroad have investigated the pharmacoeconomic evaluation, and most of the data are from the long-term and open-ended data of RCTs that used the cost-effectiveness method. The possible reason may be that (1) we use a different evaluation perspective. (2) There exist unadjusted baseline differences between the two cohorts. (3) The use of GPI and other drugs in the treatment of

TABLE 4 Probability of adverse events and sensitivity analysis of pharmacoeconomic

	BIV		UFH		Cost (CNY)
	Mean	Range	Mean	Range	
Drug costs	34.13	7.33–155.62	2613.59	2198–3225	148586
Major bleeding	4.14%	0.17–8.76%	4.41%	0.52–9.08%	83744
Minor bleeding	3.56%	0.17–9.17%	3.50%	0.17–10.8%	5204
MI	3.82%	0.24–12.8%	3.24%	0.00–13.16%	29200
Stroke	0.87%	0.52–1.06%	0.80%	0.49%–1.04%	30438
Difference	148593.33–148741.62		150784–151811		

heparin may influence economic analysis. After all, GPI increases the cost of traditional heparin anticoagulant therapy, while bivalirudin can usually be used alone. In this study, only one RCT experiment was conducted in China. Due to differences in human populations, different populations have deviations in life span or drug tolerance. In this study, no further corrections were made for these related parameters, which may have a certain degree of influence on the final analysis results. The cost parameters involved in this study were all taken from relevant data in China, and the research perspective was the whole Chinese society. Therefore, the results of this study can only be applied to clinical medication and health decision-making in China.

Although bivalirudin appeared to have a lower risk of major bleeding rate, the overall effectiveness and safety between the two groups showed no significant difference. Despite the usefulness of this study, there are still limitations. In our study, bivalirudin was associated with a reduction in the risk of major bleeding but not decreased rates of death or MACE in diabetes patients. Clinical and methodological differences common to systematic reviews led to inevitable heterogeneity. The follow-up time of most studies was less than 2 years, and the long-term efficacy and safety cannot be observed. This may affect the conclusion to a certain extent, and further subgroup analysis is needed to determine it. Among these were the supplied drugs and administration protocols, procedural techniques, the severity of coagulation and embolism, facility expertise, and patient baseline characteristics. Firstly, the dosage and type of heparin were slightly different in these included clinical trials such as some patients were given enoxaparin and others were given unfractionated heparin. Secondly, individual patient-level data were difficult to achieve, so that it is hard to further analyze the potential limitations. Finally, our cost data were retrieved from published literature which usually needs further confirmation by chart reviews, clinical trials, or real-world studies. These discrepancies might have been caused by the different including criteria in our meta-analysis. Subgroup analysis should also be performed to verify the final results for patients with or without insulin therapy.

5 | CONCLUSION

This study suggests that bivalirudin in high-risk patients is associated with a significant reduction of major bleeding compared with heparin and may be a preferred substitute for heparin plus GPIs in high-risk patients. But heparin could be a potential cost-saving drug than bivalirudin in patients for PCI in China.

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DISCLOSURE

There are no competing interests to declare.

AUTHOR CONTRIBUTIONS

K.X. and Y.D. conceived the study; S.S., F.Y., and Y.D. contributed toward the intellectual conception of the review; K.X. and B.C. extracted and analyzed the data; K.X., B.C., and Y.D. wrote the first draft of the paper; W.J., J.W., and Y.D. revised the manuscript; F.Y. and J.W. supervised the study and contributed to writing the paper.

ETHICAL APPROVAL STATEMENT

Ethics approval was not required for this research.

DATA AVAILABILITY STATEMENT

Data were derived from public domain resources. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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