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

Ke-Xin Sun1,2 | Bin Cui1,2 | Shan-Shan Cao1 | Wen-Jun Wang1,3 | Feng Yu2 | Jing-Wen Wang1 | Yi Ding1

1Department of Pharmacy, Xijing Hospital, Fourth Military Medical University, Xi'an, China
2School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, Nanjing, Jiangsu, China
3Department of Pharmacy, Shaanxi University of Chinese Medicine, Xi'an, China

Correspondence
Feng Yu, School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, Jiangsu, Nanjing 211198, China.
Email: yufengcpu@163.com

Yi Ding and Jing-Wen Wang, Department of Pharmacy, Xijing Hospital, Fourth Military Medical University, Xi'an 710032, China.
Email: dingyi007@163.com and wangjingwen8021@163.com

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
INTRODUCTION

Percutaneous coronary intervention (PCI) refers to recanalization of stenosed or occluded coronary arteries by cardiac catheterization to improve myocardial perfusion. As compared with fibrinolytic therapy and medical treatment measures, PCI has substantially improved the prognosis of patients presenting with acute coronary syndrome (ACS). 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%. 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. 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. Heparin is currently the most commonly used antithrombotic agent in patients with ACS. 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. indicated that bivalirudin was equally efficacious with less bleeding than heparin, despite its predilection for stent thrombosis. Although several meta-analyses 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. Patients with kidney dysfunction often have impaired coagulation and abnormal platelet function that increase the tendency of bleeding events when anticoagulants are used. 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. 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. 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.
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\textsuperscript{20,21}) statement for conducting systematic reviews and meta-analyses in healthcare 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 stratifying bleeding according to gender (898 female use bivalirudin vs. 1086 use heparin), three studies in which stratification was made according to anemia (1251/1243), five studies stratifying according to diabetes (2657/2585), and five studies 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; \( p = .66; \ i^2 = 56.8\%\)), 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](image-url)
**TABLE 1** Characteristics of the included studies

| Study         | Country     | Follow-up | Diseases | Dose UFH | BIV Dose | BIV (n) | UFH (n) | Mean age |
|---------------|-------------|-----------|----------|----------|----------|---------|---------|----------|
| ACUITY²⁵      | 17 countries| 1 year    | ACS      | 60 U/kg  | 1.75 mg/kg | 4612    | 4603    | 62.5     | 62.7     |
| BRIGHT²⁶      | 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     |
| EUROMAX²⁷     | 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-AMI²⁸ | 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-REACT²⁹  | 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     |
| MATRIX³⁰      | 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     |
| NAPLES³¹      | Italy       | 30 days   | ACS      | 70 U/kg  | 0.75 mg/kg; 1.75 mg/kg/h at least 30 min | 418     | 419     | 78       | 78       |
| REPLACE³²     | 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 SWEDEHEART⁷ | 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       |
| Wester³³      | 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.
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
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
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 7 | Funnel plot of the mortality stratified according to gender

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

(A)

| Study       | OR (95% CI) | Weight |
|-------------|-------------|--------|
| ACUITY      | 0.98 (0.79, 1.22) | 27.18  |
| BRIGHT      | 0.99 (0.46, 2.15) | 3.45   |
| EUROMAX     | 0.96 (0.59, 1.56) | 7.99   |
| HORIZON-AMI | 0.65 (0.43, 1.01) | 10.40  |
| ISAR-REACT  | 0.75 (0.17, 3.34) | 0.96   |
| MATRIX      | 0.70 (0.63, 1.00) | 24.73  |
| NAPLES      | 1.67 (0.80, 4.64) | 2.03   |
| REPLACE     | 0.14 (0.01, 2.73) | 0.25   |
| VALIATE-SWEDEHEART | 1.10 (0.75, 1.60) | 12.32 |
| Weeker      | 1.30 (0.85, 1.97) | 10.89  |
| Overall (I² = 16.1%, p = 0.294) | 0.93 (0.81, 1.09) | 100.00 |

NOTE: Weights are from random effects analysis

(B)

| Study       | OR (95% CI) | Weight |
|-------------|-------------|--------|
| BRIGHT      | 0.71 (0.22, 2.34) | 0.57   |
| ACUITY      | 1.12 (0.96, 1.32) | 30.02  |
| BRIGHT      | 0.69 (0.29, 1.62) | 1.03   |
| EUROMAX     | 1.09 (0.76, 1.55) | 5.53   |
| HORIZON-AMI | 1.18 (0.53, 2.65) | 1.16   |
| ISAR-REACT  | 1.16 (0.86, 1.51) | 11.02  |
| MATRIX      | 0.97 (0.65, 1.42) | 40.60  |
| NAPLES      | 3.01 (0.12, 74.03) | 0.07   |
| REPLACE     | 0.56 (0.65, 1.65) | 2.67   |
| SWEDEHEART  | 1.04 (0.74, 1.46) | 4.59   |
| Weeker      | 1.07 (0.63, 1.82) | 2.65   |
| Overall (I² = 0.0%, p = 0.921) | 1.05 (0.96, 1.14) | 100.00 |

NOTE: Weights are from random effects analysis
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 Juan35 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.41 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.41 Anemia is a common disease in PCI patients and is associated with significant increases in post-procedural death rate, reinfarction, and bleeding.40

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

|          | BIV       |           | UFH       |           | Cost  |
|----------|-----------|-----------|-----------|-----------|-------|
|          | 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| 148586 | 148586 |       |

**TABLE 4** Probability of adverse events and sensitivity analysis of pharmacoeconomic
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.

ACKNOWLEDGEMENTS

This study was supported by the National Nature Science Foundation of China [72074218]; Wu Jieping Medical Foundation [320.6750.2020-04-6].

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.

ORCID

Yi Ding https://orcid.org/0000-0002-2158-3108

REFERENCES

1. Kalra A, Bhatt DL, Rajagopalan S, et al. Overview of coronary heart disease risk initiatives in South Asia. Curr Atheroscler Rep. 2017;19:25.
2. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39(2):119-177.
3. Lu Y, Zhang H, Wang Y, et al. Percutaneous coronary intervention in patients without acute myocardial infarction in China: results from the China PEACE prospective study of percutaneous coronary intervention. JAMA Network Open. 2018;1:e185446.
4. Franchi F, Angiolillo DJ. Novel antiplatelet agents in acute coronary syndrome. Nat Rev Cardiol. 2015;12:30-47.
5. Franchi F, Rollini F, Angiolillo DJ. Antithrombotic therapy for patients with STEMI undergoing primary PCI. Nat Rev Cardiol. 2017;14:361-379.
6. Tantry US, Navarese EP, Myat A, Gurpel PA. Selection of P2Y12 inhibitor in percutaneous coronary intervention and/or acute coronary syndrome. Progr Cardiovasc Dis. 2018;60:460-470.
7. Valgimigli M, Frigoli E, Leonardi S, et al. Bivalirudin or unfractionated heparin in acute coronary syndromes. N Engl J Med. 2015;373:997-1009.
8. Steg PG, van’t Hof A, Hamm CW, et al. Bivalirudin started during emergency transport for primary PCI. N Engl J Med. 2013;369:2207-2217.
9. Anantha-Narayanan M, Anugula D, GujjuLA, et al. Bivalirudin versus heparin in percutaneous coronary intervention—a systematic review and meta-analysis of randomized trials stratified by adjunctive glycoprotein IIb/IIIa strategy. J Thorac Dis. 2018;10:3341-3360.
10. Cavender MA, Sabatine MS. Bivalirudin versus heparin in patients planned for percutaneous coronary intervention: a meta-analysis of randomised controlled trials. Lancet. 2014;384(9943):599-606.
11. Mahmood AN, Elgendy YI. Bivalirudin versus unfractio- nated heparin for percutaneous coronary intervention with radial access: a meta-analysis of randomized trials. Int J Cardiol. 2016;216:128-132.
12. Sumin AN, Korok EV, Gaifulin RA, Raikh Ol, Ivanov SV, Barbarash OL. Gender-related features and quality of life of the
14. Lutz J, Jurk K. Antiplatelet agents and anticoagulants in patients with chronic kidney disease - from pathophysiology to clinical practice. Curr Pharm Des. 2017;23:1366-1376.

15. Parikh SA, Drachman DE. Will bivalirudin have an impact in peripheral vascular interventions? Circulation. 2016;9:e003424.

16. Deharo P, Johnson T, Rahbi H, et al. Bivalirudin versus heparin plus glycoprotein IIb/IIIa inhibitor in the treatment of acute ST-segment elevation myocardial infarction. Heart. 2012;98:544-551.

17. Puyimiret E, Cohen S, Védrenne G, et al. Cost analysis of bivalirudin versus reference anticoagulants without GP IIb/IIIa inhibitors in patients undergoing percutaneous coronary intervention for acute coronary syndrome in routine clinical practice. Pompidou registry. Ann Cardiol Angéiol. 2013;62:89-94.

18. Zhu LB, Liu YH, He JM. Literature review of pharmacoeconomic evaluation of on-pump versus off-pump coronary artery bypass grafting. Klin Med. 2015;93:37-44.

19. Whayne T, Mukherjee D. Unique coronary artery disease differences in women as related to revascularization. Curr Med Chem. 2015;22:3597-3606.

20. Valgimigli M, Frigoli E, Leonardi S, et al. Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. Lancet. 2018;392:835.

21. Briguori C, Visconti G, Focaccia A, et al. Novel approaches for preventing or limiting events (Naples) III trial: randomized comparison of bivalirudin versus unfractionated heparin in patients at increased risk of bleeding undergoing transfemoral elective coronary stenting. JACC. 2015;8:414-423.

22. Ng VG, Baumbach AJH. Cost-effectiveness of bivalirudin versus heparin monotherapy in elderly patients with myocardial infarction: a prespecified subgroup analysis of the VALIDATE-SWEDHEART trial. Circulation. 2020;142.e1008671.

23. Sheng X, Murphy MJ, MacDonald TM, Wei L. Effectiveness of statins in chronic kidney disease. QJM. 2012;105:641-648.

24. Zhang J, Yang XJM. Efficacy and safety of bivalirudin versus heparin in patients with diabetes mellitus undergoing percutaneous coronary intervention: a meta-analysis of randomized controlled trials. Medicine. 2017;96:e7204.

25. Nairooz R, Sardar P, Amin H, Chatterjee S, Helmy T, Naidu SS. Short- and long-term outcomes in diabetes patients undergoing percutaneous coronary intervention with bivalirudin compared with heparin and glycoprotein IIb/IIIa inhibitors: a meta-analysis of randomized trials. Catheter Cardiovasc Interv. 2015;86:364-375.

26. Angiomax (Package Insert) (Bivalirudin) Injection. Parsippany NTMC. 2018;392:835.

27. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.

28. Ni凱英, 蕭伯, 費雪, 胡立明, 梁群. Efficacy and safety of bivalirudin versus heparin in patients undergoing percutaneous coronary intervention. Chin Health Econ. 2016;31:582-587.

29. Schulz S, Mehilli J, Ndrepepa G, et al. Bivalirudin vs. unfractionated heparin during percutaneous coronary interventions in patients with stable and unstable angina pectoris: 1-year results of the ISAR-REACT 3 trial. Eur Heart J. 2010;31:582-587.

30. Biagio G, Frigoli E, Leonardi S, et al. Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. Lancet. 2018;392:835.

31. Briguori C, Visconti G, Focaccia A, et al. Novel approaches for preventing or limiting events (Naples) III trial: randomized comparison of bivalirudin versus unfractionated heparin in patients at increased risk of bleeding undergoing transfemoral elective coronary stenting. JACC. 2015;8:414-423.

32. Exaire JE, Butman SM, Ebrahimi R, et al. Provisional glycoprotein IIb/IIIa inhibition with bivalirudin or heparin plus planned glycoprotein IIb/IIIa inhibition during percutaneous coronary intervention: predictors and outcome in the Randomized Evaluation in Percutaneous coronary intervention Linking Angiomax to Reduced Clinical Events (REPLACE)-2 trial. Am Heart J. 2006;152:157-163.

33. Wester A, Attar R, Mohammad MA, et al. Bivalirudin versus heparin in patients with myocardial infarction: a prespecified subgroup analysis of the VALIDATE-SWEDHEART trial. Circulation. 2020;142.e1008671.

34. Sheng X, Murphy MJ, MacDonald TM, Wei L. Effectiveness of statins in chronic kidney disease. QJM. 2012;105:641-648.

35. Zhang J, Yang XJM. Efficacy and safety of bivalirudin versus heparin in patients with diabetes mellitus undergoing percutaneous coronary intervention: a meta-analysis of randomized controlled trials. Medicine. 2017;96:e7204.

36. Nairooz R, Sardar P, Amin H, Chatterjee S, Helmy T, Naidu SS. Short- and long-term outcomes in diabetes patients undergoing percutaneous coronary intervention with bivalirudin compared with heparin and glycoprotein IIb/IIIa inhibitors: a meta-analysis of randomized trials. Catheter Cardiovasc Interv. 2015;86:364-375.

37. Angiomax (Package Insert) (Bivalirudin) Injection. Parsippany NTMC. 2018;392:835.

38. Kikkert WJ, van Brussel PM, Damman P, et al. Influence of chronic kidney disease on anticoagulation levels and bleeding after primary percutaneous coronary intervention in patients treated with unfractionated heparin. J Thromb Thrombolysis. 2016;41:441-451.

39. Nikolsky E, Mehran R, Aymong ED, et al. Impact of anemia on outcomes of patients undergoing percutaneous coronary intervention. Am J Cardiol. 2004;94:1023-1027.

40. Kwick CS, Tieng D, Pradhan A, et al. Meta-analysis of the prognostic impact of anemia in patients undergoing percutaneous coronary intervention. Am J Cardiol. 2016;118:610-620.

41. McKechnie RS, Smith D, Montoya C, et al. Prognostic implication of anemia on in-hospital outcomes after percutaneous coronary intervention. Circulation. 2004;110:271-277.

How to cite this article: Sun K-X, Cui B, Cao S-S, et al. Meta-analysis and cost-minimization analysis of bivalirudin versus heparin in high-risk patients for percutaneous coronary intervention. Pharmacol Res Perspect. 2021;9:e00774. https://doi.org/10.1002/prp2.774

SUN ET AL.