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Efficacy and safety of bivalirudin versus heparin in patients with diabetes mellitus undergoing percutaneous coronary intervention

A meta-analysis of randomized controlled trials

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Abstract

Background: The efficacy and safety of bivalirudin (Biva) versus heparin in patients with diabetes mellitus (DM) who undergo percutaneous coronary intervention (PCI) remain controversial. Our meta-analysis was undertaken to evaluate the efficacy and safety of Biva compared with those of heparin in patients with diabetes undergoing PCI.

Methods: We searched PubMed, EMBASE, Cochrane Library, and Clinical Trials.gov databases for randomized controlled trials (RCTs). The primary efficacy endpoint was the incidence of major adverse cardiovascular events (MACE), and the primary safety endpoint was the incidence of major bleeding. Secondary efficacy endpoints were incidence of net adverse clinical events (NACE), myocardial infarction (MI), and death. The pooled risk ratio (RR) with the corresponding 95% confidence intervals (CIs) were used to assess the efficacy and safety of Biva versus heparin.

Results: Eleven RCTs met the inclusion criteria, and 8428 patients were included. No significant difference was observed in the subgroup and overall risk of MACE (RR 0.87; 95% CI 0.74–1.02; $P = .08$; $I^2 = 39\%$) and NACE (RR 0.81; 95% CI 0.61–1.07; $P = .14$; $I^2 = 71\%$). Biva had an effect similar to that of heparin on the endpoint of death (RR 0.75; 95% CI 0.56–1.02; $P = .07$; $I^2 = 0$) and MI (RR 0.92; 95% CI 0.67–1.26; $P = .59$; $I^2 = 0$) but decreased the risk of major bleeding (RR 0.63; 95% CI 0.52–0.75; $P < .00001$; $I^2 = 0\%$).

Conclusion: The use of Biva and heparin is associated with a similar risk of MACE, NACE, death, and MI. Biva decreases the risk of major bleeding more significantly than heparin.

Abbreviations: Biva = bivalirudin, CI = confidence interval, GPI = glycoprotein platelet inhibitor, MACE = major adverse cardiovascular events, MI = myocardial infarction, NACE = net adverse clinical events, PCI = percutaneous coronary intervention, RCT = randomized controlled trial, RR = relative risk.

Keywords: bivalirudin, heparin, meta-analysis, percutaneous coronary intervention

1. Introduction

Diabetes is a major risk factor for coronary artery disease and worse outcomes after percutaneous coronary intervention (PCI) because of proinflammatory and prothrombotic state. Diabetes is usually accompanied with abnormalities of platelets, which leaded to platelet adhesion, increased glycoprotein platelet inhibitor (GPI) IIb/IIIa receptor expression levels, and elevated platelet aggregation. Patients with diabetes have a more pronounced vascular injury response and higher rates of restenosis and occlusion. The vessels in diabetes patients are more likely to be affected by atherosclerosis, and the blood is with a more considerable tendency for plaque rupture. As an anticoagulation therapy recommended by the American College of Cardiology Foundation/American Heart Association guidelines for patients with a high risk of major bleeding who undergo PCI, bivalirudin (Biva) is superior to heparin plus GPI IIb/IIIa.[1]

Antithrombotic treatment has been commonly given to patients undergoing PCI to prevent thromboembolic events. For a long period of time, heparin has been the primary choice for antithrombotic treatment. In contrast, Biva is a new direct thrombin inhibitor that has been reported to have antiischemic properties and a lower risk of bleeding during PCI.[2–4]

According to some reports, diabetes patients with acute myocardial infarction (MI) have mortality rates that are twice as high as those of nondiabetic patients.[5] Although there are a large number of randomized trials and meta-analyses on Biva and heparin efficacy and safety, various results have been obtained in different trials. The first randomized trial for Biva, an angioplasty study,[6] showed that the risk of major adverse cardiovascular events (MACE) and major bleeding was decreased by Biva. Nevertheless, the results of an HEAT-PPCI[7] trial suggested that the use of heparin was associated with a lower incidence of

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MACE, and no difference was found in major bleeding from the arms. Although Biva decreased the risk of major bleeding in the European Ambulance Acute Coronary Syndrome Angiography Trial (EUROMAX),[8] its application was associated with a higher risk of stent thrombosis and MI compared to that of heparin. Moreover, the number of randomized trials and meta-analyses evaluate the efficacy and safety of Biva versus heparin in patients with diabetes undergoing PCI is limited.

By conducting the present meta-analysis of all available randomized controlled trials (RCTs), we aimed to evaluate and compare the efficacy and safety of Biva and heparin in patients with diabetes mellitus (DM) undergoing PCI.

2. Methods

2.1. Data sources and searches

We searched PubMed, Cochrane Library, EMBASE, and Clinical Trials.gov databases from database inception until July 2016 using the keywords of "bivalirudin," "Hirulog," "Angiomax," "heparin," "Percutaneous Coronary Intervention," and "diabetes mellitus." A sensitive filter for randomized controlled trials was utilized for the search. In addition, references from randomized trials and relevant reviews were hand-searched for additional trials that were not identified in the database search.

2.2. Study selection

The following inclusion criteria were applied: patients undergoing PCI; RCTs of Biva versus heparin; clinical outcomes were reported (such as MACE, net adverse clinical events [NACE], death, MI, and major bleeding); and subgroup analysis outcomes of diabetes mellitus were reported. Reviews, meta-analysis, observational studies, and small-sample trials ($n < 50$) were excluded. The meta-analysis was complied with Preferred Reporting Items For Systematic Review and Meta-analysis (PRISMA).[9] As it is a meta-analysis study, ethical approval and informed consent are not required.

2.3. Data extraction and quality assessment

Two investigators independently extracted data from the relevant sources. Authors were contacted when data were incomplete or unclear, and a 3rd investigator was consulted to resolve disagreements and achieve consensus. We collected baseline demographic characteristics of the patients (sample size, diabetes percent, age, sex, and intervention in the experimental and control group) from eligible studies. The occurrence rates of the following events in DM patients were abstracted: MACE, NACE, mortality, MI, and major bleeding. The quality of the information accessed in each of the studies was classified as low, unclear, or high by evaluating the following 7 components: random sequence generation, allocation concealment, blinding of participants, outcome assessment, incomplete outcome data, selective outcome reporting, and "other issues" according to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions.

2.4. Date analysis

The effect size of clinical endpoints was measured by using the risk ratio (RR) with 95% confidence intervals (CIs). Two-sided *P*-values $< .05$ were considered statistically significant. Fixed-effect model was used to calculate pooled estimate; however, a random-effect model was used to obtain the combined effect when heterogeneity was evidence. Heterogeneity was assessed by the Cochran Q-test and I^2 test. A Cochran $P < .10$ and $I^2 > 50$ were considered to be indicative of significant heterogeneity. Small-study and publication bias were assessed with funnel plot and Egger test. Data analysis was conducted using RevMan 5.2 software (Nordic Cochrane Centre, Cochrane Collaboration, 2013), and sensitivity analysis was performed by Stata 11.0 (StataCorp, College Station, TX).

3. Results

3.1. Search results

We identified a total of 2672 articles with 11 trials that satisfied our inclusion criteria. As can be seen in the selection procedure depicted in Fig. 1, 4139 DM patients were randomized to a Biva (experimental) group, and 4289 DM patients were randomized to a heparin (control) group. The baseline demographic characteristics of the included studies are detailed in Table 1.[2,7,8,10–17] The quality assessment data are presented in sTable 1, http://links.lww.com/MD/B783, sFigs. 1 and 2, http://links.lww.com/MD/B783. All clinical trials included in our study were characterized by a low risk of blinding of participants and outcome assessment, incomplete outcome data, and selective outcome reporting. In addition, 2 trials were with an unclear risk of random sequence generation, and 1 trial with unclear risk of allocation concealment. In conclusion, all trials included in the present analysis are high-quality studies.

3.2. Clinical results

MACE was used as the primary efficacy endpoint, and the risk of major bleeding was the primary safety endpoint. Secondary endpoints included NACE, MI, and morality. We conducted subgroup analysis according to the different rates of GPI use in 2 arms if there are enough data about endpoint (when the rate of GPI use in Biva is larger than in heparin define as Gureater GPI use subgroup. When the rate of GPI use in Biva is equal to that in heparin define as balance GPI use subgroup).

3.2.1. Results of MACE analysis. In our study, MACE, which served as the primary efficacy endpoint, 496 DM patients occurred with MACE in Biva arm and 571 patients in heparin arm. Biva use was associated with a lower incidence of MACE than that observed after heparin application (RR = 0.81; 95% CI = 0.66–0.99; $P = .04$; $I^2 = 40\%$) in Gureater GPI use subgroup. No significant difference was found between the risk of MACE in the Biva and heparin group in balance GPI use subgroup analysis (RR = 1.01; 95% CI = 0.75–1.37; $P = .15$; $I^2 = 44\%$) and overall analysis (RR = 0.87; 95% CI = 0.74–1.02; $P = .08$; $I^2 = 39\%$) as shown in Fig. 2.

3.2.2. Results of major bleeding assessment. Major bleeding was the primary safety endpoint. In the Biva group, 174 DM patients experienced the adverse event of major bleeding, whereas their number in the heparin group was 297. Biva decreased more significantly the risk of major bleeding than heparin in both the subgroup analysis (RR = 0.60; 95% CI = 0.45–0.79; $P = .0003$; $I^2 = 0$), (RR = 0.65; 95% CI = 0.51–0.82; $P = .0002$; $I^2 = 0\%$), and the overall analysis (RR 0.63; 95% CI 0.52–0.75; $P < .00001$; $I^2 = 0\%$) as illustrated in Fig. 3.

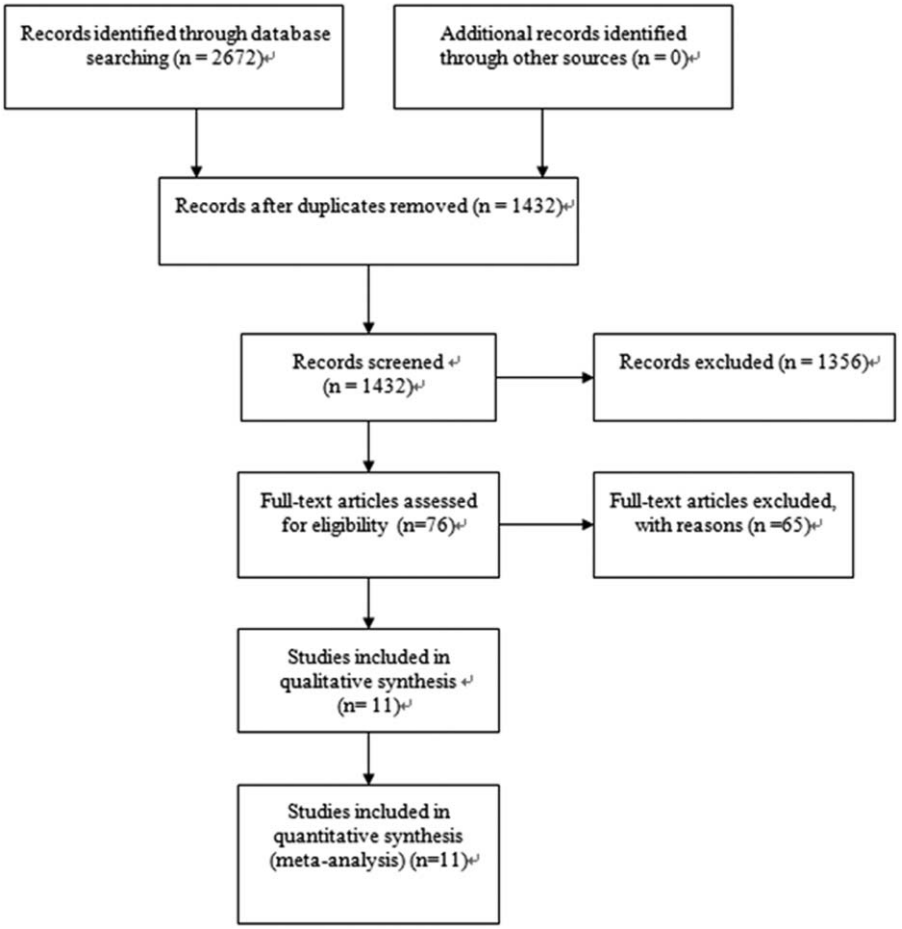

Figure 1. Flow chart showing the progress through the stages of the meta-analysis.

Table 1

Characteristics of included study.

Study	Year	Population	Anticoagulation		N	Male gender, %		Mean age		GPI, %	
			Biva	UFH		Biva	UFH	Biva	Biva	Biva	UFH
Acuity	2007	NST/UA	Biva (0.1 mg/kg bolus 0.25 mg/kg/h infusion, before PCI 0.5 mg/kg bolus 1.75 mg/kg/h infusion) + GPI	UFH (60 IU/kg plus 12 IU/kg/h to target) + GPI	2619 2561	0.74	0.73	62	63	97	97
Brave-4	2014	ST	Biva (0.75 mg/kg followed by 1.75 mg/kg/h) + prasugrel	UFH (30–100 IU/kg) + clopidogrel	271 277	0.76	0.79	66	58	3	6.1
Bright	2015	ST/NST	Biva (0.75 mg/kg followed by 1.75 mg/kg/h)	UFH (heparin 60U/kg) + tirofiban 10 μg/kg 0.15 μg/kg/min infusion)	735 730	0.827	0.821	57.3	58.2	4.4	100
Euromax	2013	ST	Biva (0.75 mg/kg followed by 1.75 mg/kg/h at least 4 hours)	UFH (100 IU/h OR 60 IU/kg + GPI)	1089 1109	0.747	0.776	61	62	11.5	69.1
Heat-ppci	2014	ST	Biva (0.75 mg/kg followed by 1.75/kg/h)	UFH (70 IU/kg)	905 907	0.71	0.73	62.9	63.6	13.5	15.5
Horizons-Ami (30d)	2008	ST	Biva (0.75 mg/kg followed by 1.75/kg/h)	UFH (60 IU/kg)	1800 1802	0.77	0.76	59.8	60.7	7.2	94.5
ISAR-REACT3	2008	PCI	Biva (0.75 mg/kg followed by 1.75 mg/kg/h)	UFH (140 IU/kg followed by placebo)	2289 2281	0.762	0.768	66.9	67	0.2	0.2
ISAR-REACT4	2011	NST	Biva (0.75 mg/kg followed by 1.75/kg/h)	UFH (70 IU/kg followed by placebo)	860 861	0.769	0.768	67.5	67.5	0	100
NAPLES	2009	PCI	Biva (0.75 mg/kg followed by 1.75 mg/kg/h)	UFH (70 IU/kg) + GPI	167 168	0.659	0.643	65	65.6	0	100
REPLACE-2	2003	PCI	Biva (0.75 mg/kg followed by 1.75 mg/kg/h)	UFH (65 IU/kg) + GPI	2994 3008	0.747	0.741	62.6	62.6	7.2	96.5
MARTIX	2015	ST/NST	Biva (0.75 mg/kg followed by 1.75/kg/h)	UFH (70–100 IU/kg without GPI or 50–70 IU/kg with GPI)	3610 3603	0.251	0.251	65.4	65.4	4.6	25.9

Acuity, Acute Catheterization and Urgent Intervention Triage strategy; Brave-4, Bavarian Reperfusion Alternatives Evaluation 4 Trial; Bright, The Bivalirudin in Acute Myocardial Infarction vs Heparin and GPI Plus Heparin Trial; Euromax, The European Ambulance Acute Coronary Syndrome Angiography; Heat-ppci, Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention; Horizons-Ami, Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; ISAR-REACT3, Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 3 Trial Investigators; ISAR-REACT4, Intracoronary Stenting and Antithrombotic Regimen:Rapid Early Action for Coronary Treatment 4 trial; NAPLES, Novel Approaches for Preventing or Limiting EventS; NAPLES3, Novel Approaches for Preventing or Limiting Events III Trial; REPLACE-2, Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events trial; MARTIX, Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox. Biva = bivariludin, GPI = glycoprotein platelet inhibitor, NST = non-ST-elevation coronary syndrome, ST = ST elevation myocardial infarction, PCI = percutaneous coronary intervention patients, UA = unstable angina, UFH = unfractionated heparin.

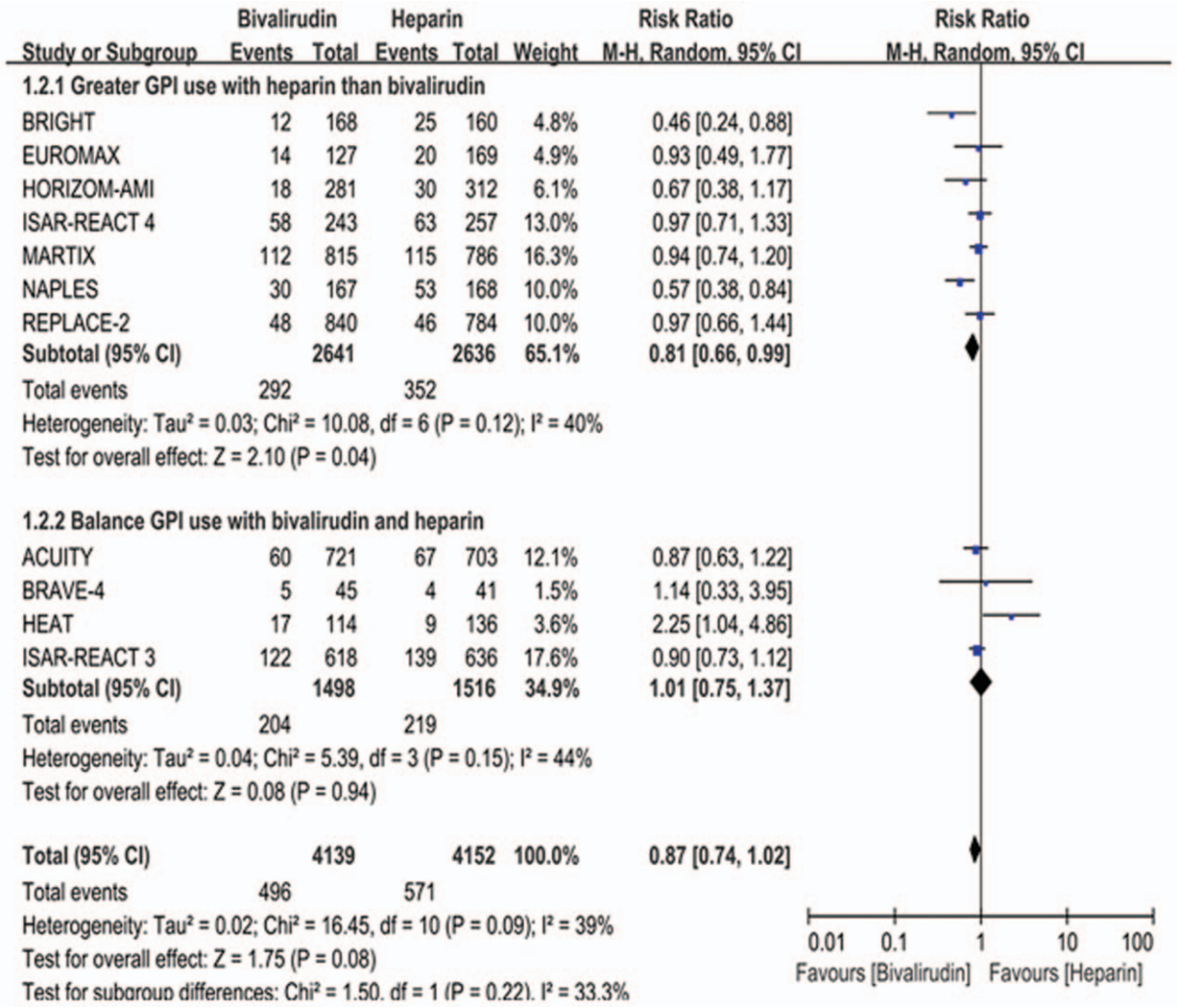

Figure 2. Forest plot of major adverse cardiovascular events (MACE).

3.2.3. Results of NACE evaluation. NACE was another efficacy endpoint which is a composite of major adverse cardiac and cerebral events (MACE, all-cause death, reinfarction, ischemia-driven target vessel revascularization, or stroke) and any bleeding events. There were 340 patients with diabetes mellitus in Biva arm and 397 patients with diabetes mellitus in heparin arm had NACE. There was no significant difference occurred between Biva and heparin in the risk of NACE both in subgroup analysis (RR 0.74; 95% CI 0.52–1.06; $P=.10$; $I^2=79\%$), (RR 1.05; 95% CI 0.76–1.43; $P=.78$; $I^2=0\%$) and overall analysis (RR 0.81; 95% CI 0.61–1.07; $P=.14$; $I^2=71\%$) as shown in Fig. 4.

3.2.4. Results of death. Death was reported in 70 DM patients assigned to the Biva and 92 patients assigned to the heparin group. In the overall analysis, no significant difference was detected between the risk of death in the Biva and heparin group (RR = 0.75; 95% CI 0.56–1.02; $P=.07$; $I^2=0$) as shown in Fig. 5.

3.2.5. Results of MI evaluation. MI occurred in 70 DM patients in the Biva and in 74 DM patients in the heparin group. No significant difference was observed between the effects of Biva and heparin on the risk of MI (RR0.92; 95% CI 0.67–1.26; $P=.59$; $I^2=0$) as shown in Fig. 6.

3.3. Sensitivity and bias analysis

Egger test results showed no significant evidence of publication bias in either endpoint (Table 2). In addition, the stability of Biva can decrease the risk of major bleeding significantly versus heparin was shown in sFig. 3, http://links.lww.com/MD/B783, similar results were obtained after excluding each individual study.

4. Discussion

This meta-analysis includes 8428 diabetes patients who underwent PCI within 11 RCTs, randomized to a Biva and a heparin group. In this meta-analysis, we found that there was no difference between Biva and heparin in the risk of NACE, MACE, death, and MI. However, Biva decreased the risk of major bleeding more significantly compared with heparin in spite of the use of different GPI in the Biva and heparin treatments.

Biva has been an alternative to heparin used as an anti-coagulation strategy for patients undergoing PCI to reduce the risk of major bleeding events. In a previous study, Biva was also suggested to possess a wider range of pharmacological properties than heparin.[5] Patients with diabetes have a high incidence of

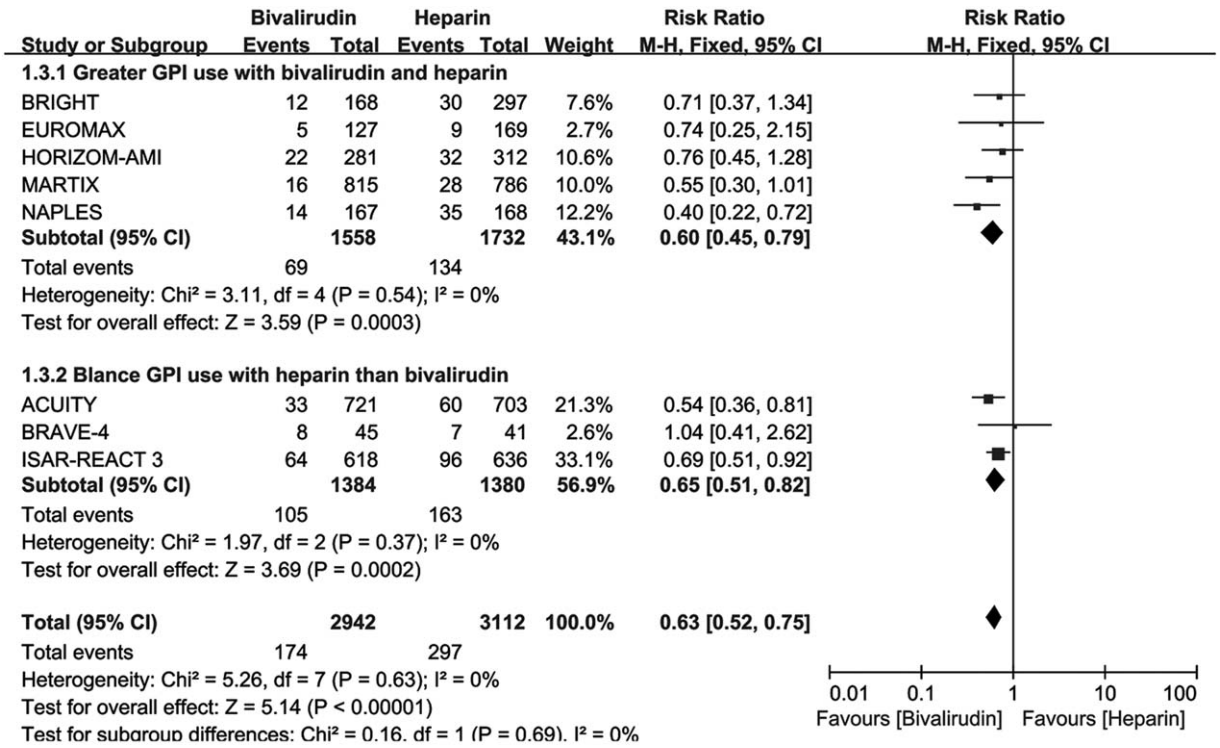

Figure 3. Forest plot of major bleeding.

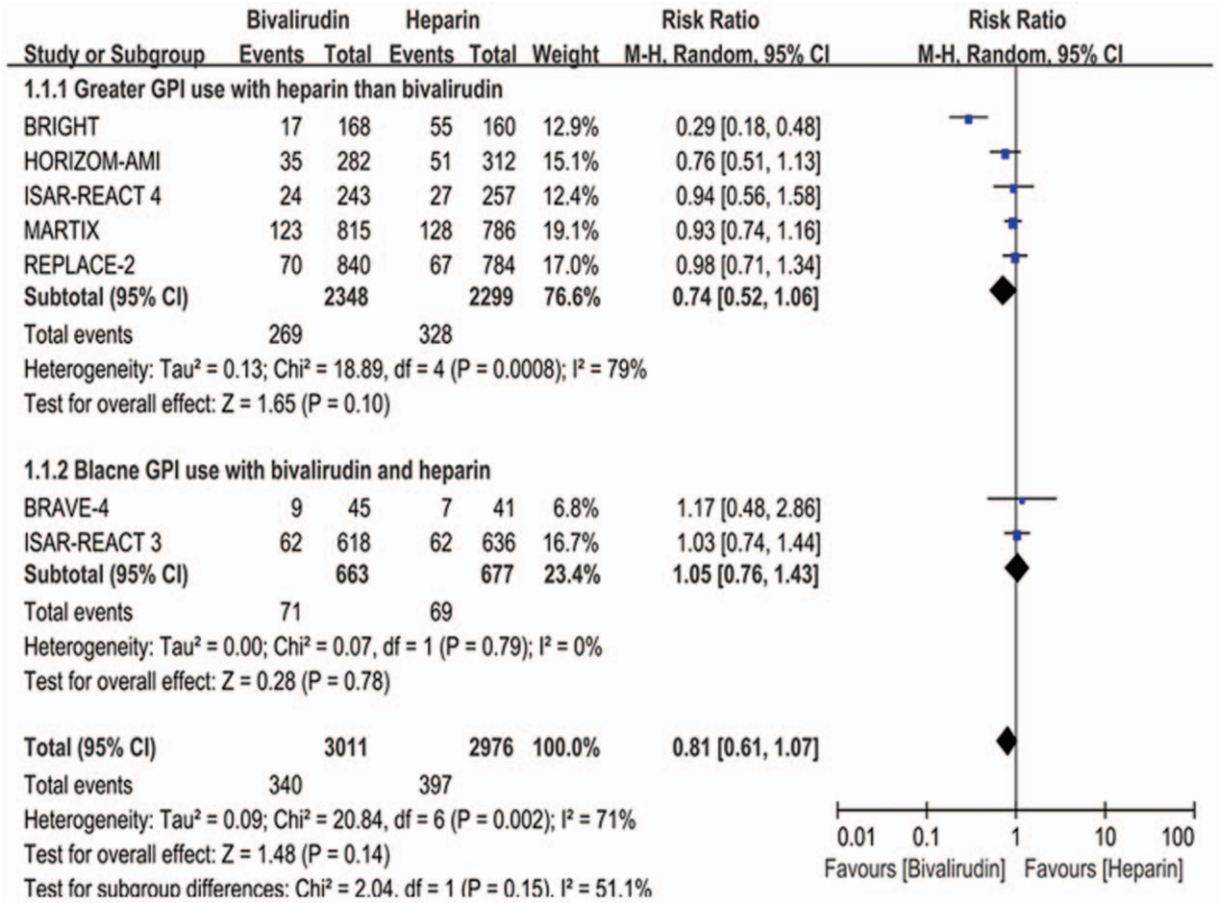

Figure 4. Forest plot of net adverse clinical events (NACE).

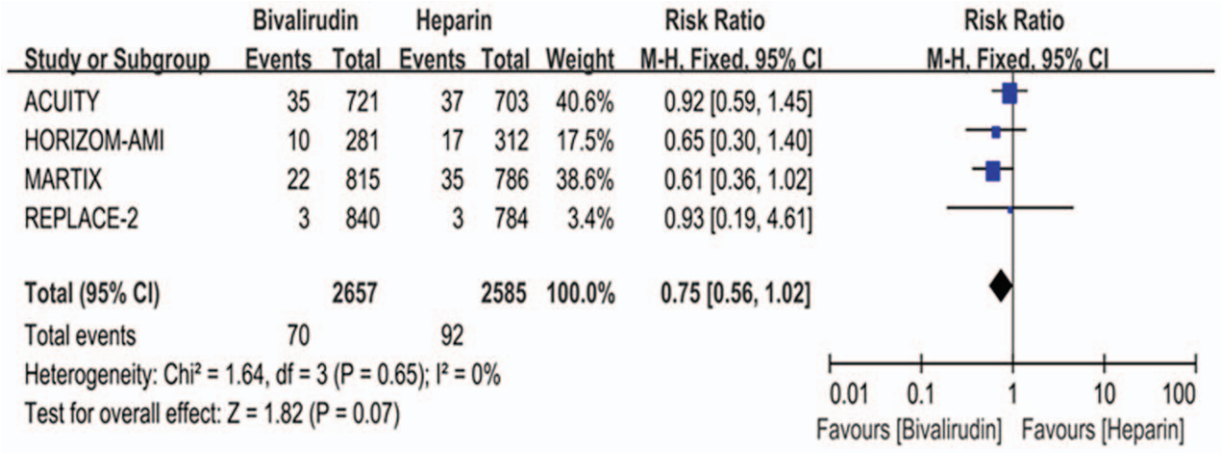

Figure 5. Forest plot of death.

Figure 6. Forest plot of myocardial infarction (MI).

coronary artery disease and particularly high rates of acute coronary syndromes and mortality. To date, the number of clinical trials on the choice of antithrombotic treatment and comparing the efficacy and safety of Biva and heparin applied in diabetes patients undergoing PCI is limited. The NAPLES[16] clinical trial is the one that has been targeted at diabetes mellitus patients undergoing PCI, in which, the rate of MI in the 2 groups was similar, and the rate of major bleeding was comparable. The conclusions of this clinical trial indicate that the influence of Biva on MI and major bleeding in DM patients undergoing elective PCI is similar to that of heparin. The MARTIX[17] clinical trial, a large-sample clinical investigation which included 1601 diabetes patients, showed that Biva use was associated with a lower risk of death and major bleeding.

To the best of our knowledge, this is the 3rd meta-analysis comparing the efficacy and safety of Biva and heparin. There was a meta-analysis published in 2015 by Nairooz et al,[18] in which they reported that the application of Biva significantly lower levels of major bleeding and mortality compared with that resulting from heparin and GPI use in diabetes patients undergoing PCI. However, our findings are not consistent with these results. We found that effect of Biva on the risk of NACE, MACE, death, and MI was similar to that of heparin, but Biva decreased the occurrence of major bleeding. These discrepancies might have been caused by the inclusion of more RCTs in our meta-analysis than in the abovementioned meta-analysis consisting of only 5 clinical trials included. Compare with the 6 clinical trials and 5924 patients included in another of the published meta-analyses,[19] we included a higher number (11) of clinical trials and analyzed one more endpoint (the risk of MI); no difference was found between Biva and heparin in this endpoint. Furthermore, we included more new clinical trials than these 2 previously published analyses, and conducted subgroup analysis to obtain more accurate results and provide more reliable evidence. Another meta-analysis[20] which major for all PCI patients state that the increased bleeding risk in the studies that compare Biva with heparin plus GPI IIb/IIIa may be due to the greater GPI IIb/IIIa use rather than the balance use of GPI IIb/IIIa. But in our analysis which major for diabetes mellitus undergoing PCI, we performed subgroup analysis on the use of different rates of GPI IIb/IIIa and established that Biva decreased the risk of major bleeding in both the subgroup and the overall analysis, and its effect was not significantly different from that of heparin. The difference GPI use rate in 2 arms has no influence on the endpoint.

The current American College of Cardiology/American Heart Association guidelines acknowledge that diabetes patients are high-risk population of bleeding, but not special antiplatelet or anticoagulant recommended. From above analysis, Biva seems to be a better choice for these high-risk populations.

Table 2

Assessment of publication bias.

Outcome	Eegger regression intercept *P* value
MACE	.694
NACE	.604
Bleeding	.851

MACE = major adverse cardiovascular events, NACE = net adverse clinical events.

Nevertheless, there were some limitations in our meta-analysis. First, several of the trials we included were without detailed descriptions of allocation concealment and blinding, which might have affected the quality of the trials. Second, the dose and type of heparin were slightly different in each of the trials, and some patients were given enoxaparin, which might have led to heterogeneity. Third, we could not obtain individual patient-level data to address some unresolved problems and potential limitations. Overall, the different design and characteristics of each trial might have caused heterogeneity. Therefore, more rigorous, large-sample, international trials are needed to confirm our results.

5. Conclusion

The use of Biva and heparin is associated with a similar risk of MACE, NACE, death, and MI. Biva decreases the risk of major bleeding more significantly than heparin.

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