Bivalirudin Anticoagulant Therapy With or Without Platelet Glycoprotein IIb/IIIa Inhibitors During Transcatheter Coronary Interventional Procedures

A Meta-Analysis

Jiabei Li, MD, Shiyong Yu, MD, Dehui Qian, MD, Yun He, MD, and Jun Jin, MD

Abstract: The safety and effectiveness of using the direct thrombin inhibitor bivalirudin during transcatheter coronary interventional procedures remains uncertain.

This study aimed to systematically assess anticoagulation with bivalirudin alone or bivalirudin plus glycoprotein (GP) IIb/IIIa inhibitors (bivalirudin-based anticoagulant therapy) in patients undergoing percutaneous coronary intervention (PCI) procedures by a meta-analysis of randomized controlled trials (RCTs).

Systematical searches of the MEDLINE, EMBASE, and Cochrane databases were conducted. RCTs comparing bivalirudin-based anticoagulant therapy with a comparable heparin therapy in patients undergoing PCI were eligible. Risk ratios (RRs) with 95% confidence intervals (CIs) served as summary statistics.

A total of 38,096 patients from 17 RCTs were randomized to the bivalirudin group (n = 18,878) or heparin group (n = 19,218) in the meta-analysis. No significant differences in death, myocardial infarction or reinfarction, ischemia-driven revascularization, or in-stent thrombosis were observed between the 2 groups (all P > 0.05). Notably, bivalirudin-based therapy showed a highly significant 34% decrease in the incidence of major bleeding (RR = 0.66; 95% CI 0.54–0.81; P < 0.001) and a 28% reduction in the need for blood transfusion (RR = 0.72; 95% CI 0.56–0.91; P < 0.01). Meta-regression analyses demonstrated that additional administration of GP IIb/IIIa receptor inhibitors (P = 0.01), especially eptifibatide (P = 0.001) and tirofiban (P = 0.002), was likely to increase the major bleeding risk associated with bivalirudin.

Bivalirudin, in comparison to heparin, is associated with a markedly lower risk of major bleeding, and the additional use of GP IIb/IIIa inhibitors may weaken this benefit.

(Abbreviations: CI = confidence interval, GP = glycoprotein, PCI = percutaneous coronary intervention, RCT = randomized controlled trial, RR = risk ratio, UFH = unfractionated heparin.)

INTRODUCTION

In patients undergoing transcatheter procedures for the treatment of coronary diseases, the optimal antithrombotic regimens for maximizing clinical efficacy and minimizing the risk of bleeding complications have been widely investigated over the past decade. The relatively new direct thrombin inhibitor bivalirudin, which offers a low bleeding risk, might be promising as an alternative to unfractionated heparin (UFH), which is routinely used during coronary interventional procedures. Before the widespread use of clopidogrel or prasugrel pretreatment, bivalirudin was associated with lower incidences of peri-procedural major bleeding as well as ischemic outcomes compared to UFH.1 Subsequently, the widely recommended oral dual antiplatelet therapy (clopidogrel or prasugrel and aspirin) seemed to weaken the benefit of bivalirudin, which was considered to be a significant decrease in bleeding risk without better clinical efficacy.2 Recently, the addition of platelet glycoprotein (GP) IIb/IIIa receptor inhibitors to anticoagulant therapy during transcatheter procedures has provided a clinical benefit of reducing ischemic outcomes.3–5 However, in conjunction with antiplatelet agents, the efficacy and safety of bivalirudin relative to UFH have not been well established. A previous meta-analysis compared bivalirudin mono- or bivalirudin-based (bivalirudin plus routine or provisional GP IIb/IIIa inhibitors) anticoagulant therapy versus heparin-based anticoagulation (UFH plus routine or provisional GP IIb/IIIa inhibitors) in patients undergoing percutaneous coronary intervention (PCI). However, the influence of the adjunctive use of GP IIb/IIIa inhibitors and other important clinical factors on ischemic and bleeding endpoints was not defined in the study. Recently, 2 meta-analyses investigated the clinical utility of bivalirudin versus UFH during PCI without planned use of GP IIb/IIIa inhibitors6 and only with the use of GP IIb/IIIa inhibitors,7 respectively. Neither study comprehensively showed the efficacy and safety profile of bivalirudin in patients undergoing coronary interventional procedures. Additionally, more recently reported results of several new trials and longer-term observations from previous trials can potentially contribute to the development of antithrombotic therapy during the procedures.9–12 We therefore performed a meta-analysis of randomized controlled trials (RCTs) to systematically evaluate the efficacy and safety of bivalirudin mono- or bivalirudin-based anticoagulant therapy in patients undergoing PCI. Meanwhile, the effects of additional use of GP IIb/IIIa inhibitors and
other clinical factors on ischemic and bleeding outcomes were also investigated in the meta-analysis.

METHODS

Literature Review

A computerized literature search was conducted of studies published from January 1990 through January 2015 in the MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials databases using the following search terms: bivalirudin, hirulog, heparin, low-molecular-weight heparin, unfractionated heparin, UFH, coronary artery/heart disease, myocardial infarction, acute coronary syndrome, unstable angina, angioplasty, percutaneous coronary intervention, PCI, invasive strategy, randomized, and human. In addition, an extensive manual searching was also performed using cross-references from the eligible articles and relevant reviews. The search was restricted to English-language literature.

Study Eligibility

RCTs were eligible for inclusion if they compared the efficacy or safety of bivalirudin mono- or bivalirudin-based anticoagulant therapy with comparable heparin therapy during PCI and reported clinical outcomes of interest. Bivalirudin/heparin-based regimens were defined as anticoagulation with bivalirudin/heparin (UFH or low-molecular-weight heparin) plus planned or provisional GP IIb/IIIa inhibitors (eg, abciximab, tirofiban, or eptifibatide). Subgroup analyses within the eligible trials were excluded. Moreover, articles published before the year 2000 and those in the form of study designs, editorials, and reviews also were excluded.

Data Extraction and Quality Assessment

Two investigators (JL and SY) reviewed all the citations in duplicate to identify eligible studies and independently conducted data extraction and quality assessment using a standardized approach. Data regarding ischemic outcomes (eg, death, nonfatal myocardial infarction or reinfarction, ischemia-driven revascularization, or in-stent thrombosis) and bleeding complications (eg, major bleeding or blood transfusion) were extracted from each of the eligible studies. The reviewers resolved differences through consensus, and any disagreements were resolved by the principal investigator of the present study (JJ). All eligible trials were assessed by the following quality criteria recommended by the Cochrane Collaboration: sequence generation of the allocation; concealment of allocation; blinding of participants, personnel, and outcome assessors; use of intention to treat analysis; and description of withdrawals and dropouts. In addition, the Jadad scale, a numerical score between 0 and 5, was used to qualitatively assess the quality of the included studies.

Data Synthesis and Analyses

We used risk ratios (RRs) with 95% confidence intervals (CIs) to express the combined results of individual studies. The pooled effects were calculated according to the Mantel–Haenszel random effects model. For studies with no event of interest in a treatment group, 1.0 was added to all cells for continuity correction. Heterogeneity across studies was quantified using the I² statistic. I² values greater than 25%, 50%, and 75% were considered evidence of low, moderate, and severe statistical heterogeneity, respectively. Sensitivity analyses, in which the pooled estimates were recalculated omitting 1 study at a time, were conducted to assess the impact of individual studies on the summary estimate of effect. Subgroup analyses were performed to assess the impacts of anticoagulant regimens, clinical settings, invasive strategies, and follow-up duration on overall estimates. Meta-regression analyses were also performed to determine the influences of clinical and demographic factors on the overall results. We assessed publication bias using a Begg funnel plot. Pooling analyses were performed with the RevMan 5.2 software (The Cochrane Collaboration, Copenhagen, Denmark), and meta-regression analyses were conducted with STATA 10.0 software (Stata Corp., College Station, TX). The results were considered statistically significant at \( P < 0.05 \) (2-sided). The study was performed in compliance with the Quality of Reporting of Meta-analyses (QUOROM) guidelines.

RESULTS

Study Selection and Characteristics

The process of study selection is illustrated in Figure 1. The electronic searches identified 658 items. After removing the duplicates, we initially screened 325 citations, of which 281 were excluded upon reviewing the titles and abstracts. Forty four potentially eligible studies were scrutinized further by elaborate review of the full text. Finally, 23 articles involving 17 RCTs were eligible for the final analysis (Figure 1).

![Flowchart of selection of studies for inclusion in meta-analysis](image1.png)

FIGURE 1. Flowchart of selection of studies for inclusion in meta-analysis. RCTs = randomized controlled trials, PCI = percutaneous coronary intervention.
## TABLE 1. Baseline Characteristics of Studies Included in the Meta-Analysis

| Study Name, Year | Study Design | Participants | Study Design | No. Enrolled (H/B) | Comparisons | Heparin Treatment | Bivalirudin Treatment | GPL % (H/B) | Primary Endpoints | Follow-up, months |
|------------------|--------------|--------------|--------------|-------------------|-------------|------------------|---------------------|-------------|-------------------|-----------------|
| ACUTY, 2006, 2007 | Open-label, multicenter | NSTE-ACS for PCI | 4603/4604 | Heparin (UFH or enoxaparin) + planned GPI vs. bivalirudin | UFH (47.9%); 60 U/kg iv bolus + 12 U/kg/h (ACT 200–200s); enoxaparin (47.4%); 1 mg/kg iv bolus (before PCI) + 0.3–0.75 mg/kg iv (just before) | 0.1 mg/kg iv bolus (before PCI) + 0.25 mg/kg iv (during PCI) + 0.5 mg/kg iv bolus (before PCI) + 1.75 mg/kg (during PCI) | 96.6%/96.7%; Eptifibatide: 59%/60.9%; Trofibrin: 19.2%/19.7%; Abciximab: 17.8%/16.3% | 1. A composite endpoint of death, MI, or unplanned revascularization | 1.12 |
| ARMYDA-7, 2012 | Open-label, two centers | CHD for PCI | 203/198 | UFH vs. bivalirudin | UFH: 75 U/kg iv bolus | Bivalirudin: 0.75 mg/kg iv bolus (just before PCI) + 1.75 mg/kg (during PCI) | 14%/12% | 2. Major bleeding | 1 |
| ARNO, 2010 | Open-label, simple center | CHD for PCI | 425/425 | UFH vs. bivalirudin | UFH: 100 U/kg iv bolus (ACT 250–300s) + protamine 0.5 mg/100 U (just after PCI); Abciximab: 28%/15% | 0.75 mg/kg iv bolus (just before PCI) + 1.75 mg/kg (during PCI) | Death, MI, or repeated coronary angioplasty | In-hospital major bleeding | In-hospital, 1.6 |
| BAS, 2001 | Double-blind, multicenter | NSTE-ACS for PCI | 2039/2059 | UFH vs. bivalirudin | UFH: 175 U/kg iv bolus + 15 U/kg/h for 18–24 hours | 1 mg/kg iv bolus (just before PCI) + 2.5 mg/kg/h for 4 hours + 0.2 mg/kg/h for 14–20 hours | 0%/0% | 2. Any bleeding event | In-hospital, 6 |
| CACHET, 2002 | Open-label, two centers | CHD for PCI | 94/30 | UFH vs. bivalirudin | UFH: 70 U/kg iv bolus (ACT > 200s) | Bivalirudin: 100%/100% | A composite endpoint of death, MI, or surgical or repeat percutaneous coronary revascularization | In-hospital composite of death or major bleeding | 1 |
| EUROMAX, 2013 | Open-label, multicenter | STEMI for PCI | 1109/1089 | Heparin (UFH or enoxaparin) + planned or provisional GPI vs. bivalirudin | UFH: 60–100 U/kg iv bolus | Enoxaparin: 0.5 mg/kg iv bolus; | 69%/11.5% | 1. Death, reinfarction, or unplanned target lesion revascularization | 1 |
| HEAT-PPCI, 2014 | Open-label, simple center | STEMI for PCI | 914/915 | UFH vs. bivalirudin | UFH: 70 U/kg iv bolus | Bivalirudin: 0.75 mg/kg iv bolus (just before PCI) + 1.75 mg/kg/h | Abciximab: 18.7%/15.9% | 1. Death, reinfarction, or unplanned target lesion revascularization | 1 |
| HORIZONS-AMI, 2008, 2011 | Open-label, multicenter | STEMI for PCI | 1802/1800 | UFH vs. bivalirudin | UFH: 60 U/kg iv bolus (ACT 200–200s) | Bivalirudin: 0.75 mg/kg iv bolus (just before PCI) + 1.75 mg/kg/h | 94.5%/7.2%; Abciximab: 52%/4.3%; Eptifibatide: 45.6%/3.2%; Trofibrin: 0.2%/0.1% | 2. Major bleeding | 1.36 |
| ISAR-REACT 3, 2005, 2010 | Double-blind, multicenter | CHD for PCI | 2281/2289 | UFH vs. bivalirudin | UFH: 140 U/kg iv bolus (ACT > 250s) | Bivalirudin: 0.75 mg/kg iv bolus (just before PCI) + 1.75 mg/kg/h | 0.2%/0.2% | 1. A composite endpoint of death, MI, urgent target-vessel revascularization | 1.12 |
| ISAR-REACT 4, 2011, 2013 | Double-blind, Double-dummy, multicenter | NSTE-ACS for PCI | 861/860 | UFH vs. bivalirudin | UFH: 70 U/kg iv bolus (ACT > 200s) | Bivalirudin: 0.75 mg/kg iv bolus (just before PCI) + 1.75 mg/kg/h | Abciximab: 100%/0% | 2. Major bleeding | 1.12 |
| NAPLES, 2009 | Open-label, simple center | CHD with diabetes for PCI | 168/167 | UFH vs. bivalirudin | UFH: 70 U/kg iv bolus (ACT > 250s) | Bivalirudin: 0.75 mg/kg iv bolus (just before PCI) + 1.75 mg/kg/h | 0.75 mg/kg iv bolus (just before PCI) + 1.75 mg/kg/h | 1. A composite endpoint of death, MI, urgent target-vessel revascularization, or major bleeding | 1 |
| NAPLES III, 2015 | Double-blind, simple center | CHD at increased bleeding risk for PCI | 419/418 | UFH vs. bivalirudin | UFH: 70 U/kg iv bolus (ACT > 250s) | Bivalirudin: 0.75 mg/kg iv bolus (just before PCI) + 1.75 mg/kg/h | 13.3%/0.5% | 1. A composite endpoint of death, MI, or unplanned revascularization, or all bleeding | In-hospital major bleeding | In-hospital, 1.12 |
| PROTECT-TIMI-30, 2006 | Open-label, multicenter | NSTE-ACS for PCI | 573/284* | Heparin (UFH or enoxaparin) + planned GPI vs. bivalirudin | UFH: 501 U/kg iv bolus (ACT 200–200s); Enoxaparin: 0.5–0.75 mg/kg iv bolus; | 0.75 mg/kg iv bolus (just before PCI) + 1.75 mg/kg/h | Abciximab: 0%/0% | 1. Coronary flow reserve | In-hospital |
| Study Name, year | No. Enrolled | Follow-up, months | Study Design | Participants | Primary Endpoints |
|------------------|-------------|-------------------|-------------|--------------|------------------|
| REPLACE-2, 2004 | 12,058       | In-hospital       | Double-blind, multicenter | UFH-treatment group (H/B) | A composite endpoint of death, MI, reinfarction, or major bleeding (H/B) |
| TEMI-Try, 2011  | 15,292       | In-hospital       | Single-blind, multicenter | UFH-treatment group (H/B) | A composite endpoint of death, MI, reinfarction, or major bleeding (H/B) |
| Xiang, 2013     | 10,000       | In-hospital       | Single-blind, multicenter | UFH-treatment group (H/B) | A composite endpoint of death, MI, reinfarction, or major bleeding (H/B) |

A total of 38,096 patients included in the present study was randomized to the bivalirudin-treatment group (n = 18,878; 49.6%) or UFH-treatment group (n = 19,218; 50.4%). The study and demographic characteristics are shown in Tables 1 and 2, respectively. Among the included 17 trials, 3,20,21,36 compared bivalirudin monotherapy versus UFH monotherapy, 3,8,22,33 compared bivalirudin versus UFH with planned GPI treatment, 3,10,11,19,30,35 compared bivalirudin versus UFH with provisional GPI treatment, and 6,12,24,28,29,32,35 compared bivalirudin monotherapy or bivalirudin plus provisional GPI treatment with UFH treatment.

A composite endpoint of death, MI, or repeat revascularization, and nine,11,19,20,22,26,30,32,35 on patients with unselected coronary heart diseases. Fourteen trials focused on patients undergoing PCI, and three,10,24,36 on those undergoing primary PCI. Six trials,20,22,29,30,35 reported in-hospital outcomes, thirteen,10,11,17,19,20,23,25,27,28,33,35,36 reported 30-day outcomes, three,20,21,32 reported 6-month outcomes, five,12,18,26,32,35 reported 12-month outcomes, and only one24 reported 36-month outcomes (Table 1). All the included trials reported clinical events of all-cause death, myocardial infarction or reinfarction, or major bleeding, and a composite outcome of death, myocardial infarction or reinfarction, and revascularization. The mean age of patients in the individual trials ranged from 58 to 70 years, and most participants were male (65.1% to 83.4%). The incidence of diabetes ranged from 13% [how effective are antithrombotic therapies in primary percutaneous coronary intervention (HEAT-PPCI)] to 100% [novel approaches for preventing or limiting events (NAPLES)], and the prevalence of previous myocardial infarction ranged from about 11% [the harmonizing outcomes with revascularization and Stents in acute myocardial infarction (HORIZONS-AMI)] to 45% (NAPLES).28 Transcatheter procedures were performed in the individual trials mainly through transfemoral access except for HEAT-PPCI (Table 2). In addition, all patients received contemporary evidence-based medical therapy. Postprocedural antiplatelet therapy included aspirin (80–325 mg/day) indefinitely and/or clopidogrel (75 mg/day) for at least 6 to 12 months. The level of evidence for each article was graded with a score of 2 to 5 according to the Jadad quality score (eTable 1, http://links.lww.com/MD/A342).

**Composite Outcomes**

The pooled analysis showed that bivalirudin was associated with a similar rate of the composite endpoint as compared with UFH (RR = 1.01; 95% CI 0.94–1.08; P = 0.85; I² = 42%). Moreover, the neutral finding was also consistently found in subgroup analyses regardless of anticoagulant regimens, clinical settings, or follow-up duration (Table 3). Additionally, meta-regression analyses did not reveal a substantial influence of clinical or demographic factors on the results (all P > 0.05; eTable 2, http://links.lww.com/MD/A342).

**All-Cause Death**

Overall, 559 of 18,878 patients died from all causes in the bivalirudin-treatment group compared with 584 of 19,218 patients in the UFH-treatment group, with no significant difference between the groups (RR = 0.97; 95% CI 0.85–1.11; P = 0.65; I² = 10%; Figure 2A). Moreover, subgroup analyses stratified by anticoagulant regimens did not reveal statistically significant differences in all-cause mortality between the 2 groups (all P > 0.05). However, when the intracoronary stenting and
| Study Name, year | Mean Age, years | Male, % | Current Smoker, % | Diabetes, % | Hypertension, % | Hyperlipidemia, % | Renal Insufficiency, % | Previous MI, % | Oral Dual Antiplatelet, % (A/T) | Any Stent Implanted, % | DES Implanted, % | Femoral, % |
|-----------------|----------------|--------|------------------|-------------|----------------|------------------|-----------------------|---------------|-------------------------------|----------------------|-----------------|-----------|
| ACUITY, 2006, 2007 | 63 | 69.9 | 29.1 | 28.1 | 67 | 57.2 | 19.1 | 31 | 92.9/68.0 | 56.4 | 36.7 | NA |
| ARMYDA-7 BIVALVE, 2012 | 70 | 71 | 15 | 63 | 91 | NA | 21 | 44 | 100/100 | NA | 28 | 98 |
| ARNO, 2010 | 68.9 | 76 | 17.5 | 21.5 | 60 | 50 | 0 | 39.5 | 100/100 | 86.5 | 76.5 | 98 |
| BAS, 2001 | 63 | 68 | NA | 21 | NA | NA | 0 | 18.1 | 100/0 | NA | NA | 100 |
| CACHET, 2002 | 63 | 75 | NA | NA | NA | NA | NA | NA | 100/NA | 88 | NA | 100 |
| EUROMAX, 2013 | 61 | 76 | 42.1 | 14 | 44 | 37 | NA | 8.8 | 100/98 | 91.7 | 31.8 | 53 |
| HEAT-PPCI, 2014 | 63 | 71 | 42.5 | 13.8 | 41.5 | 37.5 | NA | 12 | 100/100 | 92.5 | 79.8 | 18.9 |
| HORIZONS-AMI, 2008, 2011 | 60 | 76.5 | 46.1 | 16.5 | 53.5 | 43 | 16.7 | 10.9 | 99.8/98.5 | 95.4 | 86.7 | NA |
| ISAR REACT 3, 2008, 2010 | 67 | 76.5 | 14.5 | 27.5 | 89.2 | 79.7 | NA | 31.1 | 100/100 | 94.3 | 87.7 | NA |
| ISAR-REACT 4, 2011, 2013 | 67.5 | 76.9 | 23.8 | 29 | 85.5 | 68.6 | NA | 20.4 | 100/100 | 95.7 | 88.5 | 100 |
| NAPLES, 2009 | 65.3 | 65.1 | 20.6 | 100 | 76.4 | 63.9 | 37.8 | 44.7 | 100/100 | 100 | 82.4 | 100 |
| NAPLES III, 2015 | 78 | 52.5 | 20.7 | 44 | 83.5 | 56.5 | 45.8 | 40 | 100/100 | 99.6 | 82.5 | 100 |
| PROTECT-TIMI-30, 2006 | 60 | 67 | 36.9 | 40.5 | 65.6 | 55.3 | NA | 21.3 | 100/100 | 100 | 79 | NA |
| REPLACE-1, 2004 | 64.4 | 69.9 | 19.4 | 30.2 | 72.4 | NA | NA | 41.6 | 100/89.8 | 85 | NA | 97.1 |
| REPLACE-2, 2003, 2004 | 62.6 | 74.4 | 26.6 | 27.1 | 67 | NA | NA | 37 | 100/86 | 85.4 | NA | NA |
| TENACITY, 2011 | 63 | 73 | 27 | 30.5 | 80 | 82.5 | NA | 31 | 100/100 | 99.5 | 90 | NA |
| Xiang, 2013 | 58 | 83.4 | NA | NA | NA | NA | 41.9 | 100/100 | 99.1 | 95.4 | 74.5 | NA |

A/T = aspirin/thienopyridine, DES = drug-eluting stent, GPI = glycoprotein IIb/IIIa inhibitors, MI = myocardial infarction, NA = not available, PCI = percutaneous coronary intervention.
TABLE 3. Subgroup Analyses

| Subgroup               | Composite Outcomes | All-Cause Death | Major Bleeding |
|------------------------|--------------------|-----------------|---------------|
|                        | No. of Patients | RR (95% CI) | P Value | I² | No. of Patients | RR (95% CI) | P Value | I² | No. of Patients | RR (95% CI) | P Value | I² |
| Participants*          |                    |                |         |    |                |            |         |    |                |            |         |    |
| NSTE-ACS               | 16,071             | 1.02 [0.95, 1.09] | 0.59 | 0% | 16,071         | 1.13 [0.88, 1.45] | 0.32 | 19% | 12,168         | 0.69 [0.42, 1.13] | 0.14 | 51% |
| STEMI                  | 7629               | 1.15 [0.90, 1.47] | 0.27 | 63% | 7629           | 0.92 [0.69, 1.22] | 0.56 | 44% | 7629           | 0.67 [0.43, 1.05] | 0.08 | 77% |
| Unselected CHD         | 14,392             | 0.90 [0.76, 1.06] | 0.20 | 54% | 14,396         | 0.89 [0.70, 1.12] | 0.32 | 0%  | 14,394         | 0.62 [0.50, 0.75] | <0.001 | 1%  |
| Follow-up duration     |                    |                |         |    |                |            |         |    |                |            |         |    |
| In-hospital            | 6777               | 0.99 [0.88, 1.12] | 0.93 | 7%  | 6779           | 1.26 [0.75, 2.13] | 0.38 | 21% | 6135           | 0.39 [0.30, 0.50] | <0.001 | 17% |
| 30 days                | 32,152             | 1.03 [0.92, 1.16] | 0.58 | 44% | 32,154         | 1.00 [0.88, 1.14] | 0.98 | 1%  | 27,278         | 0.70 [0.62, 0.79] | <0.001 | 74% |
| 6 months               | 10,755             | 0.95 [0.81, 1.13] | 0.58 | 70% | 10,755         | 0.89 [0.46, 1.74] | 0.74 | 70% | 850            | 0.32 [0.13, 0.78] | 0.01 | –   |
| 12 months              | 16,335             | 1.02 [0.95, 1.09] | 0.58 | 0%  | 22,337         | 0.98 [0.85, 1.14] | 0.83 | 0%  | –              | –            | –     | –   |

CHD = coronary heart disease, CI = confidence interval, NSTE-ACS = non-ST segment elevation acute coronary syndrome, RR = risk ratio, STEMI = ST segment myocardial infarction.

* The longest follow-up data in the individual trials were included in the pooled subgroup analysis.

antithrombotic regimen—rapid early action for coronary treatment (ISAR REACT) 4 study27 or the evaluate the relative protection against post-PCI microvascular dysfunction and post-PCI ischaemia among anti-platelet and anti-thrombotic agents-thermolysis in myocardial infarction-30 (PROTECT-TIMI-30) study28 were removed from the subgroup of bivalirudin alone or bivalirudin plus provisional GP IIb/IIIa inhibitors versus UFH plus planned GP IIb/IIIa inhibitors, we found that the intrasubgroup difference became statistically significant ($P = 0.02$ and 0.045, respectively). Nevertheless, this process did not markedly influence the overall estimate. Moreover, in subgroup analyses and meta-regression analyses, the predefined clinical factors did not have statistically significant influences on the pooled result (Table 3 and eTable 2, http://links.lww.com/MD/A342).

Myocardial Infarction or Reinfarction, Ischemia-Driven Revascularization, and In-Stent Thrombosis

Meta-analytic pooling for myocardial infarction or reinfarction, ischemia-driven revascularization, and in-stent thrombosis showed that bivalirudin did not provide a greater advantage relative to UFH (myocardial infarction or reinfarction: $RR = 1.02$; 95% CI 0.91–1.16; $P = 0.70$; $I^2 = 39$%; ischemia-driven revascularization: $RR = 1.03$; 95% CI 0.92–1.15; $P = 0.58$; $I^2 = 40$%; and in-stent thrombosis: $RR = 1.37$; 95% CI 0.93–2.00; $P = 0.11$; $I^2 = 48$%; Figure 2B). Subgroup analyses stratified by anticoagulant regimen demonstrated that bivalirudin plus provisional GP IIb/IIIa inhibitors seemed likely to increase the risk of in-stent thrombosis compared with UFH plus provisional GP IIb/IIIa inhibitors ($RR = 3.09$; $P < 0.001$; Figure 2B). Notably, the HEAT-PPCI study10 was likely to greatly contribute to the negative result, because the statistical difference disappeared after the removal of this study from the subgroup.

Major Bleeding and Blood Transfusion

Bivalirudin showed a highly significant 34% decrease in the incidence of major bleeding ($RR = 0.66$; 95% CI 0.54–0.81; $P < 0.001$; $I^2 = 53$%; Figure 3) and a 28% reduction in the need for blood transfusion ($RR = 0.72$; 95% CI 0.56–0.91; $P < 0.01$; $I^2 = 39$%) compared with UFH. Moreover, the benefit of bivalirudin in lowering the risk of major bleeding and subsequent need for blood transfusion was statistically significant in the subgroup of bivalirudin alone or bivalirudin plus provisional GP IIb/IIIa inhibitors versus UFH plus planned GP IIb/IIIa inhibitors ($P < 0.01$). Furthermore, the beneficial effect of bivalirudin was consistently shown in the subgroup analyses stratified by follow-up duration ($P < 0.05$; Table 3). Notably, the bleeding risk with bivalirudin appeared to increase gradually and significantly with the increase in the use of GP IIb/IIIa inhibitors ($lnRR = 0.52$; $P = 0.012$, Figure 4A), especially eptifibatide ($P = 0.001$, Figure 4B) and tirofiban ($P = 0.002$, Figure 4C, eTable 2, http://links.lww.com/MD/A342).

There was no evidence for publication bias among the included studies. Funnel plots were generated for the composite endpoint, all-cause death, and major bleeding, and essential symmetries were found. Begg tests based on these data did not show any statistical significances (all $P > 0.10$; eFigure, http://links.lww.com/MD/A342).

DISCUSSION

This meta-analysis mainly showed that bivalirudin monotherapy or dual antithrombotic therapies were associated with a lower bleeding risk compared with UFH therapy. The use of GP IIb/IIIa inhibitors may weaken the benefit of bivalirudin in reducing the bleeding risk. In addition, bivalirudin, in comparison to UFH, did not significantly increase the incidence of the individual and composite ischemic endpoints of all-cause death, myocardial infarction or reinfarction, and ischemia-driven coronary revascularization as well as in-stent thrombosis.

The combination of a potent anticoagulant (heparin or bivalirudin) with antiplatelet therapy (aspirin, clopidogrel, or GP IIb/IIIa inhibitors) is routinely used during transcatheter coronary interventional procedures.37 Bivalirudin carries no risk of heparin-induced thrombocytopenia, does not require a binding cofactor such as antithrombin III, and does not activate platelets.38 Pharmacologically, these characteristics make bivalirudin an ideal alternative to heparin, especially in patients with antithrombin III deficiency or relatively low platelet levels. Indeed, the present meta-analysis indicated the favorable effect of bivalirudin on lowering the bleeding risk and transfusion rate compared with UFH, and the benefit remained consistent in different observation periods. In the era of antiplatelet mono- or dual antiplatelet therapy, a growing body of evidence...
FIGURE 2. Pooled risk ratio of bivalirudin versus heparin for all-cause mortality (A) and in-stent thrombosis (B). CI = confidence interval.
has identified the beneficial effect of bivalirudin on bleeding risk in patients undergoing transcatheter coronary procedures.\textsuperscript{21,25} However, under the conditions of the present wide use of GP IIb/IIIa inhibitors, it remains uncertain whether bivalirudin is able to exert an identical beneficial effect. The present study mainly investigated the impact of additional GP IIb/IIIa inhibitors on major bleeding associated with bivalirudin or heparin anticoagulant therapy. Unexpectedly and interestingly, we found that the use of GP IIb/IIIa inhibitors, especially eptifibatide or tirofiban, substantially reduced the superiority of bivalirudin over UFH. Specifically, with the increase in the frequency of GP IIb/IIIa inhibitor administration during coronary interventional procedures, the benefit of bivalirudin relative to heparin in lowering the bleeding risk was gradually weakened. That is, under conditions of triple antiplatelet therapy (aspirin, clopidogrel, and GP IIb/IIIa inhibitors), bivalirudin treatment might result in a bleeding risk almost identical to that of UFH therapy, and this result was also identified by our subgroup analyses based on anticoagulant regimens. Presently, achieving a balance between ischemic outcomes and bleeding events is essential in the field of antithrombotic therapy. Emerging evidence indicates the independent relationship between major bleeding with or without blood transfusion and subsequent death.\textsuperscript{39} Major bleeding may be a powerful predictor of death or poor prognosis in patients undergoing PCI.\textsuperscript{40} The HORIZONS-AMI study,\textsuperscript{23} a prospective randomized trial involving patients with ST-segment elevation myocardial infarction undergoing primary PCI, demonstrated that bivalirudin plus provisional GP IIb/IIIa inhibitors improved the event-free survival at 30 days, mainly due to a significant reduction in major bleeding as compared with that experienced with UFH plus planned GP IIb/IIIa inhibitors. However, the present study did not identify a relationship between bleeding events and ischemic outcomes of all-cause death, myocardial infarction or reinfarction, ischemia-driven revascularization, or in-stent thrombosis. Nevertheless, relative to heparin, bivalirudin did not significantly increase the incidence of composite and individual ischemic outcomes. Moreover, the neutral effect on ischemic outcomes remained highly consistent in our subgroup analyses and meta-regression analyses. Additionally, the present study did not show a pronounced additional influence of GP IIb/IIIa inhibitors on clinical prognosis. Several limitations of the meta-analysis should be considered. The majority of the included trials did not provide data regarding the precise dose of bivalirudin used. As a result, we did not consider the impact of the bivalirudin dose on its efficacy and safety endpoints, and this meta-analysis still could not confirm whether bivalirudin therapy had a dose-specific effect on ischemic and bleeding outcomes. Moreover, all of the included trials involved the use of clopidogrel, rather than prasugrel or ticagrelor, which are more effective antiplatelet agents for reducing the cardiovascular death/stroke/infarction rate, according to the recommendation for oral dual antiplatelet therapy.\textsuperscript{41,42} Therefore, it remains uncertain whether the use of prasugrel or ticagrelor could change the findings regarding the effect of bivalirudin versus UFH in patients undergoing PCI. In
addition, as in other nonpatient-level meta-analyses, the present study utilized summarized published events for each trial as opposed to individual patient data. Nevertheless, the findings in the meta-analysis were generated based on a large-scale population from RCTs, and appropriate meta-analytic techniques with random-effect models were used to pool the effect variables. Moreover, our overall analyses were not influenced by publication bias, and sensitivity analysis further confirmed the credibility of the overall estimates.

In summary, bivalirudin was found to be superior to UFH for reducing the risk of major bleeding and need for blood transfusion, with no increase in the incidence of ischemic outcomes, in patients undergoing PCI. Notably, the adjunctive use of GP IIb/IIIa inhibitors during PCI may weaken the favorable effect of bivalirudin on lowering bleeding risk.

ACKNOWLEDGMENTS

This work was supported by a grant from the National Natural Science Foundation of China (NSFC) (No. 81470300).

REFERENCES

1. Ebrahimi R, Lincoff AM, Bittl JA, et al. Bivalirudin vs heparin in percutaneous coronary intervention: a pooled analysis. J Cardiovasc Pharmacol Ther. 2005;10:209–216.

2. Bertrand OF, Jolly SS, Rao SV, et al. Meta-analysis comparing bivalirudin versus heparin monotherapy on ischemic and bleeding outcomes after percutaneous coronary intervention. Am J Cardiol. 2012;110:599–606.

3. Mrdovic I, Savic L, Lasica R, et al. Efficacy and safety of tirofiban-supported primary percutaneous coronary intervention in patients pretreated with 600 mg clopidogrel: results of propensity analysis using the Clinical Center of Serbia STEMI Register. Eur Heart J Acute Cardiovasc Care. 2014;3:56–66.

4. Muniz-Lozano A, Rollini F, Franchi F, et al. Update on platelet glycoprotein IIb/IIIa inhibitors: recommendations for clinical practice. Ther Adv Cardiovasc Dis. 2013;7:197–213.

5. Iqbal Z, Cohen M, Pollack C, et al. Update on platelet glycoprotein IIb/IIIa inhibitors: recommendations for clinical practice. Ther Adv Cardiovasc Dis. 2013;7:197–213.

6. Tarantini G, Brener SJ, Barioli A, et al. Impact of baseline hemorrhagic risk on the benefit of bivalirudin versus unfractionated heparin in patients treated with coronary angioplasty: a meta-regression analysis of randomized trials. Am Heart J. 2014;167:401.e6–412.e6.

7. Cassese S, Byrne RA, Laugwitz KL, et al. Bivalirudin versus heparin in patients treated with percutaneous coronary intervention: a meta-analysis of randomised trials. EuroIntervention. 2015;11:196–203.
8. Cavender MA, Sabatine MS. Bivalirudin versus heparin in patients planned for percutaneous coronary intervention: a meta-analysis of randomised controlled trials. *Lancet*. 2014;384:599–606.

9. Bangalore S, Pencina MJ, Kleiman NS, et al. Heparin monotherapy or bivalirudin during percutaneous coronary intervention in patients with non-ST-segment-elevation acute coronary syndromes or stable ischemic heart disease: results from the Evaluation of Drug-Eluting Stents and Ischemic Events registry. *Circ Cardiovasc Interv*. 2014;7:365–373.

10. Shahzad A, Kemp I, Mars C, et al. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. *Lancet*. 2014;384:1849–1858.

11. Xiang DC, Gu XL, Song YM, et al. Evaluation on the efficacy and safety of domestic bivalirudin during percutaneous coronary intervention. *Chin Med J (Engl)*. 2013;126:3064–3068.

12. Schulz S, Kastrati A, Ferenc M, et al. One-year outcomes with abciximab and unfractionated heparin versus bivalirudin during percutaneous coronary interventions in patients with non-ST-segment elevation myocardial infarction: updated results from the ISAR-REACT 4 trial. *EuroIntervention*. 2013;9:430–436.

13. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17:1–12.

14. Zhang S, Ge J, Yao K, et al. Meta-analysis of early versus deferred revascularization for non-ST-segment elevation acute coronary syndrome. *Am J Cardiol*. 2011;108:1207–1213.

15. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50:1088–1101.

16. Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet*. 1999;354:1896–1900.

17. Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med*. 2006;355:2203–2216.

18. Stone GW, Ware JH, Bertrand ME, et al. Antithrombotic strategies in patients with acute coronary syndromes undergoing early invasive management: one-year results from the ACUITY trial. *JAMA*. 2007;298:2497–2506.

19. Patti G, Pasceri V, D’Antonio L, et al. Comparison of safety and efficacy of bivalirudin versus unfractionated heparin in high-risk patients undergoing percutaneous coronary intervention (from the Anti-Thrombotic Strategy for Reduction of Myocardial Damage During Angioplasty-Bivalirudin vs Heparin study). *Am J Cardiol*. 2012;110:478–484.

20. Parodi G, Migliorini A, Valentì R, et al. Comparison of bivalirudin and unfractionated heparin plus protamine in patients with coronary heart disease undergoing percutaneous coronary intervention (from the Antithrombotic Regimens aNd Outcome [ARNO] trial). *Am J Cardiol*. 2010;105:1053–1059.

21. Bittl JA, Chemaitly BR, Feit F, et al. Bivalirudin versus heparin during coronary angioplasty for unstable or postinfarction angina: final report reanalysis of the Bivalirudin Angioplasty Study. *Am Heart J*. 2001;142:952–959.

22. Lincoff AM, Kleiman NS, Kottke-Marchant K, et al. Bivalirudin with planned or provisional abciximab versus low-dose heparin and abciximab during percutaneous coronary revascularization: results of the Comparison of Abciximab Complications with Hirudog for Ischemic Events Trial (CACHET). *Am Heart J*. 2002;143:847–853.

23. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med*. 2008;358:2218–2230.

24. Stone GW, Witzenbichler B, Guagliumi G, et al. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multi-centre, randomised controlled trial. *Lancet*. 2011;377:2193–2204.

25. Kastrati A, Neumann FJ, Meh Jill J, et al. Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. *N Engl J Med*. 2008;359:688–696.

26. Schulz S, Meh Jill 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.

27. Kastrati A, Neumann FJ, Schulz S, et al. Abciximab and heparin versus bivalirudin for non-ST-elevation myocardial infarction. *N Engl J Med*. 2011;365:1980–1989.

28. Tavano D, Visconti G, D’Andrea D, et al. Comparison of bivalirudin monotherapy versus unfractionated heparin plus tirofiban in patients with diabetes mellitus undergoing elective percutaneous coronary intervention. *Am J Cardiol*. 2009;104:1222–1228.

29. Gibson CM, Morrow DA, Murphy SA, et al. A randomized trial to evaluate the relative protection against post-percutaneous coronary intervention microvascular dysfunction, ischemia, and inflammation among antplatelet and antithrombotic agents: the PROTECT-TIMI-30 trial. *J Am Coll Cardiol*. 2006;47:2364–2373.

30. Lincoff AM, Bittl JA, Kleiman NS, et al. Comparison of bivalirudin versus heparin during percutaneous coronary intervention (the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events [REPLACE]-1 trial). *Am J Cardiol*. 2004;93:1092–1096.

31. Lincoff AM, Bittl JA, Harrington RA, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA*. 2002;289:853–863.

32. Lincoff AM, Kleiman NS, Kereiakes DJ, et al. Long-term efficacy of bivalirudin and provisional glycoprotein IIb/IIIa blockade vs heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization: REPLACE-2 randomized trial. *JAMA*. 2004;292:696–703.

33. Moliterno DJ, Committee TS. Investigators. A randomized two-by-two comparison of high-dose bolus tirofiban versus abciximab and unfractionated heparin versus bivalirudin during percutaneous coronary revascularization and stent placement: the tirofiban evaluation of novel dosing versus abciximab with clopidogrel and inhibition of thrombin (TENACITY) study trial. *Catheter Cardiovasc Interv*. 2011;77:1001–1009.

34. White HD, Ohman EM, Lincoff AM, et al. Safety and efficacy of bivalirudin with and without glycoprotein IIb/IIIa inhibitors in patients with acute coronary syndromes undergoing percutaneous coronary intervention 1-year results from the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial. *J Am Coll Cardiol*. 2008;52:807–814.

35. 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 Cardiovasc Interv*. 2015;8:414–423.

36. Steg PG, van ’t Hof A, Hamm CW, et al. Bivalirudin started during percutaneous coronary intervention: REPLACE-3 trial. *Circ Cardiovasc Interv*. 2013;6:2207–2217.

37. Garner WL, Linden JA, Chrysant GS. The clinical utility of bivalirudin in patients with coronary artery disease. *Cardiovasc Hematol Agents Med Chem*. 2013;11:44–48.
38. Abdel-Wahab M, Richard G. Safety of bivalirudin in patients with coronary artery disease. *Expert Opin Drug Saf.* 2012;11:141–150.

39. Mehran R, Pocock SJ, Nikolsky E, et al. A risk score to predict bleeding in patients with acute coronary syndromes. *J Am Coll Cardiol.* 2010;55:2556–2566.

40. Mehran R, Pocock S, Nikolsky E, et al. Impact of bleeding on mortality after percutaneous coronary intervention results from a patient-level pooled analysis of the REPLACE-2 (randomized evaluation of PCI linking angiomax to reduced clinical events), ACUITY (acute catheterization and urgent intervention triage strategy), and HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trials. *JACC Cardiovasc Interv.* 2011;4:654–664.

41. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2007;357:2001–2015.

42. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2009;361:1045–1057.