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Bivalirudin versus heparin in contemporary percutaneous coronary interventions for patients with acute coronary syndrome: A systematic review and meta-analysis

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Abstract

Background: *Bivalirudin is associated with fewer major bleeding events than heparin in patients undergoing percutaneous coronary intervention (PCI), but confounding effects of concomitant glycoprotein IIb/IIIa inhibitors, routine femoral artery access, and less potent effects of clopidogrel limits meaningful comparisons. The present study is a systematic review and meta-analysis to compare bivalirudin to heparin in contemporary practice.*

Methods: *The Cochrane Library, PubMed, EMBASE, and Ovid MEDLINE databases were searched for relevant studies, including comparisons between bivalirudin and heparin in the current medical era from inception to December 23, 2021. Studies reporting incidences of major adverse cardiac events (MACE) and net adverse clinical events (NACE) in patients undergoing PCI and meeting the inclusion criteria were retained. Data extraction was performed by three independent reviewers.*

Results: *The meta-analysis included 8 studies. Compared to heparin, bivalirudin during PCI was associated with a lower NACE risk, lower all-cause death, and similar MACE risk, with a pooled risk ratio of 0.82 (95% confidence interval [CI] 0.69–0.97, p = 0.02), 0.83 (95% CI 0.74–0.94, p = 0.002), and 0.93 (95% CI 0.78–1.10, p = 0.38), respectively. Moreover, the reduction in NACE was mainly attributed to reduced bleeding (22% reduction in the risk of major bleeding, 95% CI 0.63–0.97, p = 0.03).*

Conclusions: *These findings suggest that bivalirudin use during PCI reduced the risk of NACE and all-cause death but did not reduce the risk of MACE compared with heparin use in PCI. More studies specifically designed for anticoagulation strategies and a personalized anticoagulation regimen to comprehensively balance bleeding and ischemia risks are required.* (Cardiol J 2024; 31, 2: 309–320)

Keywords: percutaneous coronary intervention, bivalirudin, heparin, contemporary practices, mortality

Introduction

Primary percutaneous coronary intervention (PCI) is the optimum reperfusion strategy for patients presenting with acute myocardial infarction [1]. In the procedural phase, anticoagulant drugs combined with antiplatelet therapy are the accepted standard for preventing adverse ischemic events [2]. Bivalirudin is a direct thrombin inhibitor, working via the highly specific inhibition of thrombin. It can

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prolong activated clotting time to prevent thrombus formation during catheterization, and its inhibition of thrombin is reversible and short-lived [3, 4]. Earlier studies, such as the HORIZONS-AMI [5] and EUROMAX [6] trials, showed that anticoagulation with bivalirudin, compared to heparin plus glycoprotein IIb/IIIa inhibitors (GPI), reduced the risk of death and bleeding but increased the incidence of acute stent thrombosis. Subsequently, the HEAT-PPCI trial [7] revealed that the bleeding risks of bivalirudin and heparin were comparable, but increased rates of acute stent thrombosis were observed in the bivalirudin group. In view of this, the BRIGHT trial [8] proposed the concept of the "antithrombosis empty window period" within 4 hours after PCI because of the short--term antithrombotic effect of bivalirudin and the delayed pharmacodynamic effects of clopidogrel and demonstrated that the use of bivalirudin with a median 3-hour post-procedure PCI-dose infusion resulted in a decrease in bleeding events, without significant differences in major adverse cardiac, cerebral events, or stent thrombosis.

However, significant advances have occurred in pharmacological therapy and PCI technology in the past 20 years. For example, the recent preferred use of radial-artery access and bailout GPI is associated with fewer major bleeding complications [9–11]. Moreover, the current recommended use of potent $P2Y_{12}$ inhibitors in patients with acute coronary syndrome (ACS) undergoing PCI and in chronic coronary syndrome patients with PCI and a high ischemia risk may also confound clinical outcomes [12–14]. According to the current practice, it is unclear whether bivalirudin performs better than heparin in PCI, especially in ACS patients. Thus, this study aimed to review the outcome of bivalirudin versus heparin use in PCI according to the current practice.

Methods

Search strategy

This meta-analysis was performed in compliance with the PRISMA statement [15]. The study protocol was registered with PROSPERO (ID: CRD42022302633) at onset. PubMed, Embase, Ovid MEDLINE, and Cochrane Library databases were systematically searched for relevant studies from January 1, 2000 until December 23, 2021. The following medical subject heading terms and keywords were used to identify relevant articles: "bivalirudin" or "angiomax" or "hirulog" or "antithrombin", and "coronary stenting" or "percutaneous coronary intervention" or "PCI" or "angioplasty" or "coronary angioplasty" or "stents". Both randomized controlled trials (RCTs) and cohort studies were included, excluding other study designs (cross-sectional and case-control studies). The references of studies were also checked for suitable articles. No language restriction was applied.

Study selection

Several assessments were performed, followed by the removal of duplicate articles after the initial screening. The titles and abstracts of relevant publications were further screened for suitability before full article retrieval. Additionally, meeting abstracts, editorials, and reviews were also checked and excluded from the analysis [16]. Studies included were those that: 1) compared bivalirudin with heparin in PCI; 2) were published in peer-reviewed journals with available full texts; 3) reported cardiovascular clinical outcomes; 4) reported the bailout use of GPI; 5) included the use of radial-artery access and potent $P2Y_{12}$ inhibitors; and 6) included mainly patients with ACS. Trials with the routine use of GPI, exclusive use of femoral-artery access, or clopidogrel were excluded. Three investigators (ZXC, JYZ, and FBL) independently reviewed all retrieved studies, and differences were resolved via consensus.

Data extraction and quality assessment

Study data, including the first author's name, study design, location of study, sample size, clinical baseline characteristics, post-procedure infusion of bivalirudin, types of major adverse cardiac events (MACE), types of net adverse clinical events (NACE), frequency of patients in the bivalirudin and heparin groups, and incidence of mortality, were independently extracted by three investigators (JYZ, ZXC, CL). The definitions of MACE and NACE endpoints differed slightly between studies, but MACE basically included death, myocardial infarction (MI), and stroke, while NACE basically included MI, death from any cause, stroke, and major bleeding (see Table 3). The study quality was evaluated according to the Newcastle-Ottawa Quality scale. High-quality studies were defined as studies with a modified Newcastle-Ottawa score of ≥ 5 (maximum, 9).

Statistical analysis

Risk ratios of NACE, MACE, and particular events were estimated for each study between the bivalirudin and heparin groups. The heterogeneity

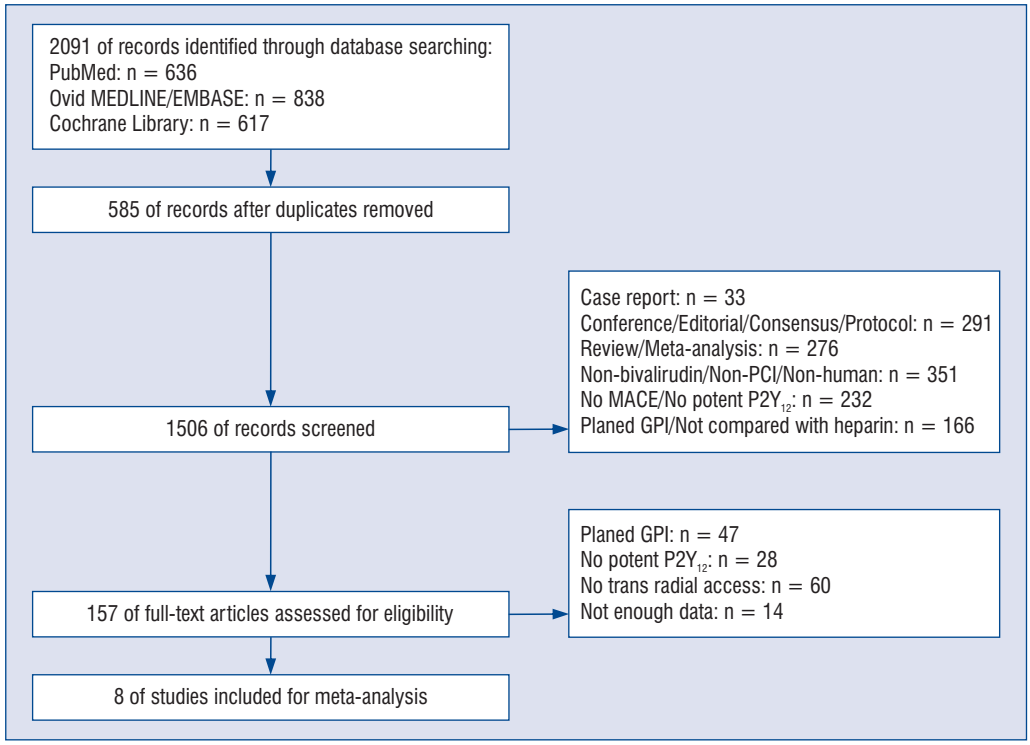

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) flow diagram of the study selection. PCI — percutaneous coronary intervention; DAPT — dual antiplatelet therapy; GPI — glycoprotein IIb/IIIa inhibitors; MACE — main adverse cardiac events.

of the effect measure was assessed by the Q and I^2 statistics. A random-effects model (DerSimonian and Laird method) was applied if heterogeneity was detected ($p < 0.10$ or $I^2 \geq 25\%$); otherwise, a fixed-effects model (Mantel-Haenszel) was used. Subgroup analyses were conducted by the study design (randomized vs. cohort) and by bivalirudin infusion strategies during PCI (extended vs. non-extended). Sensitivity analyses, excluding one study at a time, were performed to clarify whether the results were due to a study with an extreme result. Publication bias was assessed using the Begg adjusted rank correlation test and Egger regression asymmetry test. A p-value of < 0.05 was considered statistically significant. R version 4.1.2 software were used for the statistical analyses.

Results

Study selection

Six hundred thirty six publications were identified in PubMed, 617 publications in the Cochrane Library, and 838 publications in EMBASE and Ovid MEDLINE combined. Of these 2091 studies, 585 were duplicates. Eight of the remaining studies [6, 7, 17–22] met the inclusion criteria. Details of the search strategy are shown in Figure 1.

Study characteristics and quality assessment

Of the 8 included studies [6, 7, 17–22], 4 were randomized trials or prespecified subgroup analyses of randomized trials, whereas the others were retrospective or prospective cohort studies. Five of the included studies reported the NACE rates between the bivalirudin and heparin groups [6, 17–19, 21], while 7 reported MACE rates [6, 7, 17–21]. Three of the included studies had subgroups or cohorts with extended post-procedure infusion of bivalirudin [6, 18, 21]. The mean risk-of--bias score in the Newcastle-Ottawa scale was 8.3, and all included studies were high quality (score > 5). For the quality assessment of RCTs, the scale mainly included the following: (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); and (7) other bias. The general characteristics and definitions of outcome events in the included studies are summarized in Tables 1–3.

Risk of NACE in ACS patients undergoing PCI with bivalirudin vs. heparin

Five of the studies with NACE as the outcome provided the number of patients with bivalirudin and heparin. The effects of bivalirudin were heterogeneous among these studies, with a pooled risk ratio of 0.82 (95% confidence interval [CI] 0.69–0.97, p = 0.03, Fig. 2). This suggests that patients with ACS undergoing PCI with bivalirudin had an 18% reduction in NACE risk compared to those using heparin during the procedure. This calculation also revealed a significant reduction in bleeding in the bivalirudin group compared to the heparin group, with a pooled risk ratio of 0.78 (Fig. 2). The subgroup of patients that received an extended bivalirudin infusion after PCI had a 27% reduction in NACE risk compared to those using heparin during PCI, with a pooled risk ratio of 0.73 (95% CI 0.55–0.98, p < 0.01, Fig. 3).

Risk of MACE in ACS patients undergoing PCI with bivalirudin vs. heparin

Seven of the studies with MACE as the outcome provided the number of patients with bivalirudin or heparin during PCI. The effects of bivalirudin were heterogeneous among these studies, with a pooled risk ratio of 0.93 (95% CI 0.78–1.10, p = 0.38). Patients with ACS undergoing PCI with bivalirudin showed a reduced risk of all-cause mortality (Fig. 2) compared to those that used heparin during the procedure. However, the risk of cardiac death, MI, ischemic stroke, or stent thrombosis was similar between the two groups.

A subgroup analysis was performed of post--procedure bivalirudin infusions compared with heparin use during the procedure; bivalirudin demonstrated superior performance in the subgroup. Bivalirudin resulted in a decrease in NACE, greater decrease in major bleeding events, and lower risk of stent thrombosis (Fig. 3) compared with the group that did not use post-procedure bivalirudin infusion. In this subgroup, bivalirudin still reduced the risk of all-cause death and cardiac death (**Suppl. Fig. 1**) in patients undergoing PCI.

Furthermore, a subgroup analysis was performed of all RCT studies, which showed similar results as those above, including a decrease in NACE, without an increase in MACE or stent thrombosis events (**Suppl. Fig. 2**).

Stratified analysis and publication bias

To explore the study heterogeneity, stratified analyses across several key study characteristics and clinical factors was performed. Examining RCTs and non-randomized studies separately showed similar conclusions compared to when both study types were combined. The Egger weighted regression and Begg rank correlation approaches found no evidence of publication bias in the reporting of the findings.

Discussion

This systematic review and meta-analysis examined the effectiveness and safety of bivalirudin compared with heparin in contemporary PCI. According to available research, this is the first meta-analysis in the current medical era to assess this topic in this population. The present findings indicated that patients with ACS using bivalirudin during PCI had an 18% reduction in NACE risk compared to those using heparin. The reduction in NACE was mainly attributed to a reduction in bleeding. In addition, bivalirudin use in patients with ACS undergoing PCI did not show an increased risk of MACE, including stent thrombosis, compared to those with heparin use during PCI. Moreover, compared with the subgroup of non-extended bivalirudin infusion, the extended infusion subgroup showed reduced all-cause death and cardiac death when the heparin group was used as a control, which was most likely due to the reduced incidence of ischemic cardiovascular events in the early postprocedural period.

These results demonstrate that using bivalirudin is feasible and favorable in patients with ACS undergoing PCI because it does not increase MACE while reducing bleeding events. However, the proportion of transradial access, potency of the $P2Y_{12}$ inhibitors administered, type of stent, and use of extended infusion after PCI varied among the included studies. These factors may lead to the fluctuation of the benefit difference between bivalirudin and heparin. Moreover, age, sex, combined hypertension, combined diabetes, renal insufficiency, and lesion characteristics may also contribute to the different outcomes for patients undergoing PCI with bivalirudin or heparin. Because these heterogenous factors may confound the results, more studies comparing bivalirudin and heparin alone in contemporary clinical practice are needed to illustrate the best anticoagulation regimens during PCI.

Table 1. Baseline characteristics of the included studies.

Research, year	Study type	Quality score	Setting	Type of patients	Study design	Bolus after procedure
Zhang, 2020	Cohort study	7	The First Affiliated Hospital of Zhengzhou University	High-bleeding--risk ACS	Retrospective	Bivalirudin for up to 4 h after the procedure
Chen, 2020	Cohort study	8	The First Affiliated Hospital of USTC	STEMI	Retrospective	
HEAT-PPCI, 2014	RCT	8	Liverpool Heart and Chest Hospital (UK)	STEMI	Prospective	
MATRIX, 2018	RCT	9	78 hospitals in Italy, the Netherlands, Spain, and Sweden	ACS	Prospective	Full dose for up to 4 h or at a reduced dose of 0.25 mg/kg/h for at least 6 h
VALIDATE-SWEDEHEART, 2017	RCT	9	Uppsala Clinical Research Center	STEMI and NSTEMI	Prospective	
NCDR CathPCI, 2017	Cohort study	8	More than 1,800 sites across the United States	STEMI	Prospective	
SWEDEHERT, 2016	Observational registry study	8	Swedish Coronary Angiography and Angioplasty Register (SCAAR)	STEMI	Prospective	
EUROMAX, 2014	Pre-speciedanalysis	9	Nine European countries	STEMI	Prospective	The infusion of bivalirudin should be continued for at least 4 h after PCI at a dose of be 0.25 mg/kg/h; however, continuation of the full dose (1.75 mg/kg/h) used during PCI was also permitted

ACS — acute coronary syndrome; DAPT — dual antiplatelet therapy; PCI — percutaneous coronary intervention; RCT — randomized controlled trial; STEMI — ST-segment elevation myocardial infarction

Table 2. Baseline characteristics of the included studies.

Research, year	Age, years	Male, n (%)	Hypertension, n (%)	Diabetes, n (%)	Dyslipidemia, n (%)	CKD, n (%)	Previous PCI, n (%)
Zhang, 2020							
Bivalirudin (n = 361)	69.4 ± 10.1	213 (59.0%)	242 (67.0%)	130 (36.0%)	–	99 (27.4%)	92 (25.5%)
Heparin (n = 462)	66.4 ± 11.0	252 (54.5%)	302 (65.4%)	188 (40.7%)	–	133 (28.8%)	120 (26.0%)
Chen, 2020							
Bivalirudin (n = 412)	80.34 ± 4.54	257 (62.4%)	–	–	–	–	–
Heparin (n = 260)	78.73 ± 3.92	157 (60.4%)	–	–	–	–	–
HEAT-PPCI, 2014							
Bivalirudin (n = 905)	62.9 (53.7, 74.0)	647 (71.5%)	362 (40%)	114 (13%)	327 (37%)	–	76 (8%)
Heparin (n = 907)	63.6 (54.0, 73.8)	663 (73.1%)	388 (43%)	136 (15%)	342 (38%)	–	54 (6%)
MATRIX, 2018							
Bivalirudin (n = 3610)	65.4 ± 11.9	2731 (75.7%)	2264 (62.7%)	824 (22.8%)	1596 (44.2%)	48 (1.3%)	536 (14.8%)
Heparin (n = 3603)	65.4 ± 11.9	2764 (76.7%)	2222 (61.7%)	793 (22.0%)	1558 (43.2%)	47 (1.3%)	504 (14.0%)
VALIDATESWEDEHEART, 2017							
Bivalirudin (n = 3004)	68 (59, 75)	2229 (74.2%)	1557 (51.8%)	491 (16.3%)	953 (31.7%)	–	456 (15.2%)
Heparin (n = 3002)	68 (60, 75)	2177 (72.5%)	1548 (51.6%)	508 (16.9%)	936 (31.2%)	–	426 (14.2%)
NCDR CathPCI, 2017							
Bivalirudin (n = 29660)	60.3 ± 12.3	22,201 (74.9%)	19,456 (65.6%)	7,553 (25.5%)	17,009 (57.4%)	–	5,331 (18.0%)
Heparin (n = 37708)	60.4 ± 12.4	28,294 (75.0%)	24,707 (65.5%)	9,432 (25.0%)	21,742 (57.7%)	–	6,917 (18.3%)
SWEDEHERT, 2016							
Bivalirudin (n = 16891)	67.7 ± 12	11841 (70.1%)	7432 (44%)	2415 (14.3%)	3547 (21%)	/	1351 (8%)
Heparin (n = 3724)	68.7 ± 12	2530 (68%)	1748 (47%)	543 (14.6%)	893 (24%)	–	398 (10.7%)
EUROMAX, 2014							
Bivalirudin (n = 1089)	61 (52, 71)	814 (21.9%)	459 (42.2%)	127 (11.7%)	398 (36.6%)	147 (14.7%)	97 (8.9%)
Heparin (n = 460)	62 (53, 73)	356 (77.4%)	243 (52.8%)	80 (17.4%)	417 (37.6%)	165 (16.5%)	51 (11.1%)

CKD — chronic kidney disease; PCI — percutaneous coronary intervention

The main factors influencing the effect of periprocedural anticoagulation (bivalirudin or heparin) are discussed below.

Bailout uses of GPI

Bivalirudin is associated with fewer major bleeding events than heparin in patients undergoing PCI, but the confounding effect of concomitant GPI limits a meaningful comparison. Anantha-Narayanan et al. [23] performed a systematic review and meta-analysis to compare bivalirudin and heparin with and without adjunctive GPI in PCI. The study included 26 comparison groups (22 original studies and 4 subgroup analyses) with

Table 3. Baseline characteristics of the included studies.

Research, year	Previous MI, n (%)	Current smoking, n (%)	Transradial access, n (%)	Potent $P2Y_{12}$, n (%)	Outcome measurement	NACE	MACE or MACCE
Zhang, 2020							
Bivalirudin (n = 361)	89 (24.7%)	104 (28.8%)	333 (92.2%)	229 (63.4%)	30 days	All-cause death, recurrent MI, ischemia-driven target vessel revascularization, stroke, and BARC 2–5 bleeding events	MI, death from any cause, or stroke
Heparin (n = 462)	107 (23.2%)	128 (27.7%)	405 (87.7%)	315 (68.2%)			
Chen, 2020							
Bivalirudin (n = 412)	32 (7.8%)	86 (20.9%)	347 (84.2%)	–	1 year		All-cause death, recurrent MI, ischemia-driven target vessel revascularization, and stroke
Heparin (n = 260)	27 (10.4%)	41 (15.8%)	234 (90.0%)	–			
HEAT-PPCI, 2014							
Bivalirudin (n = 905)	122(14%)	–	727 (80%)	801(89.0%)	28 days	All-cause mortality, MI, stroke, or BARC 3 or 5	All-cause mortality, cerebro-vascular accident, reinfarction, or additional unplanned target lesion revascularization
Heparin (n = 907)	93 (10%)	–	744 (82%)	819(91.0%)			
MATRIX, 2018							
Bivalirudin (n = 3610)	530 (14.7%)	1307 (36.2%)	1676 (46.4%)	713 (19.8%)	1 year	Death from any cause, MI, or major bleeding	All-cause mortality, MI, or stroke
Heparin (n = 3603)	501 (13.9%)	1302 (36.1%)	1688 (46.8%)	690 (19.2%)			
VALIDATESWEDEHEART, 2017							
Bivalirudin (n = 3004)	490 (16.3%)	716 (23.8%)	2708 (90.1%)	2916 (97.1%)	30 days		
Heparin (n = 3002)	484 (16.1%)	710 (23.7%)	2716 (90.5%)	2927 (97.5%)			
NCDR CathPCI, 2017							
Bivalirudin (n = 29660)	4,894 (16.5%)	–	29660 (100%)	14521 (47.7%)	30 days		Death, MI, stroke
Heparin (n = 37708)	6,384 (16.9%)	–	37708 (100%)	15777 (51.1%)			
SWEDEHERT, 2016							
Bivalirudin (n = 16891)	2010 (11.9%)	5219 (30.9%)	10641 (63%)	–	1 year		Death, MI, stroke
Heparin (n = 3724)	617 (16.6%)	1038 (27.9%)	2269 (61%)	–			
EUROMAX, 2014							
Bivalirudin (n = 1089)	80 (7.4%)	–	510 (47.7%)	578 (60.5%)	30 days	Death, MI, IDR, stroke, or major bleeding	Death, MI, IDR, or stroke
Heparin (n = 460)	48 (10.4%)	–	245 (54.1%)	194 (50.9%)			

IDR — ischemia-driven revascularization; BARC — Bleeding Academic Research Consortium; MACE — major adverse cardiac event; MI — myocardial infarction; NACE — net adverse cardiac event; ST — stent thrombosis

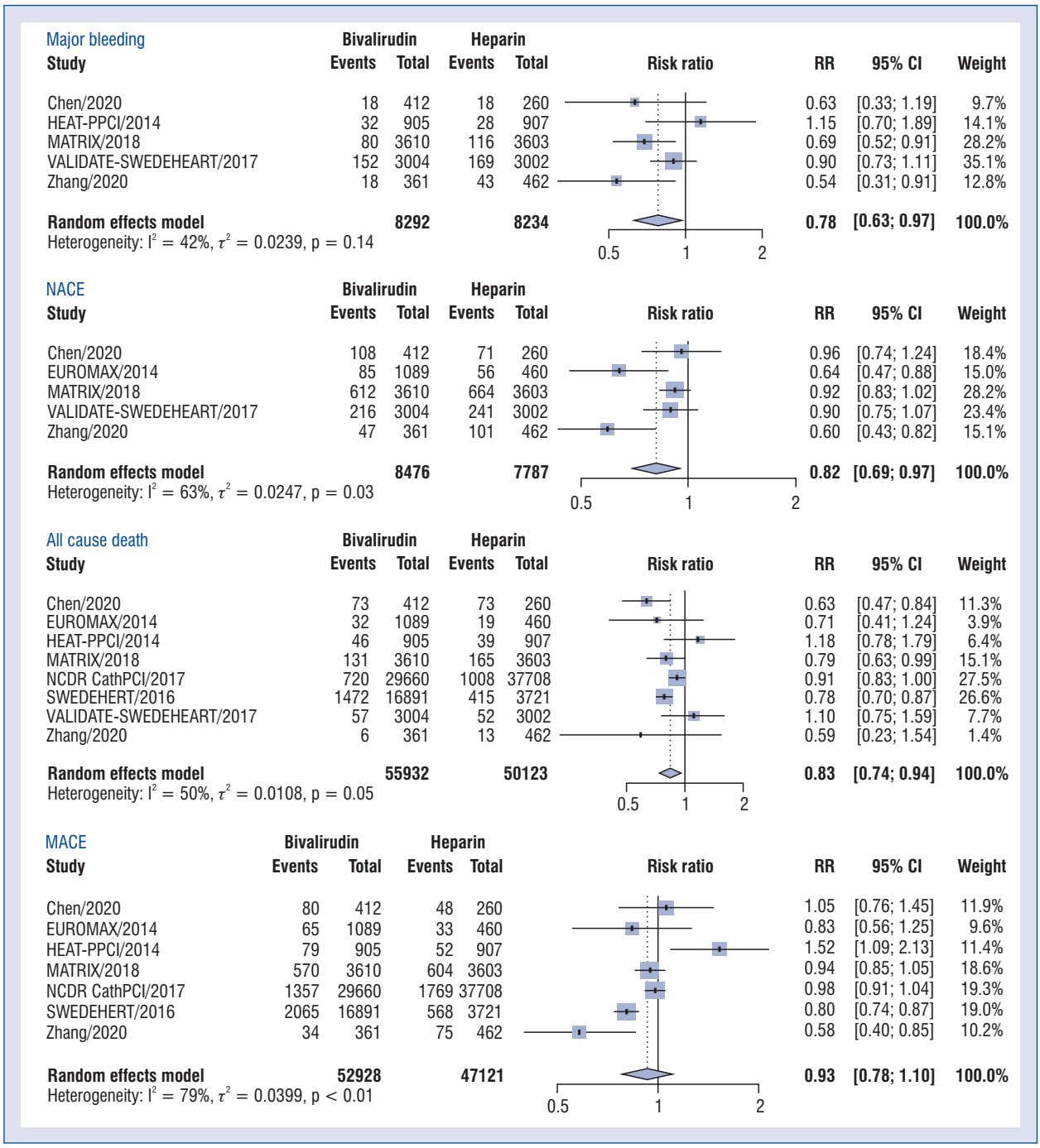

Figure 2. Pooled relative risks of net adverse clinical events (NACE), all-cause death, main adverse cardiac events (MACE), and major bleeding in patients receiving bivalirudin vs. heparin during percutaneous coronary intervention. Major bleeding was defined as a bleeding event of the Bleeding Academic Research Consortium (BARC) type 2, 3, and 5 or BARC 3 and 5 according to the included studies; RR — risk ratio.

53,364 patients and demonstrated that bivalirudin use is associated with a lower risk of major bleeding regardless of GPI use in the heparin arm. This persisted even after retaining studies with GPI use in the bivalirudin arm, which was expected to bias the results towards the null. The prespecified analysis from the EUROMAX trial yielded a similar conclusion [24], which illustrates that bivalirudin reduces major bleeding compared to that using heparin therapy with bailout or routine GPI. The trial also indicated that routine GPI was not superior to bailout GPI regarding MACE or stent

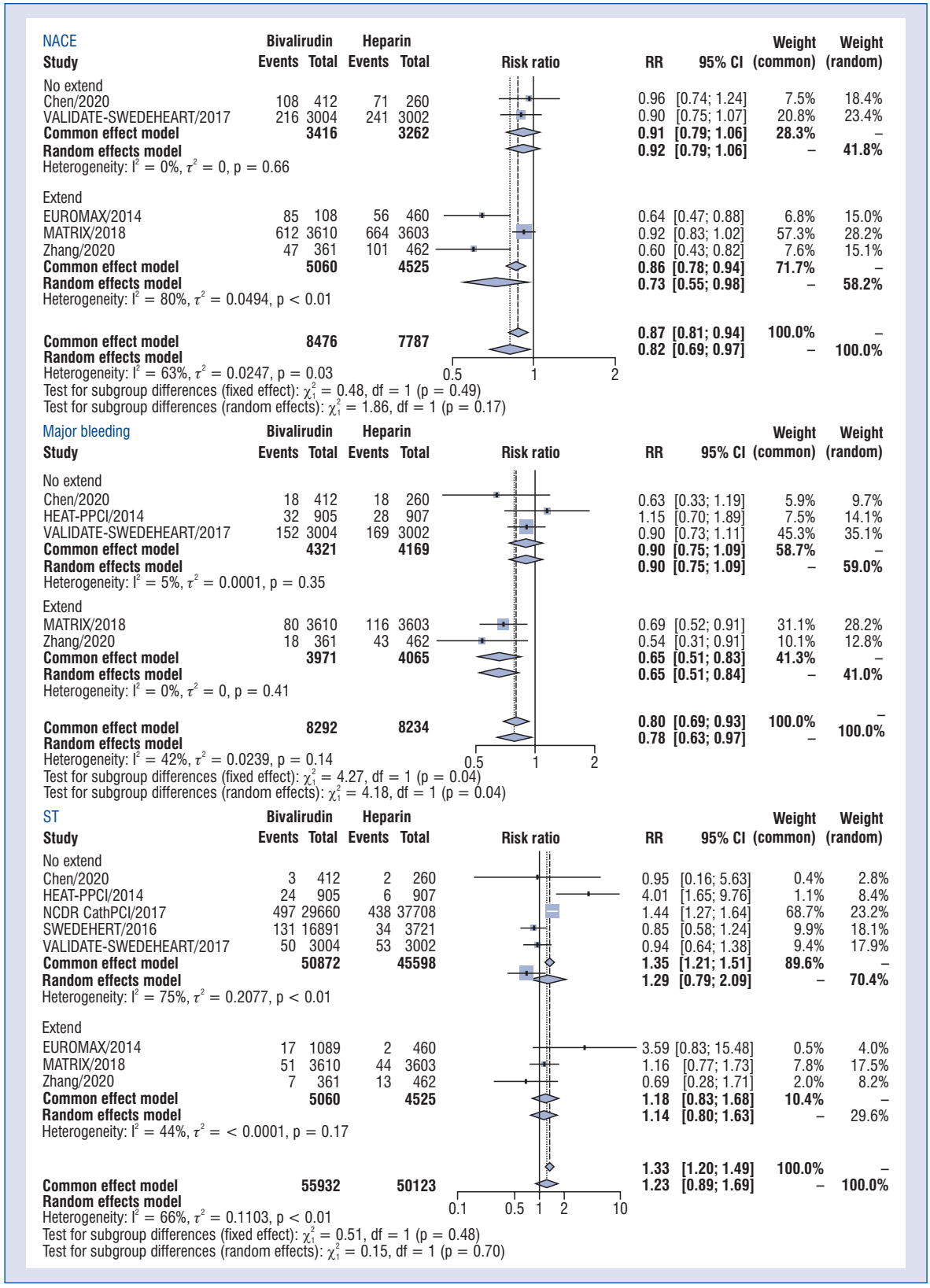

Figure 3. Pooled relative risks of net adverse clinical events (NACE), stent thrombosis (ST), and major bleeding in patients receiving bivalirudin vs. heparin in the extended infusion subgroup. Major bleeding was defined as a bleeding event of the Bleeding Academic Research Consortium (BARC) type 2, 3, and 5 or BARC 3 and 5 according to the included studies; RR — risk ratio.

thrombosis. Bailout GPI is still a relevant choice currently because routine GPI use does not appreciably prevent ischemic events, such as MACE and stent thrombosis.

Preferred transradial coronary interventions

In the era of femoral artery access, several studies have shown that bivalirudin reduced the risk of bleeding in patients compared to that of heparin. However, it is unclear if the bleeding benefit of bivalirudin remains relevant considering the current increase in the use of transradial access. MacHaalany et al. [9] conducted research involving all-comers and demonstrated no additional benefit in terms of the bleeding risk with the use of bivalirudin compared with the use of heparin when PCI was performed via radial access. Moreover, a study conducted by Jovin et al. [20] with patients from the NCDR CathPCI database in whom PCI was predominantly performed via radial access showed that the risk of bleeding did not significantly differ between the bivalirudin and heparin groups. These results illustrated that the ability of bivalirudin to prevent bleeding is attenuated among patients that undergo PCI via transradial access [25]. However, with the bailout use of GPI and the emergence of the bivalirudin extended infusion strategy, the advantages of bivalirudin have been rediscovered. In a meta-analysis by Kheiri et al. [26] that included 10 RCTs with 16,328 patients for whom transradial access during PCI was exclusively performed, the use of bivalirudin was significantly associated with a reduction in short-term NACE (30-day) compared with heparin. Moreover, in the BRIGHT study, the majority of the patients (79%) had radial access, and bivalirudin still exhibited a bleeding benefit [8]. This finding is consistent with the results of the current study, which suggests that although theoretically possible, the advantage of bivalirudin in reducing bleeding might be attenuated by transradial access, and it may still benefit patients in the contemporary medical setting.

Post-procedure bivalirudin infusion

In the present study, subgroup analysis showed that patients had better outcomes with respect to MACE, cardiac death, and stent thrombosis, when extended infusion strategy of bivalirudin was chosen. A single-center study by Frere et al. [27] prospectively enrolled 30 patients undergoing PCI for non-ST elevation ACS to investigate the antithrombotic efficacy of bivalirudin compared to unfractionated heparin during PCI. The study showed that an optimal inhibition of platelet reactivity was obtained 4 h after the PCI procedure. Another reason that patients with STEMI require a post-procedure PCI-dose of bivalirudin is that morphine and early gastrointestinal mucosal edema in STEMI inhibit the effect of $P2Y_{12}$ inhibitors [28]. Previous post hoc analyses have suggested that a prolonged infusion of high-dose bivalirudin after the procedure may prevent early stent thrombosis [16, 17]. As noted earlier, the BRIGHT trial proposed the concept of an "antithrombosis empty window period" within 4 hours after surgery because of the short antithrombotic effect of bivalirudin and the delayed pharmacodynamic effects of clopidogrel. The study demonstrated no significant differences in major adverse cardiac or cerebral events or stent thrombosis between the bivalirudin group with a median 3-h post-procedure PCI-dose infusion and those with heparin and GPI, while bivalirudin resulted in a decrease in bleeding events [8]. Moreover, Fahrni et al. [29] conducted a meta-analysis to compare the effect of prolonged PCI-dose bivalirudin infusion on clinical outcomes in patients undergoing primary PCI. The study included 6 RCTs comprising 17,294 patients and showed that prolonging the bivalirudin infusion at the PCI dose (1.75 mg/kg/h) for 3 h eliminated excess risk of acute stent thrombosis and maintained bleeding benefits [30]. Valgimigli et al. [21] reported outcomes of the MATRIX trial, where 3,610 patients were assigned to receive bivalirudin with or without prolonged post-PCI bivalirudin infusion. The results showed that a post-PCI full-dose bivalirudin infusion was associated with improved outcomes when compared with a no or low-dose post-PCI infusion or heparin. These findings suggest that the infusion of bivalirudin after PCI is effective in reducing the incidence of stent thrombosis in the early postoperative period without increasing the patient's risk of bleeding. However, these studies mostly occurred in the era without potent $P2Y_{12}$ inhibitors, radial artery access, or routine GPI.

The BRIGHT-4 study is a randomized controlled clinical trial that aimed to compare the treatment of post-PCI bivalirudin high-dose infusion with heparin monotherapy. The study found that the treatment of post-PCI bivalirudin high--dose infusion can reduce the relative risk of primary endpoint events by 31% (3.06% vs. 4.39%, $p = 0.0070$) compared with heparin monotherapy, including a 25% relative risk reduction in all-cause mortality (2.96% vs. 3.92%, $p = 0.0420$) and a 79% relative risk reduction in major bleeding (0.17% vs.

0.80%, p = 0.0014) within 30 days [32]. This study mainly used the potent $P2Y_{12}$ inhibitor ticagrelor, with the majority using the radial artery approach and without routine use of GPI, all of which suggest that the BRIGHT-4 study is more in line with contemporary clinical practices. Although the results of the BRIGHT-4 study were not yet published at the time of this meta-analysis, the conclusion of the present study is almost identical to the conclusion of the BRIGHT-4 study. Both studies suggest that bivalirudin has great value and prospects in today's clinical context. Therefore, based on the data included in this meta-analysis and the conclusion of the BRIGHT-4 study, it is believed herein, that in the next version of the guidelines, although the recommendation of bivalirudin may not replace heparin as the routine anticoagulant used in PCI due to the long-term experience with heparin and its simpler administration method, the recommendation level of bivalirudin may increase.

Limitations of the study

There were some limitations to the current study. First, the meta-analysis included both RCTs and cohort studies, which enhanced the heterogenicity of the studies, as observational data are subject to possible observable and unobservable confounding factors. Second, definitions for MACE and NACE were not consistent across studies, and this might have resulted in measurement bias because some studies reported NACE with major bleeding alone, whereas some included only minor bleeding. Third, the proportions of GPI, novel $P2Y_{12}$ inhibitors, and radial access differed among studies, which also contributed to the heterogeneity of this study. Finally, because the BRIGHT-4 study was not published before December 2021, when the search was completed for this meta-analysis, the BRIGHT-4 study was not included in this study.

Conclusions

Previous studies revealed that bivalirudin reduced the incidence of major bleeding in patients with ACS undergoing PCI compared to those receiving heparin, but it increased the risk of postoperative stent thrombosis. The meta-analysis, herein, revealed that bivalirudin is favorable in PCI in contemporary practice because it did not increase the risk of MACE and reduced the risks of NACE and all-cause death. In the contemporary medical era, with the use of new $P2Y_{12}$ antagonists and post-procedure bivalirudin infusion, the efficacy and safety of bivalirudin is reiterated. In conclusion, bivalirudin may be a better choice for patients with ACS during PCI compared with heparin alone in current medical practice.

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