Systematic review/Meta-analysis

Efficacy and safety of bivalirudin and heparin with or without glycoprotein IIb/IIIa inhibitors in patients of acute coronary syndrome undergoing percutaneous coronary intervention: a systematic review and network meta-analysis

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Abstract

Introduction: Recent clinical trials have revealed that bivalirudin has comparable efficacy to heparin. In this network meta-analysis, we aimed to compare the efficacy and safety of bivalirudin and heparin administered as monotherapy or with glycoprotein IIb/IIIa inhibitors, in patients of acute coronary syndromes undergoing percutaneous coronary intervention (PCI).
Material and methods: We performed a systematic search of PubMed and Embase to identify studies with acute coronary syndrome patients > 18 years, who underwent PCI, and were treated with bivalirudin or heparin either as monotherapy or with glycoprotein IIb/IIIa inhibitors. Outcomes were major bleeding, major adverse cardiovascular events (MACE), all-cause mortality, reinfarction, stent thrombosis and cardiovascular death. Pooled relative risks (RR) were calculated using the net-meta module with/and random effects model with a 95% confidence interval (CI) for statistical significance. Higgins I^2 statistic was used to assess heterogeneity.
Results: A total of 23 randomized controlled trials comprising 72,628 patients were included. Bivalirudin monotherapy compared to heparin monotherapy demonstrated no significant difference in risk of bleeding (RR = 0.83, 95% CI: 0.64–1.08, p = 0.17), MACE (RR = 0.99, 95% CI: 0.93–1.05, p = 0.72) and other outcomes. Bivalirudin combined with GP IIb/IIIa inhibitors had an increased risk of stent thrombosis compared with heparin monotherapy (RR = 3.62, 95% CI: 1.002–13.14). In major bleeding, heparin with GP IIb/IIIa inhibitors had a statistically significant RR of 1.454 (95% CI: 1.006–2.1009, p = 0.045).

Conclusions: Bivalirudin and heparin have similar efficacy and safety profiles in patients undergoing PCI for ACS. The choice of the anticoagulant should be individualized based on patient and procedural characteristics.

Key words: percutaneous coronary intervention, bivalirudin, heparin, network meta-analysis, systematic review.

Introduction

Acute myocardial infarction (AMI) is the leading cause of mortality in individuals with cardiovascular diseases, encompassing ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) [1, 2]. Annually, over a million people in the United States are hospitalized due to AMI. The immediate primary treatment is to restore blood flow via revascularization either with primary percutaneous coronary intervention (PCI) or coronary artery bypass surgery [3]. However, PCI procedure is associated with the risk of thrombosis because it triggers the coagulation system, leading to platelet activation, aggregation, and the potential blockage of blood vessels [4].

To prevent these complications, standard therapy involves administering antithrombotic medications during and shortly after PCI. Bivalirudin is commonly used as an alternative to heparin in acute coronary syndrome cases. Traditionally, unfractionated heparin was the go-to medication for periprocedural PCI. Yet, recent trials have revealed that bivalirudin not only exhibits anti-coagulation properties but also lowers the incidence of bleeding complications especially with femoral access during PCI compared to heparin [5]. Most studies have compared bivalirudin to heparin alongside glycoprotein (GP) IIb/ IIIa inhibitors, but there is a lack of data supporting a comparison between bivalirudin and heparin used alone.

Therefore, we aimed to compare the efficacy and safety of bivalirudin and heparin, used alone or in combination with GP IIb/IIIa inhibitors, in patients with acute coronary syndromes undergoing PCI.

Material and methods

The search strategy and methodology of our systematic review and network meta-analysis is consistent with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) extension statement of network meta-analysis guidelines. The checklist of these guidelines is shown in Supplementary file S1. The methodological quality was assessed using the assessing the methodological quality of systematic reviews-2 (AMSTAR-2) guidelines checklist. These are reported in Supplementary file S2. This review was not registered.

We performed a systematic literature search using PubMed and Embase databases from inception till September 2023. No language filters were applied. We used citation pearl matching/searching/growing techniques to identify any missed studies that could potentially be included. The detailed search strategy for each database is given in Supplementary file S2.

Studies were deemed eligible to be included if they were randomized controlled trials and included at least one of the following comparisons: (i) bivalirudin monotherapy vs heparin monotherapy, (ii) bivalirudin monotherapy vs heparin with GP IIb/IIIa inhibitors, (iii) bivalirudin with GP IIb/IIIa inhibitors vs heparin with GP IIb/IIIa inhibitors or (iv) bivalirudin with GP IIb/IIIa inhibitors vs heparin monotherapy. The target population was adults with acute coronary syndromes i.e., STEMI, NSTEMI, and unstable angina (UA) undergoing PCI. Studies were excluded if they reported non randomized data, reported data for PCI in stable coronary artery disease, did not report data for the primary or secondary outcomes, and included patients with < 18 years of age.

The primary outcome variables were major adverse cardiovascular events (MACEs) and major bleeding. The secondary outcomes were all-cause death, reinfarction, stent thrombosis and cardiac/cardiovascular death. MACE was defined as a composite of all-cause mortality, myocardial infarction and revascularization. If any trial did not provide MACE according to our standardized definition, we calculated MACE ourselves wherever required data was available. Major bleeding was as defined by Bleeding Academic Research Consortium type 3 or 5.

The studies identified through our database search were imported to Endnote X9 (Clarivate Analytics) and duplicate records were removed. Two authors (HN and MH) independently reviewed the titles and abstracts of imported studies. This was followed by the full-text screening leading to inclusion of studies that satisfied the eligibility criteria. A senior author was consulted in case of disagreements. We extracted data on a pre-piloted data extraction form on Microsoft Excel. Extracted data was compared and any discrepancies were resolved through mutual discussion. We extracted information on study characteristics (author, year of publication, country where the study was conducted, baseline characteristics of patients and data pertaining to clinical outcomes).

We report the mean with standard deviations (SD) for baseline characteristics and study out-

comes. Statistical analysis was conducted by R Studio paired with CRAN-R software version 4.3.1 (The R Foundation for Statistical Computing, Vienna, Austria). A *net-meta* module was used along with the random-effects model and pooled outcomes were reported as risk ratio (RR) with 95% confidence interval (CI) with a probability value of $p < 0.05$ was considered to be statistically significant. The overall net graph for this was also reported. Since heparin monotherapy was used as a reference against which the efficacies of all other strategies were compared, it was given an RR of 1.00. Treatments were ranked based on *p*-values from a *net-rank* module. We also did pairwise comparisons of treatment nodes using inverse variance and DerSimonian-Laird method to estimate between study variance [6]. Higgins I-squared (I^2) statistic was determined as a measure of statistical heterogeneity where values of ≤ 50% corresponded to low to moderate heterogeneity while values ≥ 75% indicated high heterogeneity. The potential inconsistencies between the direct and indirect evidence within the network were evaluated by using the design by treatment approach. Assessment of global inconsistencies was done using a generalized Cochran's Q statistic and local inconsistencies by using the "separate the indirect from direct design evidence" approach [7]. Publication bias was assessed by visually inspecting a funnel plot and mathematically using the Egger's test.

Treatments were also ranked based on the surface under the cumulative ranking curve (SUCRA) scores using the net-rank module. 10,000 iterations were run to calculate the SUCRA scores. The higher the SUCRA scores, the better the treatment [8]. We did separate sub-analyses for patients based on their clinical presentation: STEMI, NSTEMI and UA.

The quality assessment for the included studies was performed using Cochrane risk of bias for the randomized clinical trials [9]. This tool assesses the risk of bias across five domains, namely using signaling questions such as (i) randomization process, (ii) deviations from intended interventions, (iii) missing outcome data, (iv)_measurement of outcome and (v) selection of reported results. The results of risk of bias assessment were visualized through traffic light plots created using the robvis tool.

Results

The search strategy yielded 1951 studies, from which 262 duplicates were removed. After a thorough assessment, twenty-three randomized control trials [10–32] were included in the current meta-analysis. A detailed breakdown of the search strategy and study selection process is provided in Supplementary file S3 and PRISMA flowchart in Figure 1, respectively.

The detailed forest plots and funnel plots with Egger's *p*-test values are provided in Supplementary files S4 and S5, respectively.

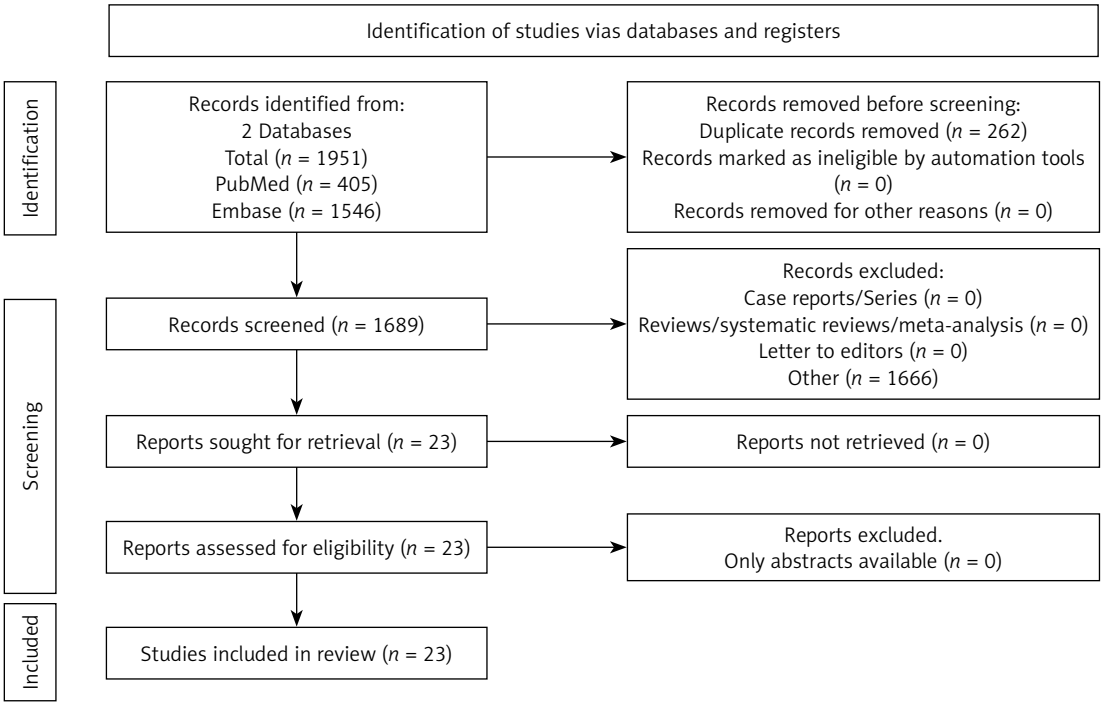

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow of the search strategy for the systematic review and meta-analysis. From: Pape MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372: n71. dot. 10.1136/bmj.n71

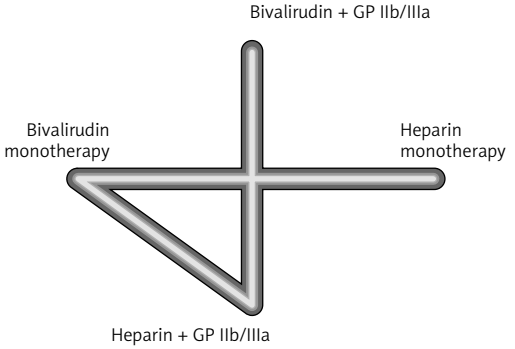

Figure 2. Network diagram of included comparisons

The total patient cohort was 72, 628 of which 4,954 were treated with bivalirudin plus GP IIb/IIIa inhibitors, 33,133 with bivalirudin monotherapy, 11,595 with heparin plus GP IIb/IIIa inhibitors, and 22,946 with heparin monotherapy. The trials were conducted in 2001-2022, with most of them being multicenter ones. Of the total patients, 53,495 (73.6%) were males.

The mean age ranged from 55 to 70 in the included trials. Femoral access predominated in earlier trials, whereas later studies often utilized radial access. Additionally, baseline cardiovascular risk factors such as hypertension, diabetes mellitus, smoking, hyperlipidemia, prior myocardial infarction were well balanced across treatment groups.

Data was categorized into three groups: bivalirudin plus GP IIb/IIIa inhibitors, bivalirudin monotherapy, and heparin plus GP IIb/IIIa inhibitors. The net graph is given in Figure 2 and is well connected. Heparin monotherapy served as the reference group, with its RR adjusted to 1 for the calculation of RR with a 95% CI to determine the statistical significance of the other groups. A summary of study characteristics is provided in Table I [8–17].

Major bleeding

The data regarding major bleeding risk was extracted from twenty-one studies comprising 72,089 patients. The analysis revealed that bivalirudin plus GP IIb/IIIa inhibitors and bivalirudin monotherapy had a statistically insignificant/non-significant RR of 1.143 (95% CI: 0.707–1.847, p = 0.585) and 0.834 (95% CI: 0.643–1.082, p = 0.172), respectively whereas heparin plus GP IIb/IIIa inhibitors had a statistically significant RR of 1.454 (95% CI: 1.006–2.1009, p = 0.045). Moderate heterogeneity (I^2 = 43.6%) was present among studies.

Major adverse cardiovascular events

Regarding MACE, the data was extracted from twenty-one studies with 72,179 patients in total. The analysis revealed statistically insignificant/

Table I. Characteristics of included randomized controlled trials (RCTs)

Title	2006	Year of study	Type of study	Type of blinding	Total no. of patients	Interventions and dose	Duration of follow-up	Primary outcomes	Secondary outcomes
	Lincoff *et al.* (2001)	2001	Randomized pilot trial	The study was not blinded	268	Bivalirudin: 0.5 mg/kg bolus, infusion of 1.75 mg/kg/h for the duration of the procedure plus planned abciximab and heparin: 70 U/kg bolus plus planned abciximab	7 days	Death, MI, repeat percutaneous coronary revascularization	-
HERO-2 trial	White *et al.* (2001)	2001	Randomized controlled trial (HERO-2 trial)	Open label randomization	17073	Bivalirudin: a bolus of 0.25 mg/kg followed by I/V of 0.5 mg/kg/h for 12 h and 0.25 mg/kg/h for next 36 h. Heparin: given a bolus of 5000 U followed by infusion of 1000 U/h in patients weighing 80 kg or more, and 800 U/h in those weighing less than 80 kg. The heparin infusion was continued for at least 48 h	30 days	Mortality	Reinfarction, stroke, intracerebral bleeding, bleeding events and non-fatal reinfarction
	Antman *et al.* (2002)	2002	Randomized controlled trial	Double blinding	133	Unfractionated heparin: bolus of 70 U/kg followed by an infusion of 15U/kg/h for a minimum of 72 h. Bivalirudin: bolus of 0.1 mg/kg followed by an infusion of 0.25 mg/kg/h for a minimum of 72 h	14 days	A composite of all-cause mortality or nonfatal recurrent MI	Death, nonfatal MI, or major hemorrhage

Table I. Cont.

Title	2006	Year of study	Type of study	Type of blinding	Total no. of patients	Interventions and dose	Duration of follow-up	Primary outcomes	Secondary outcomes
	Lincoff *et al.* (2003)	2003	Randomized controlled trial	Double blinding	6010	Bivalirudin: 0.75 mg/kg bolus plus 1.75 mg/kg/h for the duration of PCI with provisional GP IIb/IIIa inhibition. Heparin: 65 U/kg bolus with planned GP IIb/IIIa inhibition	30 days	Quadruple composite of death, MI, severe myocardial ischemia or in-hospital major bleeding	Death, MI or urgent revascularization
SWITCH III	Waksman *et al.* (2013)	2005/2013	Randomized pilot study (SWITCH III)	Open label	100	Bivalirudin: 0.75 mg/kg bolus followed by infusion of 1.75 mg/kg/h. Heparin: minimum dose of 60 U/kg IV for ACT > 200 s	24 h	In-hospital major bleeding	In-hospital death (nonhemorrhagic related), vascular access site complications, MI, need for repeat revascularization, procedural complication, and catheter thrombosis
	Chu *et al.* (2006)	2006	Cohort study	No blinding mentioned	672	Bivalirudin: bolus of 0.75 mg/kg, followed by an IV of 1.75 mg/kg/h. UFH/Unfractionated heparin: bolus of 40 U/kg and additional heparin to achieve an activated clotting time of 250–300 s	30 days in hospital and 6 months after PCI	Death, Q-wave MI, and TLR or TVR	–
	Stone *et al.* (2006)	2006	Randomized controlled trial	Open label	13,819	UFH/Unfractionated heparin: bolus of 60 IU/kg plus an infusion of 12 IU/kg/h to achieve an activated partial-thromboplastin time of 50 to 75 s before angiography and an activated clotting time of 200 to 250 s during PCI. Enoxaparin: 1 mg/kg was administered SC twice a day before angiography, an IV bolus of 0.3 mg/kg was given if last SC dose was 8 h earlier, 0.75 mg/kg if 16 h earlier. Bivalirudin: an IV bolus of 0.1 mg/kg and infusion of 0.25 mg/kg/h [14, 15] Before PCI, an additional IV bolus of 0.5 mg/kg was given and infusion was increased to 1.75 mg/kg/h	25 to 35 days	Death from any cause, MI, or unplanned revascularization for ischemia, major bleeding	–

Table I. Cont.

Title	2006	Year of study	Type of study	Type of blinding	Total no. of patients	Interventions and dose	Duration of follow-up	Primary outcomes	Secondary outcomes
	Geuns *et al.* (2007)	2007	Randomized controlled trial	Open label	78	Bivalirudin: bolus of 0.75 mg/kg and an infusion of 1.75 mg/kg/h for the duration of the procedure and for 4 h after completion of PPCI. UFH/Unfractionated heparin: administered a dose as per standard institutional practice	5 days	IS assessed by CMR	Index of microcirculatory resistance (IMR), CMR assessed microvascular obstruction (MVO) and ejection fraction, biomarkers for thrombin activity and cell injury
	Kastrati *et al.* (2008)	2008	Randomized controlled trial	Double blinding	4,570	Bivalirudin: 0.75 mg/kg bolus followed by infusion of 1.75 mg/kg/h for duration of the procedure. UFH/Unfractionated heparin: 140 U/kg bolus followed by placebo infusion for duration of the procedure	30 days	Death, MI, urgent target-vessel revascularization due to myocardial ischemia, major bleeding	Composite of death, myocardial infarction, or urgent target-vessel revascularization
	Stone *et al.* (2008)	2008	Randomized controlled trial	Open label	3602	Heparin: IV bolus of 160 IU/kg with subsequent boluses aimed at activated clotting time of 200–250 s. Bivalirudin: IV bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h	30 days	Major bleeding or major adverse cardiovascular events, including death, reinfarction, target-vessel revascularization for ischemia, and stroke	–
	Tavano *et al.* (2009)	2009	Randomized controlled trial	No blinding mentioned	366	Bivalirudin: bolus of 0.75 mg/kg before start of intervention followed by infusion of 1.75 mg/kg/h for the duration of the procedure. UFH/Unfractionated heparin plus tirofiban: UFH bolus of 70 U/kg plus tirofiban bolus of 10 microgram/kg followed by infusion of 0.15 µg/kg/min for 12 h	30 days	Death, MI, myocardial ischemia requiring urgent surgical intervention or repeat percutaneous coronary revascularization	–

Table I. Cont.

Title	2006	Year of study	Type of study	Type of blinding	Total no. of patients	Interventions and dose	Duration of follow-up	Primary outcomes	Secondary outcomes
	Kastrati *et al.* (2011)	2011	Randomized controlled trial	Double blinding	1721	Abciximab plus heparin: bolus of 0.25 mg/kg of abciximab followed by infusion of 0.125 µg/kg/min for 12 h, and a bolus dose of 70 U/kg of heparin. Bivalirudin: bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h for the duration of the procedure	30 days	Death, large recurrent myocardial infarction, urgent target-vessel revascularization, or major bleeding	Death, any recurrent myocardial infarction, or urgent target-vessel revascularization and a safety endpoint of major bleeding
	Deshpande *et al.* (2012)	2012	Randomized controlled trial	Open label	101	UFH/Unfractionated heparin: bolus of 70 IU/kg and if required a subsequent bolus of 20 IU/kg aimed at an activated clotting time of 200–250 s. Bivalirudin: bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h. Tirofiban: given to both groups as a 25 µg/kg bolus followed by an infusion of 0.15 µg/kg/min for a period of 4 h after the procedure	30 days	Time to sheath removal and ambulation	Periprocedural myocardial damage, access site bleeding and major adverse cardiac events (MACE)
	Xiang *et al.* (2013)	2013	Randomized controlled trial	Single blinding	218	Bivalirudin: 0.75 mg/kg bolus before the PCI procedure, followed by 1.75 mg/kg/h after the PCI procedure. Heparin sodium: 130 U/kg bolus before PCI	30 days	ACT, PCI success, MACE within 24 h, survival	–
BRAVE 4	BRAVE-4 trial (2014)	2014	Randomized controlled trial (BRAVE 4)	Open label	548	Prasugrel: loading dose of 60 mg orally, followed by a maintenance dose of 10 mg daily. Bivalirudin: bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/h for the duration of PCI	30 days	Death, recurrent MI, unplanned revascularization of the infarct related artery (IRA), definite stent thrombosis, stroke, or major bleeding	Death, recurrent MI, definite stent thrombosis, unplanned IRA-revascularization or stroke
	Feldman *et al.* (2014)	2014	Randomized controlled trial	Double blinding	100	UFH/Unfractionated heparin: bolus of 60 U/kg. Bivalirudin: a loading dose of 0.75 mg/kg, followed by infusion of 1.75 mg/kg/h for the duration of the procedure	(Review)	Major and minor bleeding and port of entry complications	Periprocedural myocardial infarction (PPMI) and major adverse cardiac events (MACE) in-hospital

Table I. Cont.

Title	2006	Year of study	Type of study	Type of blinding	Total no. of patients	Interventions and dose	Duration of follow-up	Primary outcomes	Secondary outcomes
	Shahzad *et al.* (2014)	2014	Randomized controlled trial	Open label	1812	Heparin: bolus of 70 U/kg bodyweight before the procedure. Bivalirudin: bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h for the duration of the procedure	28 days	Proportion of patients who had at least one major adverse cardiac event (MACE)	Stent thrombosis rates, cardiac enzyme release, and minor bleeding
BRIGHT	Han *et al.* (2015)	2015	RCT/ Randomized controlled trial	Open label	2194	Bivalirudin: bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h during the PCI procedure and for at least 30 min but no more than 4 h afterwards. Heparin: a bolus dose of 100 U/kg. Heparin plus tirofiban: heparin 60 U/kg and tirofiban 10 µg/kg boluses were given followed by a 0.15 µg/kg/min tirofiban infusion for 18 to 36 h	30 days	Major cardiac events or cerebral events, or any bleeding	Major adverse cardiac or cerebral events and any bleeding
	Valgimigli *et al.* (2015)	2015	Randomized controlled trial	Open label	7213	Bivalirudin: bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/h until completion of the PCI. Heparin: a dose of 70 to 100 U/kg in patients not receiving GP IIb/IIIa inhibitors and at a dose of 50 to 70 U/kg in patients receiving GP IIb/IIIa inhibitors	30 days	Major adverse cardiovascular events, which were defined as a composite of death from any cause, myocardial infarction, or stroke	Death from cardiovascular causes, and stent thrombosis
	Erlinge *et al.* (2017)	2017	Randomized controlled trial	Open label	6006	Bivalirudin: bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/h. Heparin: 70–100 U/kg bolus	180 days	Death from any cause, myocardial infarction, or major bleeding events	Separate analyses of the primary endpoint in the STEMI and NSTEMI strata, the individual components of the primary endpoint, stroke, and stent thrombosis

Table I. Cont.

Title	2006	Year of study	Type of study	Type of blinding	Total no. of patients	Interventions and dose	Duration of follow-up	Primary outcomes	Secondary outcomes
	Wang *et al.* (2019)	2018/2019	Randomized controlled trial	No blinding mentioned	123	Bivalirudin: 0.75 mg/kg bolus followed by an infusion of 1.75 mg/kg//h up to 4 h after the procedure. UFH/Unfractionated heparin: 100 IU/kg bolus	6 months	All-cause death, target vessel revascularization (TVR), and acute myocardial infarction during hospitalization	–
	Faour *et al.* (2021)	2021	Randomized controlled trial	Open label	83	Bivalirudin: a bolus and infusion (0.75 mg/kg bolus + 1.75 mg/kg/h infusion) as soon as PCI was planned and continued for 4 h post-PCI. Heparin: was given immediately before PCI at a dose of 70–100 U/kg, and this was adjusted to 50–70 U/kg in patients receiving glycoprotein IIb/IIIa inhibitors	90 days	Infarct size measured by peak troponin levels as a multiple of the local upper reference limit (Tn/URL)	Periprocedural change in hemoglobin adjusted for red cells transfused, TIMI (thrombolysis in myocardial infarction) bleeding, ST-segment recovery and infarct size determined by the Selvester QRS score
BRIGHT-4	Li *et al.* (2022)	2022	Randomized controlled trial	Open label	6016	Bivalirudin: a bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/h during the PCI procedure and for 2–4 h afterwards. Heparin: bolus of 70 U/kg was administered. Additional heparin was administered if the 5-min post-bolus activated clotting time was less than 225 s	30 days	Death or Bleeding Academic Research Consortium (BARC) types 3–5 bleeding	Major adverse cardiac or cerebral events and stent thrombosis

non-significant RR for all three groups. Bivalirudin plus GP IIb/IIIa inhibitors had RR of 0.963 (95% CI: 0.814–1.138, $p = 0.660$), bivalirudin monotherapy had RR of 0.989 (95% CI: 0.928–1.052, $p = 0.719$) and heparin plus GP IIb/IIIa inhibitors had RR of 0.938 (95% CI: 0.83–1.052, $p = 0.276$). These findings suggest comparable efficacy across all treatment options regarding MACE. There was no heterogeneity among studies ($I^2 = 0\%$).

All-cause mortality

Analysis of data regarding all-cause mortality, consisting of 71,805 patients from twenty studies, also showed a statistically insignificant/non-significant RR for all three groups with no heterogeneity among studies ($I^2 = 0\%$). Bivalirudin plus GP IIb/IIIa inhibitors had RR of 1.023 (95% CI: 0.736–1.422, $p = 0.891$), bivalirudin monotherapy had RR of 0.976 (95% CI: 0.901–1.058, $p = 0.559$) and heparin plus GP IIb/IIIa inhibitors had RR of 1.113 (95% CI: 0.854–1.450, $p = 0.428$).

Cardiovascular deaths

In regard to cardiovascular deaths associated with various antithrombotic regimens compared to heparin monotherapy, data was extracted from eight studies consisting of 25,698 patients. Bivalirudin plus GP IIb/IIIa inhibitors had RR of 1.053 (95% CI: 0.616–1.801, $p = 0.847$), bivalirudin monotherapy had RR of 0.861 (95% CI: 0.674–1.1007, $p = 0.233$) and heparin plus GP IIb/IIIa inhibitors had RR of 1.337 (95% CI: 0.840–2.127, $p = 0.220$). These findings suggest that none of the treatments significantly differ from heparin monotherapy in reducing cardiovascular death. There was no heterogeneity ($I^2 = 0\%$) among studies.

Stent thrombosis

Moreover, in stent thrombosis, eleven studies consisting of 29,314 patients were analyzed.

Bivalirudin plus GP IIb/IIIa showed an increased risk with RR = 3.62 (95% CI: 1.002–13.14), with $p = 0.049$. Bivalirudin monotherapy had RR of 0.963 (95% CI: 0.486–1.907, $p = 0.914$) and heparin plus GP IIb/IIIa inhibitors had RR of 1.363 (95% CI: 0.485–3.832, $p = 0.556$). Moderate heterogeneity ($I^2 = 40.9\%$) was present among studies.

Reinfarction

Nineteen studies, consisting of 54,983 patients, were evaluated to assess the reinfarction risk. The result showed statistically insignificant/non-significant RR among the treatments compared to heparin monotherapy. Bivalirudin plus GP IIb/IIIa inhibitors had RR of 1.008 (95% CI: 0.768–1.321, $p = 0.953$), bivalirudin monotherapy had RR of 1.023 (95% CI: 0.898–1.166, $p = 0.723$) and heparin plus GP IIb/IIIa inhibitors had RR of 0.972 (95% CI: 0.812–1.162, $p = 0.755$). Low heterogeneity ($I^2 = 2\%$) was present among studies.

The risk of bias assessment of studies using the Cochrane ROB2 tool is given in Supplementary file S6. Five studies had some concerns regarding risk of bias, the rest of the studies had low bias. Furthermore, we included pairwise comparisons of treatment groups in Supplementary file S7. Supplementary file S8 shows direct and indirect estimates of assessed outcomes.

Moreover, Supplementary file S9 portrays the p-score ranking of treatment groups in bar charts in all outcomes. The results of Higgins I^2 for heterogeneity are provided in Supplementary file S10. A table of patient baseline characteristics of included studies is provided in Supplementary file S11.

Subgroup analysis

Subgroup analyses stratified by clinical presentation (STEMI + NSTEMI combined, STEMI alone, and NSTEMI/UA alone) did not demonstrate statistically significant risk ratios across outcomes. In the STEMI + NSTEMI subgroup, bivalirudin monotherapy showed no significant differences compared with heparin monotherapy in major bleeding (RR = 0.71, 95% CI: 0.45–1.12; $p = 0.14$), stent thrombosis (RR = 0.81, 95% CI: 0.28–2.40; $p = 0.71$), MACE (RR = 0.99, 95% CI: 0.89–1.10; $p = 0.87$), all-cause mortality (RR = 0.95, 95% CI: 0.68–1.32; $p = 0.75$), reinfarction (RR = 0.98, 95% CI: 0.85–1.13; $p = 0.76$), or cardiovascular death (RR = 0.87, 95% CI: 0.62–1.21; $p = 0.41$).

Similarly, in the STEMI-only subgroup, no statistically significant differences were observed across major bleeding (RR = 1.63, 95% CI: 0.53–5.03; $p = 0.40$), stent thrombosis (RR = 2.93, 95% CI: 0.10–81.00; $p = 0.52$), MACE (RR = 1.18, 95% CI: 0.59–2.39; $p = 0.64$), all-cause mortality (RR = 0.99, 95% CI: 0.90–1.08; $p = 0.84$), or reinfarction (RR = 1.95, 95% CI: 0.12–32.85; $p = 0.64$).

Across all ACS subgroups, bivalirudin combined with GP IIb/IIIa inhibitors and heparin combined with GP IIb/IIIa inhibitors also showed wide confidence intervals and non-significant p-values, indicating insufficient statistical power for definitive conclusions. The detailed subgroup analysis of outcomes stratified according to type of myocardial infarction is given in Supplementary file S12.

The results of our meta-analysis are summarized in Figure 3.

Discussion

This systematic review and meta-analysis aimed to compare the efficacy and safety of bi-

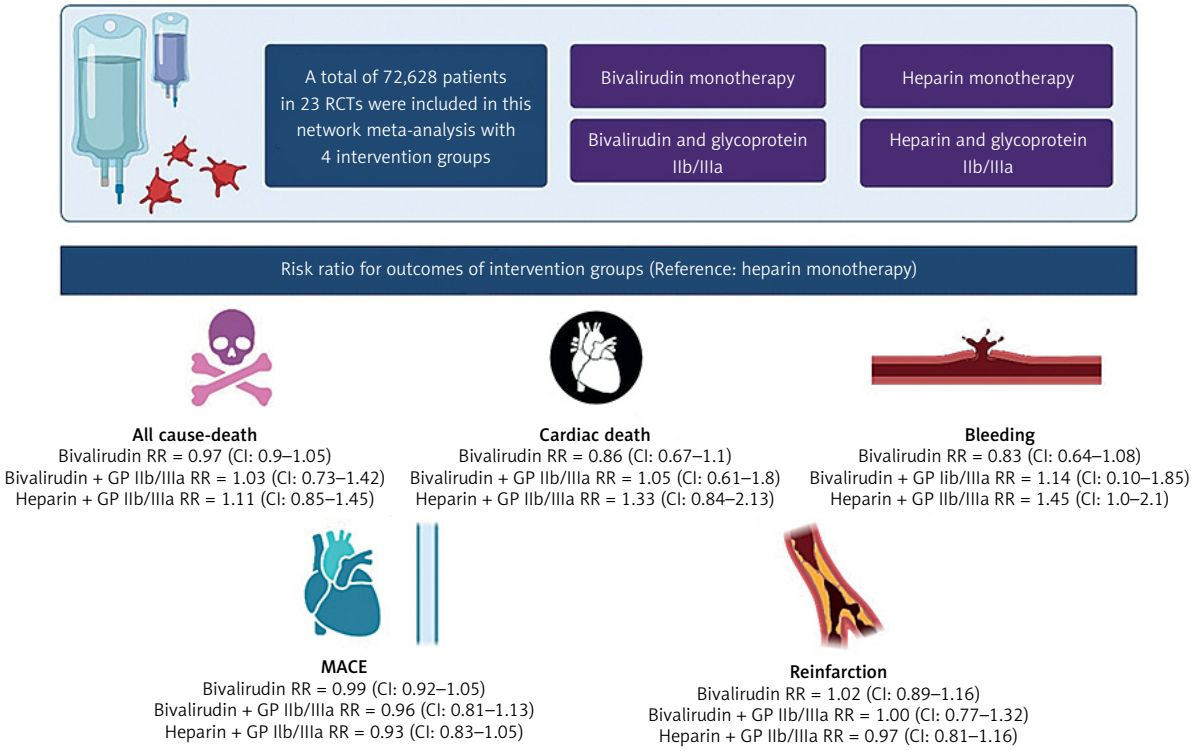

Figure 3. Graphical abstract of outcomes comparison between bivalirudin vs heparin in patients undergoing PCI

valirudin and heparin, used alone or in combination with GP IIb/IIIa inhibitors, in patients with acute coronary syndromes undergoing PCI. Our meta-analysis rigorously evaluated 23 randomized controlled trials encompassing a total of 72,628 patients distributed across distinct treatment groups, namely: bivalirudin monotherapy, bivalirudin combined with GP IIb/IIIa inhibitors, heparin combined with GP IIb/IIIa inhibitors, and heparin monotherapy. We conducted a network meta-analysis to enable a comprehensive comparison of the relative efficacy and safety of these common choices of anticoagulants through direct and indirect comparison of treatments to facilitate clinical decision making. Our study revealed that bivalirudin monotherapy did not show any statistically significant differences in efficacy outcomes compared to heparin monotherapy.

For the outcome of MACE, all of the treatment groups showed comparable risk ratios with narrow confidence intervals indicating that none of the treatment groups demonstrated superiority. This is also consistent with major clinical trials in which both heparin and bivalirudin monotherapy showed similar MACE outcomes such as Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction trial (11.9% vs. 11.9%, HR = 1.00) and the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment trial (8.7% vs. 8.3%, RR = 0.94) [18, 19].

Similarly in the outcome of all-cause mortality, the treatment groups showed comparable risk ratios. The Acute Catheterization and Urgent Intervention Triage Strategy trial conducted in 2006 on 13,819 patients also showed comparable outcome of all-cause mortality (1.3% vs. 1.5% vs. 1.6%) of heparin plus a glycoprotein IIb/IIIa inhibitor, bivalirudin plus a glycoprotein IIb/IIIa inhibitor, or bivalirudin alone, respectively [16].

Stent thrombosis remains a clinically significant outcome in anticoagulant trials where PCI has been performed. Our analysis identified an elevated risk of stent thrombosis when bivalirudin was administered with GP IIb/IIIa inhibitors. This observation is consistent with findings from HORIZONS-AMI trial (1.3% in the bivalirudin group vs. 0.3% in the heparin group; $p < 0.001$) which reported higher acute stent thrombosis with bivalirudin – even when bleeding outcomes improved [18]. Mechanistically, bivalirudin's short half-life (25 min) and rapid clearance may permit rebound thrombin activity if post-PCI infusion is omitted [33]. Furthermore, earlier-generation drug-eluting stents used in many RCTs were more thrombogenic, influencing the absolute risk observed.

Subgroup analyses stratified by clinical presentation (STEMI vs. NSTEMI/UA) did not show statistically significant differences in treatment effect for any major outcome in our analysis. However, wide confidence intervals indicate insufficient statistical power to detect clinically meaningful

interactions. This limitation mirrors conclusions from patient-level analyses such as ACUITY and HORIZONS, which similarly reported non-significant interactions between clinical presentation and anticoagulation strategy [16, 18]. Therefore as no significant risk ratios were detected, the findings should be interpreted as inconclusive, not confirmatory of uniform treatment performance.

Furthermore, the pharmacologic differences between bivalirudin and heparin have clinical relevance. Bivalirudin is a specific, direct and reversible thrombin inhibitor with predictable kinetics, minimal plasma protein binding, and no requirement for antithrombin III. Bivalirudin prolongs activated partial thromboplastin time, prothrombin time, thrombin time and activated clotting time [34]. Heparin, however, indirectly inhibits thrombin and is more susceptible to variability from acute phase reactants. Heparin binds to antithrombin III and this binding induces a conformational change in antithrombin III, significantly augmenting its ability to inactivate several clotting factors, notably thrombin (factor IIa) and factor Xa. By inactivating thrombin, heparin blocks the conversion of fibrinogen to fibrin, preventing clot formation and prolonging the clotting time of blood [35]. These differences influence their bleeding and thrombosis profiles but, as our results and current literature suggest, do not translate into clear differences in ischemic protection when used with modern PCI techniques. However, in the treatment of both suspected and confirmed heparin-induced thrombocytopenia, bivalirudin may be an effective and safe alternative option and appears to reduce the rate of heparin-induced thrombocytopenia related amputation [36].

Another major factor moderating anticoagulant effect is the evolution of antiplatelet therapy. Many older trials used clopidogrel alone, which has slower and variable platelet inhibition. More recent studies incorporate potent agents such as prasugrel and ticagrelor, which significantly reduce early platelet reactivity. In patients who have an acute coronary syndrome, treatment with ticagrelor as compared with clopidogrel significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke, however no significant difference in the rates of major bleeding were found between the ticagrelor and clopidogrel [37]. Another trial reports that prasugrel therapy was associated with significantly reduced rates of ischemic events but with an increased risk of major bleeding. Overall mortality however did not differ significantly between treatment groups [38]. Our findings must be interpreted with this evolution in mind.

Historically, bivalirudin produced significant bleeding reductions in trials performed during the femoral-access era. Early meta-analyses reported a significant reduction in major bleeding (p = 0.001) [39]. However, with the widespread adoption of radial access, bleeding rates across PCI have declined substantially. A meta-analysis shows that there was a lower risk of major bleeding with radial access when compared with femoral access (odds ratio [OR] = 0.46, 95% CI: 0.35–0.59) [40]. Our pooled analysis similarly shows non-significant trends toward reduced bleeding with bivalirudin, suggesting that its initial bleeding advantage is less pronounced in modern practice.

Additionally, earlier trials involving bare-metal and first-generation DES also introduce heterogeneity. New-generation drug eluting stents, such as everolimus-eluting platforms, lower thrombosis rates [41], As trials evolved, absolute event rates decreased, reducing the ability to detect incremental benefit from specific anticoagulants. This may contribute to the neutral ischemic findings in our analysis.

Lastly, the role of glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors is prevention of platelet aggregation by blocking glycoprotein IIb/IIIa receptors on the platelet's plasma membrane and inhibiting fibrinogen binding [42]. These inhibitors increase the risk of bleeding [43]. GP IIb/IIIa inhibitors were used variably across included trials. Some of the trials used them routinely such as CACHET or; REPLACE-2 [10, 13]. However, they were used selectively or bailout only in HORIZONS-AMI and they were not used at all in the RAFT trial [18, 31]. This heterogeneity complicates pooled interpretation. However, modern guidelines recommend restricting GP IIb/IIIa inhibitors to bailout scenarios due to bleeding risk. Our findings support this approach, as major bleeding increased when GP IIb/IIIa inhibitors were added to heparin.

To our knowledge, this study represents one of the most comprehensive network meta-analyses evaluating bivalirudin and heparin, administered alone or in combination with glycoprotein IIb/IIIa inhibitors in patients of ACS undergoing percutaneous coronary intervention. By integrating both direct and indirect comparisons across 23 randomized controlled trials with over 72,000 patients, this analysis provides a broader, more connected evidence base than conventional pairwise meta-analyses.

Methodologically, the review adhered to PRISMA and AMSTAR-2 guidelines, applied rigorous study selection criteria, and used random-effects models to account for clinical and methodological variability. The inclusion of only randomized controlled trials enhances internal validity and reduces bias. The presentation of SUCRA ranking provides an interpretable hierarchy of comparative effects across multiple outcomes, while acknowledging

that ranking probabilities alone do not imply clinical superiority without statistically significant contrasts in direct comparisons.

Furthermore, the study evaluated a comprehensive set of clinically relevant endpoints including bleeding, MACE, reinfarction, all-cause mortality, cardiovascular death, and stent thrombosis, offering an integrated assessment of both efficacy and safety profiles. This is especially valuable given the changes in procedural landscape, antiplatelet therapy changes, and heterogeneity in GP IIb/IIIa inhibitor use across trial eras.

Several limitations warrant consideration. First, although the total sample size was large, certain comparisons particularly those involving bivalirudin plus GP IIb/IIIa inhibitors had a limited number of trials and demonstrated relatively wider confidence intervals. This restricts statistical power and limits the precision of effect estimates, particularly for infrequent outcomes such as stent thrombosis and cardiovascular death. Consequently, non-significant subgroup comparisons should be interpreted as inconclusive rather than confirmatory of consistent treatment effects.

Second, substantial heterogeneity exists across included studies due to differences in the procedural era, arterial access strategies, antiplatelet regimens, and stent generation. Older trials were predominantly femoral-access based and used clopidogrel as the primary P2Y12 inhibitor, whereas contemporary practice uses radial access and newer antiplatelet agents such as ticagrelor. These procedural and pharmacologic changes reduce generalizability across eras and may attenuate or exaggerate observed differences between anticoagulants. Similarly, variation in the GP IIb/IIIa inhibitor utilization adds complexity to interpretation and may introduce effect modification that could not be fully explored.

In addition, some studies reported results using intention-to-treat analysis while others relied on per-protocol populations, introducing additional variability.

In addition to the above, the reliance on aggregated study-level data limits the ability to perform more granular analyses. Individual patient data meta-analysis would enable adjustment for important confounders, such as baseline thrombotic risk, renal function, and timing of P2Y12 loading dose that could not be controlled for in this network analysis.

Furthermore, follow-up durations varied, and several trials emphasized short-term (30-day) endpoints. Longer follow-up would improve insight into late stent thrombosis, recurrent ischemia, and long-term mortality. Additionally, open-label trial designs introduce the possibility of performance or ascertainment bias, especially for subjective outcomes such as bleeding or rehospitalization.

Although no anticoagulant strategy unequivocally outperformed the others across all endpoints, our findings support several clinically relevant trends. Bivalirudin demonstrated favorable safety signals, particularly regarding bleeding although these did not consistently reach statistical significance. Conversely, the increased risk of early stent thrombosis observed with bivalirudin and GP IIb/IIIa inhibitors remains an important consideration in acute myocardial infarction. These findings underscore the need for individualized anticoagulant selection during PCI, taking into account bleeding risk, thrombotic burden, arterial access site, and the potency of the concomitant antiplatelet regimen.

The absence of significant differences in MACE, cardiovascular mortality, and reinfarction between bivalirudin and heparin suggests that clinical decision-making should prioritize contextual factors rather than presuming inherent superiority of any treatment group. In settings where rapid reversibility, cost efficiency, or operator familiarity are paramount, heparin remains a practical choice. Conversely, in patients at heightened bleeding risk or with suspected heparin-induced thrombocytopenia, bivalirudin may provide a clinically meaningful advantage. The variability in GP IIb/IIIa inhibitor usage across trials, and the consistent increase in bleeding when these agents were used routinely highlight their optimal role as bail-out therapy rather than routine adjuncts.

Furthermore, the convergence of event rates across anticoagulants likely reflects the evolution of PCI practice, including widespread adoption of radial access, newer-generation stents with improved safety profiles, and more potent antiplatelet strategies.

Future research should prioritize large-scale, head-to-head RCTs comparing anticoagulants under standardized radial-access strategies and contemporary antiplatelet therapy. Stratified analyses by ACS subtype, thrombotic burden, renal function, and access site are warranted to define patient-level predictors of benefit. Longer-term follow-up is also needed to evaluate recurrent ischemia, late thrombosis, and the durability of clinical effects beyond the typical 30-day to 1-year time frame.

In conclusion, this network meta-analysis compared efficacy of bivalirudin and heparin, used alone or with glycoprotein IIb/IIIa inhibitors, in ACS patients undergoing PCI. No strategy demonstrated clear overall superiority. When comparing bivalirudin plus GP IIb/IIIa inhibitors and heparin plus GP IIb/IIIa inhibitors with heparin monotherapy, the risk of stent thrombosis was significantly

increased in the group receiving bivalirudin plus GP IIb/IIIa inhibitors and risk of major bleeding was significantly more/higher in the group receiving heparin plus GP IIb/IIIa inhibitors.

These findings highlight the need for individualized anticoagulant selection based on bleeding risk, thrombotic burden, access strategy, and background antiplatelet therapy. Future studies should include contemporary standardized head-to-head trial, longer follow-up and patient-level subgroup analyses to identify individuals who may benefit from specific anticoagulation strategies.

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Conflict of interest

The authors declare no conflict of interest.

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