

## ORIGINAL ARTICLE - CLINICAL SCIENCE

# Revisiting the Efficacy and Safety of Bivalirudin in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Percutaneous Coronary Intervention: Insights From a Mixed Treatment Comparison Meta-Analysis of Randomized Trials

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## ABSTRACT

**Background:** Randomized trials of bivalirudin in patients with ST elevation myocardial infarction (STEMI) have yielded heterogeneous results.

**Aims:** Our aim was to evaluate the efficacy and safety of four antithrombin regimens—unfractionated heparin (UFH), bivalirudin (stopped soon after percutaneous coronary intervention [PCI]), extended bivalirudin (continued for a few hours after PCI), and combined UFH and a Gp2b3a inhibitors (GPI) in patients who present with STEMI.

**Methods:** A PubMed, EMBASE, and [clinicaltrials.gov](https://clinicaltrials.gov) databases were searched for randomized clinical trials (RCTs) of the above antithrombin in patients with STEMI. The primary outcome was net adverse cardiovascular events (NACE). The primary ischemic endpoint was major adverse cardiovascular events (MACE), and the primary safety endpoint was major bleeding, and other endpoints included all-cause mortality and stent thrombosis. The primary analysis compared the effect of these antithrombin regimens in reference to UFH using a mixed treatment comparison meta-analysis.

**Results:** In the 14 RCTs evaluating 25,415 patients with STEMI, when compared to UFH monotherapy, extended bivalirudin lowered NACE (OR = 0.71 with 95% CI: 0.53–0.96; moderate level of confidence) driven by a significant decrease in major bleeding (OR = 0.42 with 95% CI: 0.26–0.68; high level of confidence) without any significant difference in MACE or all-cause mortality. When compared with UFH monotherapy, UFH+GPI reduced risk of MACE (OR = 0.76 with 95% CI: 0.60–0.97; high level of confidence) but at the expense of an increase in major bleeding (OR = 1.48 with 95% CI: 1.11–1.98; high level of confidence) with no difference in NACE or all-cause mortality. For major bleeding, extended bivalirudin infusion ranked #1, bivalirudin ranked #2, UFH monotherapy ranked #3, and combined UFH and GPI ranked #4. For NACE, extended bivalirudin infusion ranked #1, bivalirudin ranked #2, combined UFH and GPI ranked #3, and UFH monotherapy ranked #4. Cluster plots for MACE and major bleeding demonstrated that extended bivalirudin had the best balance for efficacy and safety.

**Abbreviations:** CI, confidence interval; MACE, major adverse cardiovascular events; NACE, net adverse clinical outcomes; OR, odds ratio; PCI, percutaneous coronary intervention; RCT, randomized controlled trials; STEMI, ST-segment elevation myocardial infarction; SUCRA, surface under the cumulative ranking; UFH, unfractionated heparin.

**Conclusions:** In patients undergoing PCI for STEMI, extended bivalirudin offers the best balance for primary ischemic (MACE) and safety (major bleeding) outcomes.

## 1 | Introduction

Percutaneous coronary intervention (PCI) is the standard treatment for patients who present with ST-segment elevation myocardial infarction (STEMI). The 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization gives unfractionated heparin a class I recommendation for antithrombin during PCI and bivalirudin only as an alternative in patients who develop heparin induced thrombocytopenia [1]. Furthermore, glycoprotein 2b3a inhibitors (GPI) are recommended for PCI with large thrombus burden, no-reflow or slow flow (class 2a) [1]. The 2023 ESC guidelines for acute coronary syndrome recommends bivalirudin with full-dose post-PCI infusion as an alternative to UFH in patients with STEMI undergoing PCI [2]. The weaker recommendation for bivalirudin stems from heterogeneous results of prior clinical trials [3–9]. However, recent clinical trials reported lower bleeding and all-cause mortality with bivalirudin compared with UFH [8, 10, 11]. Traditionally, bivalirudin monotherapy was used for the duration of PCI and its termination resulted in increase in ischemic outcomes including stent thrombosis [3]. Newer studies extended bivalirudin use for several hours after PCI which seem to have mitigated the excess risk of stent thrombosis [3–9].

The aim of this study was to evaluate the efficacy and safety of four antithrombin regimens—UFH, bivalirudin (stopped soon after PCI), extended bivalirudin (continued for several hours after PCI), and combined UFH and GPI in patients undergoing PCI with STEMI using a network meta-analysis of randomized controlled trials (RCTs).

## 2 | Methods

This meta-analysis and systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [12]. This analysis was not considered for institutional review board review as this was a trial level meta-analysis of published clinical trial data. The data that support the findings of this study are available from the corresponding author upon reasonable request.

### 2.1 | Search Strategy and Selection Criteria

A time limited search until March 20, 2024 was conducted using PubMed and EMBASE databases. The following Medical Education Subject Headings (MeSH) were used for this search: “Bivalirudin,” “Heparin,” “Gp2b3a inhibitors,” and “STEMI.” To identify gray literature, [www.clinicaltrials.gov](http://www.clinicaltrials.gov) was searched. We also searched references of the eligible studies to identify further studies. There was no language restriction for the search.

The inclusion criteria were randomized clinical trials (RCTs) that compared the effect of UFH monotherapy (reference), bivalirudin (infusion stopped soon after PCI), and extended bivalirudin (infusion continued for few hours after PCI), and combined UFH and GPI in STEMI patients undergoing PCI on net adverse cardiovascular event (NACE), major adverse cardiovascular events (MACE), major bleeding, stent thrombosis, and all-cause mortality. Primary analysis compared effect of various anticoagulation regimen in reference to UFH using a mixed treatment comparison meta-analysis. Studies comparing two different GPI as well as studies without a comparison arm, observational studies, and review articles were excluded.

We used population, intervention, comparison, and outcome (PICO) criteria for study selection [13]. Population of interest: PCI in STEMI patients; Intervention: bivalirudin, extended bivalirudin, and combined UFH and GPI; Comparator: UFH monotherapy; Outcomes: NACE, MACE, major bleeding, stent thrombosis, and all-cause mortality.

## 3 | Data Analysis

### 3.1 | Data Extraction and Quality Assessment

The studies were screened, data abstracted and quality assessed by two independent authors (M. H. M. and S. B.). Nonrelevant studies were excluded based on title followed by abstract. Full text studies were then screened for final selection on the basis of above-mentioned, prespecified inclusion criteria. Discrepancies were resolved by discussion. Methodological quality of included trials were assessed using the Cochrane Risk of Bias Tool which assessed selection, allocation, performance, detection, attrition, and reporting bias (Table S1) [14].

Antithrombin regimens were categorized into four groups: (1) UFH monotherapy (reference) (2) bivalirudin, (3) extended bivalirudin, and (4) combined UFH and GPI.

### 3.2 | Study Outcomes

Primary outcome was NACE, primary ischemic endpoint was MACE, primary safety endpoint was major bleeding. In addition, all-cause mortality and stent thrombosis were assessed. Primary analysis compared effect of various anticoagulation regimen in reference to UFH using a mixed treatment comparison meta-analysis. Definitions of major bleeding and MACE varied in these trials and are summarized in Table S2.

### 3.3 | Statistical Analysis

Continuous variables were reported as mean with standard deviation and categorical variables were expressed as

**TABLE 1** | Baseline characteristics of included trials.

Refer- ences	Type of trial	Duration of enrollment	Radial/ femoral access (%)	Bail out Gp2b3a use (%)	Ongoing antiplatelets	P2Y12 inhibitors loading (%)	Total parti- pants	Age (ye- ars)	Gen- der (% males)	Out- comes assessed	Extended bivalirudin duration
Antoniucci et al. <sup>24</sup>	Randomized, open-label	2001–2002	NA	1.5% (UFH mono- therapy)	Aspirin	100% (clopidogrel or ticlopidine loading after PCI)	400 (200 vs. 200)	63.5	77.30%	30-day	NA
Erlinge et al. <sup>9</sup> VALI- DATE- SWEDE HEART	Randomized, open-label	NA	NA	NA		100% (Ticagrelor 94.9%, prasugrel 2.1%, and cangrelor 0.3%)	3005 (1501 vs. 1504)	68	NA	30-day	Completion of last vial
Han et al. <sup>8</sup> BRIGHT	Randomized, open-label	2012–2013	78.5/21.5	4.4% (extended bivalirudin group) and 5.6% (UFH mono- therapy)	All patients received an oral PCI of 300 mg aspirin if not taking aspirin long-term (100–300 mg otherwise) and 300–600 mg clopidogrel if not taking long-term clopidogrel	100% (clopidogrel 100%)	2194 (735 vs. 729 vs. 730)	57.9	82.10%	30-day	30 min to 4 h
Jia et al. <sup>22</sup>	Randomized, open-label	2008–2010	86.1/10.6	NA	Aspirin and P2Y12 inhibitors	100% (clopidogrel 100%)	660 (330 vs. 330)	59.3	78.20%	30-day	NA
Le May et al. <sup>28</sup> ASSIST	Randomized, open-label	2005–2008	87.2/12.8	< 10% (UFH mono- therapy)	Aspirin and P2Y12 inhibitors	100% (clopidogrel 100%)	400 (201 vs. 199)	60.5	76.30%	30-day	NA
Li et al. <sup>7</sup> BRIGHT-4	Randomized, open-label	2019–2022	93.1/6.9	11.5% (extended bivaliru- din) and	Aspirin and P2Y12 inhibitors	100% (clopidogrel 34%, ticagrelor 66%)	6016 (3007 vs. 3009)	60.6	78.50%	30-day	2–4 h

(Continues)

TABLE 1 | (Continued)

Refer- ences	Type of trial	Duration of enrollment	Radial/ femoral access (%)	Bail out Gp2b3a use (%)	Ongoing antiplatelets	P2Y12 inhibitors loading (%)	Total parti- pants	Age (ye- ars)	Gen- der (%) males	Out- comes assessed	Extended bivalirudin duration
				13.7% (UFH mono- therapy)							
Mehilli et al. <sup>27</sup> BRAVE3	Randomized, double blind	2003–2008	NA	0% (UFH mono- therapy)	Aspirin and P2Y12 inhibitors	100% (clopidogrel 100%)	800 (401 vs. 399)	62.1	74.50%	30-day	NA
Montalesc- ot et al. <sup>25</sup> ADMIRAL	Randomized, double blind	1997–1998	NA	NA	Aspirin	100% (ticlopidine)	300 (149 vs. 151)	60.9	81.70%	30-day	NA
Schulz et al. <sup>5</sup> BRAVE 4	Randomized, open-label	NA	0.18/99.8	3% (bivalirudi- n) and 6.1% (UFH mono- therapy)	Prasugrel in bivalirudin arm and clopidogrel in heparin arm	100% (50% clopidogrel, 50% prasugrel)	548 (271 vs. 277)	61.4	77.40%	30-day	NA
Shahzad et al. <sup>6</sup> HEAT- PPCI	Randomized, open-label	2012–2013	81/19	13% (bivalirudi- n) and 15% (UFH mono- therapy)	Aspirin + clopido- grel/prasugrel/ ticagrelor	99.5% (10.9% clopidogrel, prasugrel 27.4%, ticagrelor 61.9%)	1812 (905 vs. 907)	63.3	72.30%	28-day	NA
Steg et al. <sup>4</sup> EUROMA- X	Randomized, open-label	2010–2013	47.1/52.9	7.9% (extended bivaliru- din) and 25.4% (UFH mono- therapy)	Aspirin + clopido- grel/ticlopidine/ prasugrel/ ticagrelor	98% (clopidogrel 49.7%, ticlopidine 0.1%, prasugrel 29.9%, ticagrelor 19.3%)	2198 (1089 vs. 1109)	61.6	76.20%	30-day	At least 4 h
Stone et al. <sup>3</sup> Horizon- AMI	Randomized, open-label	2005–2007	NA	7.5% (UFH mono- therapy)	Aspirin (324 mg orally or 500 mg IV) + clopidogrel (300 or 600 mg)	100% (clopidogrel 99.6% and	3602 (1802 vs. 1800)	60.2	76.60%	30-day	NA

(Continues)

TABLE 1 | (Continued)

Refer- ences	Type of trial	Duration of enrollment	Radial/ femoral access (%)	Bail out Gp2b3a use (%)	Ongoing antiplatelets	P2Y12 inhibitors loading (%)	Total parti- pants	Age (ye- ars)	Gen- der (%) males	Out- comes assessed	Extended bivalirudin duration
					before PCI + aspirin	ticlopidine 0.4%)					
Tcheng et al. <sup>26</sup> CA- DILLAC	Subgroup analysis of CADILLAC	NA	NA	6.0% (UFH mono- therapy)	Aspirin	100% (ticlopidine)	2082 (1052 vs. 1030)	59.5	72.90%	30-day	NA
Ten Berg et al. <sup>23</sup> On- TIME2	Randomized, open-label (phase 1) and double blind (phase 2)	2004–2007	NA	28.5% (UFH mono- therapy)	Aspirin and P2Y12 inhibitors	100% (clopidogrel)	1398 (709 vs. 689)	61.8	76.00%	30-day	NA

Abbreviations: MACE, major adverse cardiovascular events; NA, not available; NACE, net adverse clinical events.

frequency/percentage. All analyses were performed in the intention-to-treat populations. Adverse events using odds ratio (OR), 95% confidence intervals (CI) were calculated for binary outcomes [15]. Frequentist estimation of network meta-analysis models were used for UFH monotherapy, bivalirudin, extended bivalirudin, and combined UFH and GPI. Effect size of each study and treatment was evaluated using interval plot with UFH monotherapy as the reference group [16–19]. Other pairs of comparisons was also performed. We rank ordered the anti-thrombin regimens using surface under the cumulative ranking (SUCRA) [16–19]. SUCRA is used to provide hierarchy of treatments with larger SUCRA value indicated better rank of treatment [20]. Finally, network funnel plot was used to estimate publication bias and small study effects [16, 17]. Inconsistency between the trials was analyzed at network level, loop level, and between direct and indirect comparisons [16]; a  $p < 0.05$  was considered for statistically significant heterogeneity. Relative ranking of interventions on basis of two different outcomes was measured using cluster ranking [17, 18]. A  $p < 0.05$  was considered statistically significant. To assess quality of evidence and evaluate confidence in specific pairwise comparison, we used study limitations, indirectness, inconsistency, imprecision, and publication bias and graded level of confidence as high, moderate, and low [21]. Stata version 17.0 software (Stata Corporation) with mvmeta package was used for all the statistical analyses.

4 | Results

The initial search yielded 1243 reports, which were screened by reviewing the title or abstract of which 14 RCTs were included in the final meta-analysis (Figure S1) [3–9, 22–28].

4.1 | Baseline Characteristics

Of the 14 RCTs, 7 evaluated NACE, 13 evaluated MACE, 13 evaluated major bleeding, 8 evaluated stent thrombosis, and 13 evaluated all-cause mortality including a total of 25,415 patients of which 10,531 were randomized to UFH monotherapy group (13 trials) (reference group), 2976 patients were randomized to Bivalirudin group (3 trials), 6334 to extended Bivalirudin group (4 trials), 5574 to combined UFH and GPI group (9 trials). The mean age was 61.5 years with 77.1% of randomized participants being men. The baseline characteristics of the study population are provided in Table 1 and information regarding treatment arms is provided in Table 2 [3–9, 22–28].

5 | Outcomes

5.1 | Net Adverse Clinical Events

Seven trials contributed data for the outcome of NACE, (Figures 1A and S2A). When compared with UFH monotherapy, there was a significantly lower risk of NACE with extended Bivalirudin (OR = 0.71 with 95% CI: 0.53–0.96; moderate level of confidence [Table 2]). There was no significant difference among other pairs of comparators

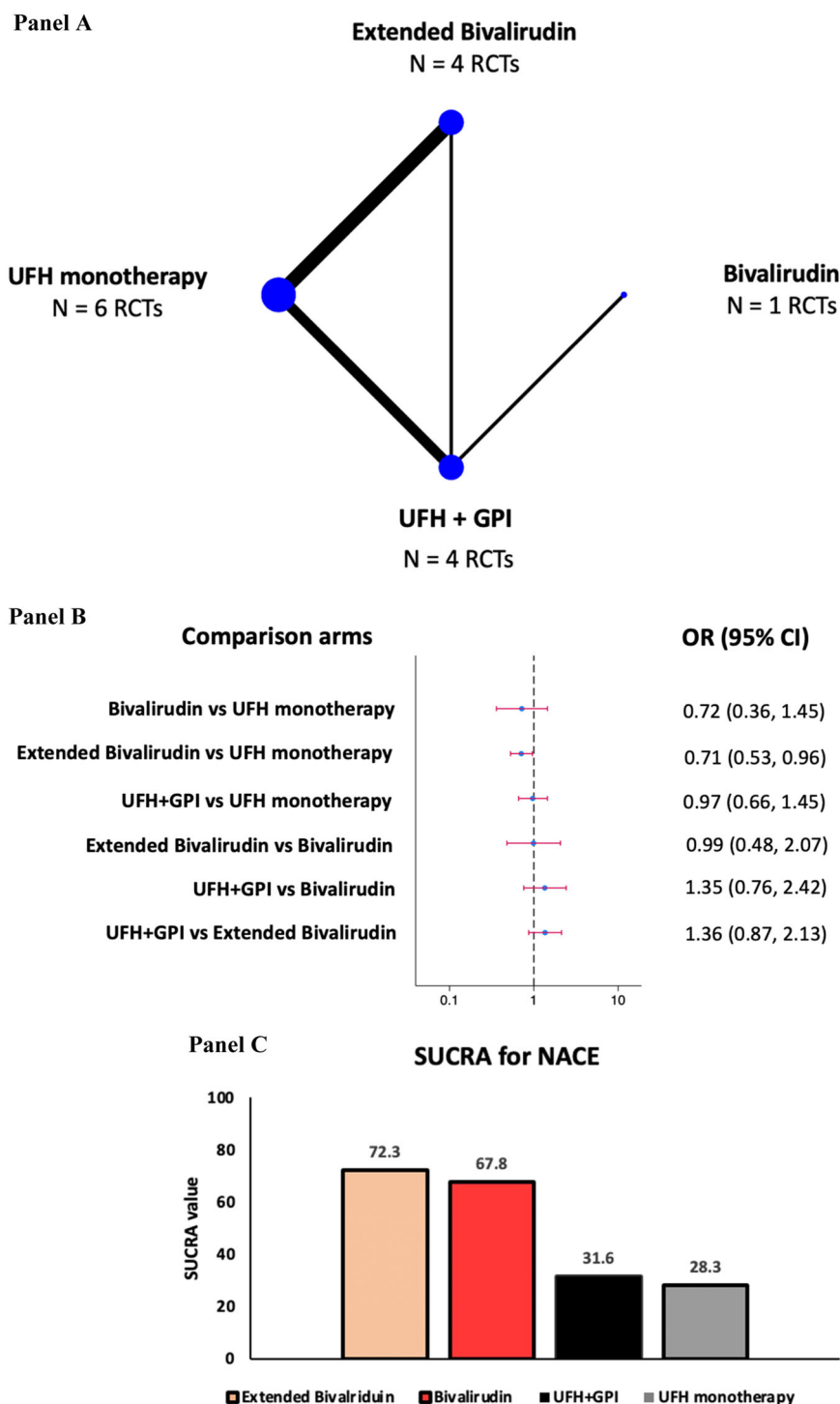
**TABLE 2** | Quality of evidence.

Outcomes	Direct comparisons	Nature of evidence	Confidence	Downgrading due to
NACE	Bivalirudin vs. UFH monotherapy	Indirect	Low	Indirectness, inconsistency
	Extended Bivalirudin vs. UFH monotherapy	Mixed	Moderate	Inconsistency
	UFH+GPI vs. UFH monotherapy	Mixed	Moderate	Inconsistency
	Extended Bivalirudin vs. Bivalirudin	Indirect	Low	Indirectness, inconsistency
	UFH+GPI vs. Bivalirudin	Mixed	Moderate	Inconsistency
	UFH+GPI vs. Extended Bivalirudin	Mixed	Moderate	Inconsistency
MACE	Bivalirudin vs. UFH monotherapy	Mixed	High	
	Extended Bivalirudin vs. UFH monotherapy	Mixed	High	
	UFH+GPI vs. UFH monotherapy	Mixed	High	
	Extended bivalirudin vs. bivalirudin	Indirect	Moderate	Indirectness
	UFH+GPI vs. bivalirudin	Mixed	High	
	UFH+GPI vs. extended bivalirudin	Mixed	High	
Major bleeding	Bivalirudin vs. UFH monotherapy	Mixed	High	
	Extended bivalirudin vs. UFH monotherapy	Mixed	High	
	UFH+GPI vs. UFH monotherapy	Mixed	High	
	Extended bivalirudin vs. bivalirudin	Indirect	Moderate	Indirectness
	UFH+GPI vs. Bivalirudin	Mixed	High	
	UFH+GPI vs. Extended Bivalirudin	Mixed	High	
All-cause mortality	Bivalirudin vs. UFH monotherapy	Mixed	Moderate	Inconsistency
	Extended bivalirudin vs. UFH monotherapy	Mixed	Moderate	Inconsistency
	UFH+GPI vs. UFH monotherapy	Mixed	Moderate	Inconsistency
	Extended bivalirudin vs. bivalirudin	Indirect	Low	Indirectness, inconsistency
	UFH+GPI vs. bivalirudin	Mixed	Moderate	Inconsistency
	UFH+GPI vs. extended bivalirudin	Mixed	Moderate	Inconsistency
Stent thrombosis	Bivalirudin vs. UFH monotherapy	Mixed	Moderate	Imprecise
	Extended bivalirudin vs. UFH monotherapy	Mixed	High	
	UFH+GPI vs. UFH monotherapy	Mixed	High	
	Extended bivalirudin vs. bivalirudin	Indirect	Moderate	Indirectness
	UFH+GPI vs. bivalirudin	Mixed	High	
	UFH+GPI vs. extended bivalirudin	Mixed	Moderate	Imprecise

Abbreviations: MACE, major adverse cardiovascular events; NACE, net adverse clinical events; UFH, unfractionated heparin.

(Figure 1B). Antithrombin regimen with extended bivalirudin infusion ranked #1, followed by bivalirudin (ranked #2), combined UFH and GPI (ranked #3), and UFH monotherapy (ranked #4) (Figure 1C). There was no evidence of small study effect, publication bias, but there was

inconsistency in the overall network meta-analysis ( $p = 0.003$ ) (Figure S2B). Further exploration of inconsistency showed no evidence of inconsistency at the level of loop (Figure S2C). Inconsistency between direct and indirect estimates were observed for extended bivalirudin



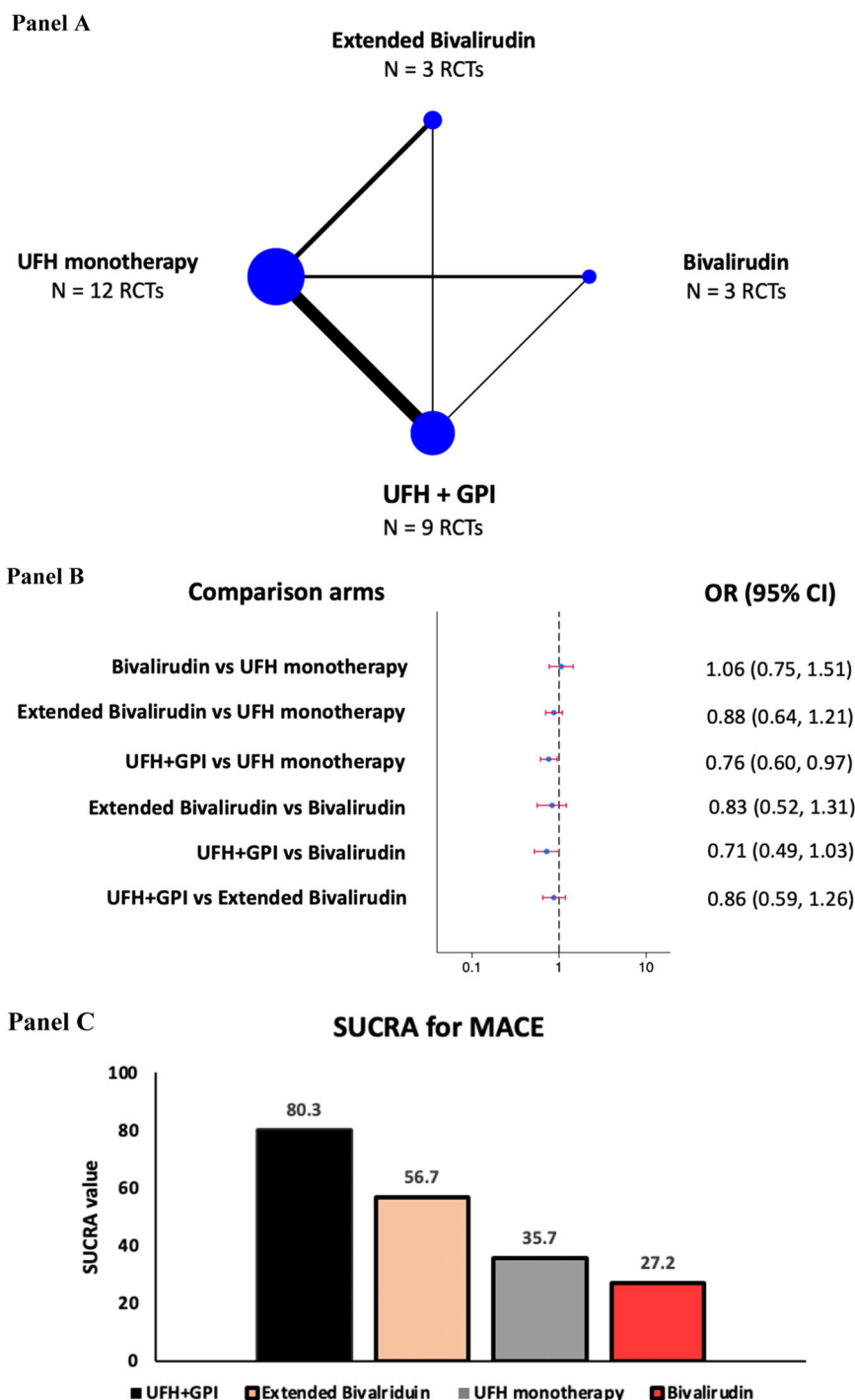
**FIGURE 1** | Effect of antithrombin regimen on net adverse clinical outcomes. (A) Network map, (B) interval plot, (C) SUCRA bar chart. CI, confidence interval; GPI, glycoprotein 2b3a inhibitors; NACE, net adverse clinical events; OR, odds ratio; SUCRA, surface under the cumulative ranking area; UFH, unfractionated heparin. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

versus UFH monotherapy and extended bivalirudin versus combined UFH and GPI (Table S3).

## 5.2 | Major Adverse Cardiovascular Events

Thirteen trials contributed data for the outcome of MACE (Figures 2A and S3A). When compared with UFH monotherapy, there was a significantly lower risk of MACE with

combined UFH and GPI (OR = 0.76 with 95% CI: 0.60–0.97; high level of confidence [Table 2]) (Figure 2B). There was no significant difference among other pairs of comparators. Anticoagulation with combined UFH and GPI infusion ranked #1, followed by extended bivalirudin (ranked #2), UFH monotherapy (ranked #3), and bivalirudin (ranked #4) (Figure 2C). There was no evidence of small study effect, publication bias, or inconsistency in the overall network meta-analysis ( $p = 0.12$ ) (Figure S3B).

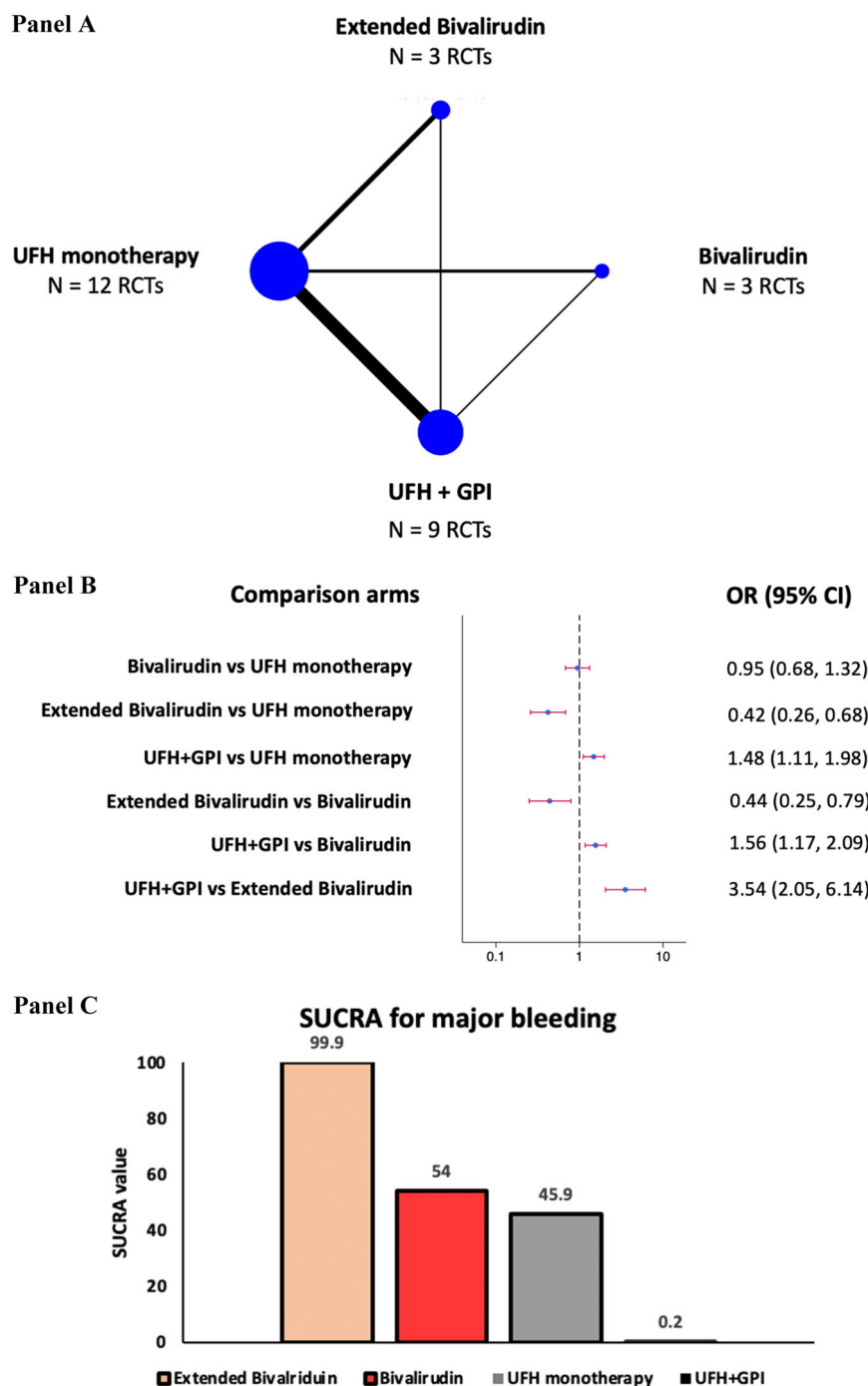


**FIGURE 2** | Effect of antithrombin regimen on major adverse cardiovascular events. (A) Network map, (B) interval plot, (C) SUCRA bar chart. CI, confidence interval; GPI, glycoprotein 2b3a inhibitors; OR, odds ratio; MACE, major adverse cardiac events; SUCRA, surface under the cumulative ranking area; UFH, unfractionated heparin. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/ced.31276)]

### 5.3 | Major Bleeding

Thirteen trials contributed data for the outcome of major bleeding (Figures 3A and S4A). When compared with the UFH monotherapy, there was significantly lower risk of major bleeding with extended Bivalirudin (OR = 0.42 with 95% CI: 0.26–0.68; high level of confidence [Table 2]) and higher risk with combined UFH and GPI (OR = 1.48 with 95% CI: 1.11–1.98; high level of confidence [Table 2]), (Figure 3A). There was higher risk of major bleeding with

combined UFH and GPI compared to both bivalirudin (OR = 1.56 with 95% CI: 1.17–2.09; high level of confidence [Table 2]) and extended bivalirudin (OR = 3.54 with 95% CI: 2.05–6.14; high level of confidence [Table 2]). Anticoagulation with extended bivalirudin infusion ranked #1, followed by Bivalirudin (ranked #2), UFH monotherapy (ranked #3), and combined UFH and GPI (ranked #4) (Figure 3B). There was no evidence of small study effect, publication bias or inconsistency in the overall model ( $p = 0.84$ ) (Figure S4B).



**FIGURE 3** | Effect of antithrombin regimen on major bleeding. (A) Network map, (B) interval plot, (C) SUCRA bar chart. CI, confidence interval; GPI, glycoprotein 2b3a inhibitors; OR, odds ratio; SUCRA, surface under the cumulative ranking area; UFH, unfractionated heparin. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/cd.31276)]

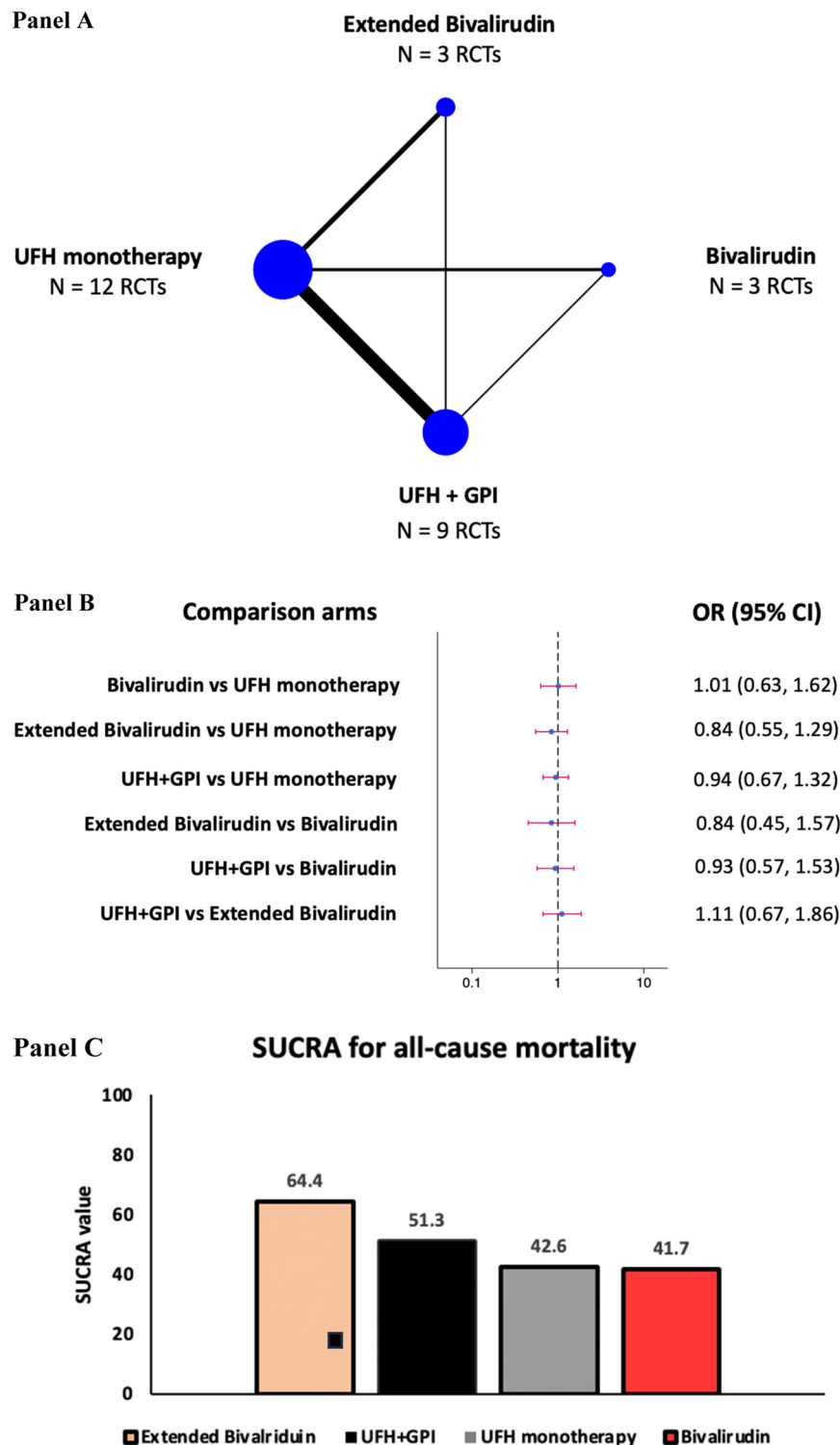
## 5.4 | All-Cause Mortality

Thirteen trials contributed data for the outcome of all-cause mortality (Figures 4A and S5A). When compared with the UFH monotherapy, there was no significant difference in all-cause mortality with any pairs of comparisons (Figure 4B). There was no evidence of small study effect or publication bias, but there was inconsistency in the overall network meta-analysis ( $p = 0.008$ ) (Figure S5B). There was evidence of inconsistency at the level of loop consisting of bivalirudin, UFH monotherapy, and combined UFH and GPI (Figure S5C). Inconsistency between direct and

indirect estimates were observed for UFH monotherapy versus combined UFH and GPI, bivalirudin versus UFH monotherapy, and bivalirudin versus combined UFH and GPI (Table S4).

## 5.5 | Stent Thrombosis

Eight trials contributed data for the outcome of stent thrombosis (Figures 5A and S6A). When compared with the UFH monotherapy, there was no significant difference in stent thrombosis with any pairs of comparison (Figure 5B). There was no evidence



**FIGURE 4** | Effect of antithrombin regimen on all-cause mortality. (A) Network map, (B) interval plot, (C) SUCRA bar chart. CI, confidence interval; GPI, glycoprotein 2b3a inhibitors; OR, odds ratio; SUCRA, surface under the cumulative ranking area; UFH, unfractionated heparin. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/ecd.31276)]

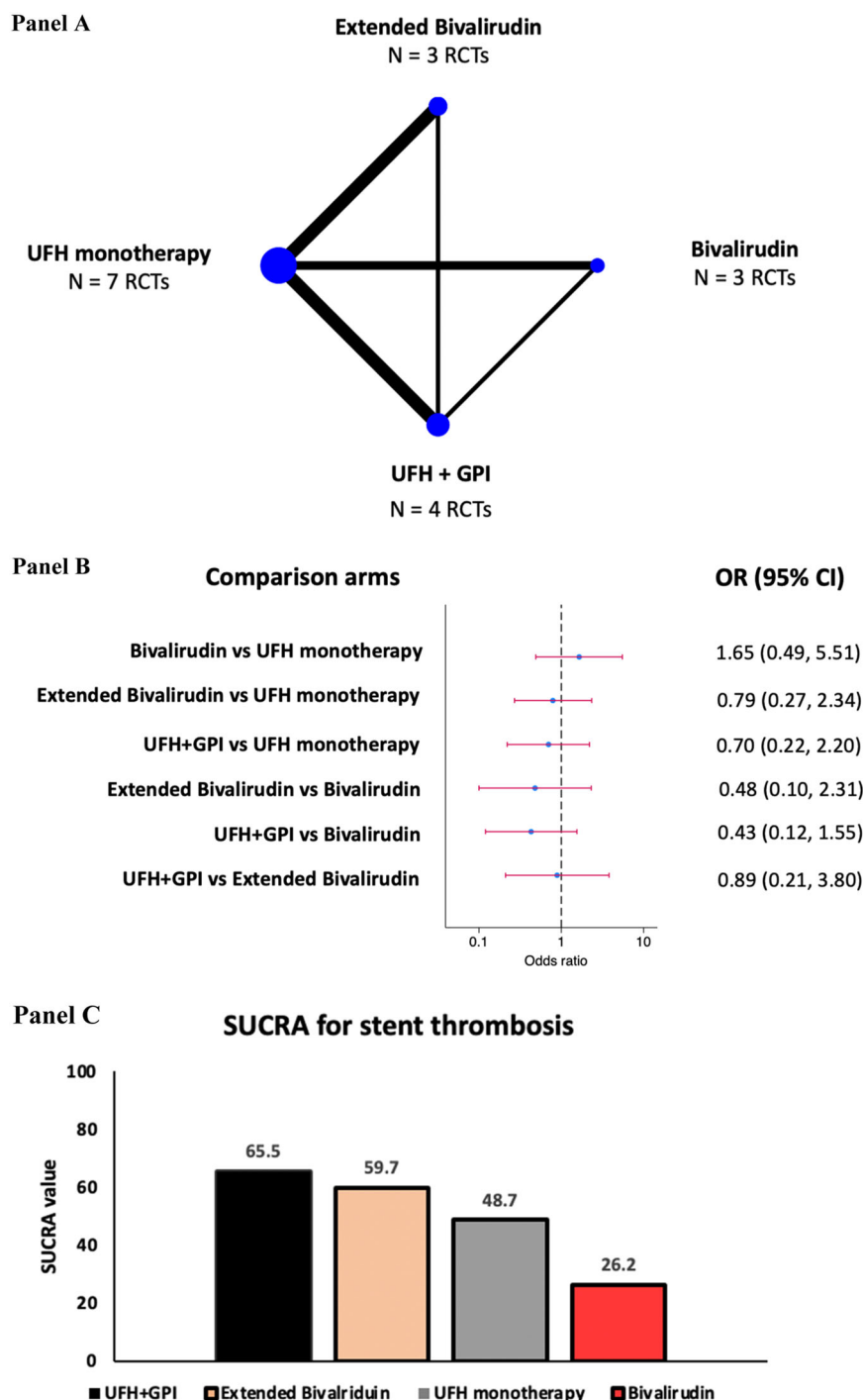
of small study effect, publication bias or inconsistency in the overall network meta-analysis ( $p = 0.88$ ) (Figure S6B).

## 5.6 | Cluster Ranking

Cluster plot for major bleeding and MACE showed that extended bivalirudin offered the optimal balance for efficacy and safety (Figure 6).

## 6 | Discussion

In this analysis of 14 RCTs including 25,415 patients with STEMI undergoing PCI, when compared to UFH monotherapy, extended bivalirudin lowered NACE driven by a significant decrease in major bleeding without any increase in MACE or all-cause mortality. When compared with UFH monotherapy, combined UFH and GPI lower risk of MACE but at the expense

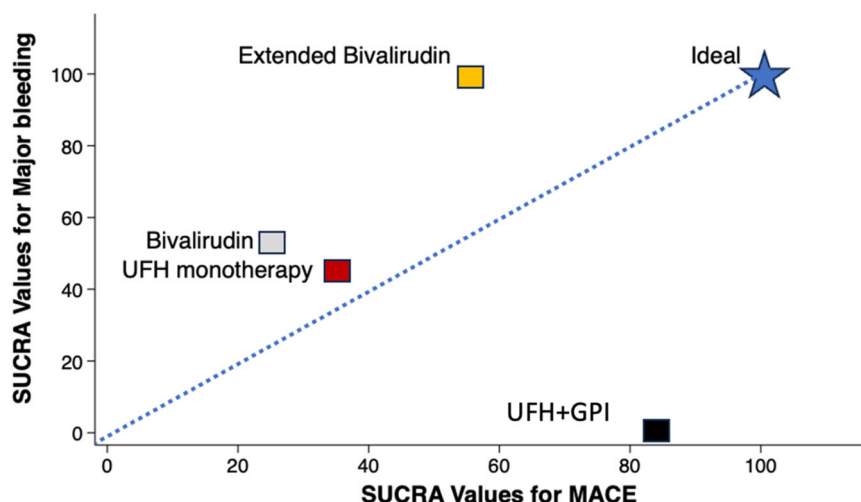


**FIGURE 5** | Effect of antithrombin regimen on stent thrombosis. (A) Network map, (B) interval plot, (C) SUCRA bar chart. CI, confidence interval; GPI, glycoprotein 2b3a inhibitors; OR, odds ratio; SUCRA, surface under the cumulative ranking area; UFH, unfractionated heparin. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

of increase in major bleeding with no significant difference in NACE or all-cause mortality. For major bleeding, antithrombin regimen with extended bivalirudin infusion ranked #1, bivalirudin (ranked #2), followed by UFH monotherapy (ranked #3), and combined UFH and GPI (ranked #4). For NACE, antithrombin regimen with extended bivalirudin infusion ranked #1, followed by bivalirudin (ranked #2), combined UFH and GPI (ranked #3), and UFH monotherapy (ranked #4). For MACE, antithrombin regimen with combined UFH and GPI infusion ranked #1, followed by extended bivalirudin (ranked #2), UFH

monotherapy (ranked #3), and bivalirudin (ranked #4). Cluster plots for MACE and major bleeding showed that extended bivalirudin had the best balance for efficacy and safety.

Traditionally, UFH has been used as the primary antithrombin regimen during PCI and is recommended by ACC/AHA/SCAI Guideline for Coronary Artery Revascularization [1]. Bivalirudin, which is recommended as an alternative to heparin has been shown to have reduction in bleeding complications [1]. The latest trials on Bivalirudin for PCI in STEMI have shown



**FIGURE 6** | Cluster rank of MACE and major bleeding. MACE, major adverse cardiovascular events; SUCRA, surface under the cumulative ranking area; UFH, unfractionated heparin. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/cd.1276)]

favorable bleeding profile compared to UFH [8, 10]. This is the first network meta-analysis of its kind which evaluated the efficacy and safety of antithrombin regimens use during PCI in STEMI patients using UFH monotherapy as a reference. A meta-analysis by Capodanno and colleagues, on bivalirudin versus heparin using five RCTs found a significant reduction in major bleeding with bivalirudin (OR 0.58, 95% CI: 0.40–0.85) but comparable 30-day mortality [29]. In a recent multicenter open labeled RCT in China enrolling a total of 6016 patients with STEMI undergoing primary PCI, extended bivalirudin significantly reduced the composite of all-cause mortality or BARC types 3–5 major bleeding when compared with UFH [7]. In our network meta-analysis, we divided bivalirudin into extended bivalirudin (where bivalirudin infusion is continued for few hours after PCI) and bivalirudin (where bivalirudin infusion is stopped soon after PCI) and found that extended bivalirudin lowered NACE driven by a significant decrease in major bleeding without any increase in MACE or all-cause mortality compared to UFH monotherapy.

Of note, for the outcome of major bleeding, extended bivalirudin was ranked higher than bivalirudin. This could be attributed to proportionally higher transradial access in the extended bivalirudin trials than the bivalirudin trials. For example, BRAVE 4 trial has 99.8% femoral access in bivalirudin group among others [5]. In contrast, trials with extended Bivalirudin were recently conducted with majority of patients undergoing transradial access and transradial access is associated with lower risk of bleeding for example 78.5% transradial access in BRIGHT and 93.1% in BRIGHT-IV [3, 8, 30]. Our meta-analysis highlights that extended bivalirudin is the best anti-coagulation strategy and should be used in STEMI patients undergoing PCI. All in all, decision for antithrombin regimen selection during PCI for STEMI should be individualized based on patient's bleeding risk versus ischemic risk.

## 6.1 | Study Limitations

The results of this analysis should be interpreted considering certain limitations. First, patient level data was not available so

granular details were not available and utilized. Second, only three and four trials evaluated Bivalirudin and extended bivalirudin respectively, so future trials evaluating its impact would further unveil the importance of extended bivalirudin. Third, the trials of bivalirudin extended therapy were more contemporary with greater use of transradial access and hence whether these results apply to patients undergoing transfemoral access is not known. Finally, there was varying proportion of radial access used in the included trials.

## 7 | Conclusions

In this analysis of 14 RCTs in patients undergoing PCI for STEMI, when compared to UFH monotherapy, extended bivalirudin lowered NACE driven by a significant decrease in major bleeding without any increase in MACE, stent thrombosis or all-cause mortality. Extended bivalirudin was the most efficacious and safest antithrombin regimen choice in patients undergoing PCI for STEMI with lower risk of major bleeding and MACE.

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The authors have nothing to report.

## Conflicts of Interest

Sripal Bangalore is on Advisory board for Abbott Vascular, Boston Scientific, Biotronik, Amgen, Pfizer, Merck, REATA, Inari, and Truic. The other authors declare no conflicts of interest.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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### Supporting Information

Additional supporting information can be found online in the Supporting Information section.