

# Prolonged High-Dose Bivalirudin Infusion Reduces Major Bleeding Without Increasing Stent Thrombosis in Patients Undergoing Primary Percutaneous Coronary Intervention: Novel Insights From an Updated Meta-Analysis

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**Background**—The optimal antithrombotic therapy in patients with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention (PCI) remains a matter of debate. This updated meta-analysis investigated the impact of (1) bivalirudin (with and without prolonged infusion) and (2) prolonged PCI-dose (1.75 mg/hg per hour) bivalirudin infusion compared with conventional antithrombotic therapy on clinical outcomes in patients undergoing primary PCI.

**Methods and Results**—Eligible randomized trials were searched through MEDLINE, EMBASE, Cochrane database, and proceedings of major congresses. Prespecified outcomes were major bleeding (thrombolysis in myocardial infarction major and Bleeding Academic Research Consortium 3–5), acute stent thrombosis, as well as all-cause and cardiac mortality at 30 days. Six randomized trials (n=17 294) were included. Bivalirudin compared with heparin (+/– glycoprotein-IIb/IIIa inhibitor) was associated with reduction in major bleeding (odds ratio [OR]: 0.65, 95% CI: 0.48–0.88,  $P=0.006$ , derived from all 6 trials), increase in acute stent thrombosis (OR: 2.75, 95% CI: 1.46–5.18,  $P=0.002$ , 5 trials), and lower rate of all-cause mortality (OR: 0.81, 95% CI: 0.67–0.98,  $P=0.03$ , 6 trials) as well as cardiac mortality (OR: 0.69, 95% CI: 0.55–0.87,  $P=0.001$ , 5 trials). The incidence of acute stent thrombosis did not differ between the prolonged PCI-dose bivalirudin and comparator group (OR: 0.81, 95% CI: 0.27–2.46,  $P=0.71$ , 3 trials), whereas the risk of bleeding was reduced despite treatment with high-dose bivalirudin infusion (OR: 0.28, 95% CI: 0.13–0.60,  $P=0.001$ , 3 trials).

**Conclusions**—Bivalirudin (with and without prolonged infusion) compared with conventional antithrombotic therapy in ST-segment-elevation myocardial infarction patients undergoing primary PCI reduces major bleeding and death, but increases the rate of acute stent thrombosis. However, prolonging the bivalirudin infusion at PCI-dose (1.75 mg/kg per hour) for 3 hours eliminates the excess risk of acute stent thrombosis, while maintaining the bleeding benefits. (*J Am Heart Assoc.* 2016;5:e003515 doi: 10.1161/JAHA.116.003515)

**Key Words:** bivalirudin • meta-analysis • myocardial infarction • percutaneous coronary intervention

Primary percutaneous coronary intervention (PCI) is now standard treatment for patients with an ST-segment-elevation myocardial infarct (STEMI),<sup>1,2</sup> significantly reducing major adverse cardiovascular events.<sup>3,4</sup>

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Coronary artery plaque rupture initiates acute coronary syndromes (ACS) by activating the coagulation cascade, and adjunctive antiplatelet as well as antithrombotic therapy is necessary to minimize peri- and postprocedural thrombotic events.<sup>5–8</sup> However, the use of these agents is frequently associated with an increase of bleeding, which is itself associated with a higher mortality.<sup>9–11</sup>

Unfractionated heparin (UFH) is the standard antithrombotic agent during PCI and in the setting of ACS.<sup>12</sup> However, UFH has a number of limitations including the need for anti-thrombin III as cofactor, and a highly variable dose–response relation, resulting in a narrow therapeutic window.<sup>13,14</sup> These considerations have encouraged investigations of alternative antithrombotic strategies. The role of bivalirudin, a direct thrombin inhibitor, has been investigated in 6 randomized trials in STEMI patients undergoing primary PCI,<sup>15–20</sup> but has resulted in conflicting

evidence in terms of major bleeding, acute stent thrombosis, and death.

A recently published meta-analysis by Shah et al, comparing bivalirudin with heparin in patients undergoing primary PCI, demonstrated a significant reduction in “protocol-defined” major bleeding and death in the bivalirudin group, but revealed an increase in acute stent thrombosis.<sup>21</sup> However, the impact of a prolonged infusion of the short-acting bivalirudin on clinical outcomes and the optimal dose of the prolonged bivalirudin infusion (low dose at 0.25 mg/kg per hour versus PCI-dose at 1.75 mg/kg per hour) remains a matter of debate.

The aim of our updated meta-analysis was to investigate the impact of bivalirudin compared with conventional antithrombotic therapy on major bleeding (defined as thrombolysis in myocardial infarction [TIMI] major and Bleeding Academic Research Consortium [BARC] 3–5 bleeding), acute stent thrombosis, and mortality in STEMI patients undergoing primary PCI, and to assess whether prolonged bivalirudin infusion at PCI-dose (1.75 mg/kg per hour) influences the rate of acute stent thrombosis and major bleeding.

## Methods

This review was guided by methods recommended by the Cochrane Handbook for Systematic Reviews of Intervention<sup>22</sup> and accomplished in compliance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement in healthcare interventions.<sup>23</sup>

## Eligibility and Search Strategy

We considered data from all randomized controlled trials comparing bivalirudin with heparin among STEMI patients undergoing primary PCI.

Relevant studies were searched through MEDLINE, the Cochrane database, the EMBASE database, as well as www.clinicaltrials.gov, www.clinicaltrialresults.org, www.tctmd.com, www.europcr.com, and www.acc.org websites until February 21, 2016 without language restrictions. In addition, prior meta-analysis on the same topic as well as the reference lists of included studies were reviewed to identify further citations. The following key words were used: myocardial infarction and bivalirudin.

Inclusion criteria for the meta-analysis comparing bivalirudin with conventional antithrombotic therapy were the following: randomized treatment allocation, inclusion of STEMI patients, and the intention to undergo PCI. Studies were excluded if thrombolysis rather than PCI was used for reperfusion treatment. For the subgroup analysis comparing prolonged PCI-dose bivalirudin with heparin in STEMI patients, we included only studies where administration of a prolonged

infusion at the higher dose of bivalirudin (1.75 mg/kg per hour) was part of the protocol. The original authors obtained institutional review committee approval and patient informed consent for each included study.

## Data Extraction and Validity Assessment

Two independent investigators (G.F. and M.W.) selected the studies for inclusion, and any disagreements were resolved by consensus with a third reviewer (R.K.K.). The data were analyzed according to the intention-to-treat principle. The original investigators were contacted to request relevant missing data.

## End-Point Selection

Selected end points were all-cause mortality, cardiac mortality, and major bleeding at 30 days as well as acute stent thrombosis for the analysis comparing bivalirudin versus conventional antithrombotic therapy. Major bleeding at 30 days and acute stent thrombosis were the prespecified outcome measurements for the subgroup analysis comparing prolonged PCI-dose bivalirudin with conventional antithrombotic therapy. The prognostically more relevant TIMI major bleeding<sup>24</sup> (rather than the protocol-defined non-coronary artery bypass graft [CABG]–major bleeding) was considered in the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI), Bavarian Reperfusion Alternatives Evaluation 4 (BRAVE 4), and European Ambulance Acute Coronary Syndrome Angiography (EURO-MAX) trial; and BARC 3 to 5 bleeding was used in the How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention (HEAT-PPCI), Bivalirudin in Acute Myocardial Infarction versus Heparin and GPI Plus Heparin (BRIGHT), and Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox (MATRIX) trial (Table). Acute stent thrombosis was defined according to the Academic Research Consortium criteria.<sup>25</sup>

## Statistical Analysis

Statistical analysis was performed by Review Manager, version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark). Odds ratios (OR) and 95% CI were used as summary statistics. The statistical heterogeneity for each end point of interest was assessed by using the Higgins  $I^2$  test.<sup>26</sup>  $I^2$  values between 0% and 30% and  $P > 0.1$  were considered not to be relevant, according to the Cochrane guidelines.<sup>22</sup> The fixed-effect model with the Mantel-Haenszel method was used to calculate the summarized ORs. In case of relevant heterogeneity with an  $I^2 > 30%$  or  $P < 0.1$ , we used the random effects model by DerSimonian and Laird instead to calculate the pooled ORs.<sup>22</sup>

**Table.** Study Characteristics

	Study Name (Ref)					
	HORIZONS-AMI <sup>15</sup>	EUROMAX <sup>16</sup>	BRAVE 4 <sup>17</sup>	HEAT-PPCI <sup>18</sup>	BRIGHT <sup>19</sup>	MATRIX <sup>20</sup>
Study design	Multicenter, open label	Multicenter, open label	Multicenter, open label	Single-center, open label	Multicenter, open label	Multicenter, open label
Year of publication	2008	2013	2014	2014	2015	2015
Patients (n) ITT	3602	2198	544*	1812	1925 <sup>†</sup>	7213 <sup>‡</sup>
Age, y	60	62	61	63	57	65
Radial access (%)	na	47	0	81	78	50
Clopidogrel (%)	96	51	97 with Heparin	11	100	38
Thienopyridine (%)	0	49	99 with Bivalirudin	89	0	55
Initial heparin bolus, IU/kg	60	100 without GPI, 60 with GPI	70 to 100	70	100 without GPI, 60 with GPI	70 to 100 without GPI, 50 to 70 with GPI
Prolonged bivalirudin infusion after PCI (dose, n%, mean duration)	Stopped immediately after PCI	1.75 mg/kg per hour (22.5%), 0.25 mg/kg per hour (77.5%), 4.5 hours	Stopped immediately after PCI	Stopped immediately after PCI	1.75 mg/kg per hour (100%), 3 hours	1.75 mg/kg per hour (34.4%), 0.25 mg/kg per hour (59.0%), 6.2 hours
GPI use in bivalirudin arm (%)	8	12	3	13	5	5
GPI use in heparin arm (%)	98	69	6	15	6 and 100	26
Definition major bleeding	TIMI major bleeding <sup>§</sup> at 30 days	TIMI major bleeding <sup>§</sup> at 30 days	TIMI major bleeding <sup>§</sup> at 30 days	BARC type 3 to 5 <sup>  </sup> at 28 days	BARC type 3 to 5 <sup>  </sup> at 30 days	BARC type 3 and 5 <sup>  </sup> at 30 days

BARC indicates Bleeding Academic Research Consortium; BRAVE 4, Bavarian Reperfusion Alternatives Evaluation 4; BRIGHT, Bivalirudin in Acute Myocardial Infarction versus Heparin and GPI Plus Heparin; CABG, coronary artery bypass graft; EUROMAX, European Ambulance Acute Coronary Syndrome Angiography; GPI, glycoprotein IIb/IIIa inhibitors; HEAT-PPCI, How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention; HORIZONS-AMI, Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction; ITT, intention-to-treat; MATRIX, Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox; na, not available; NSTEMI, non-ST-segment-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment-elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

\*Randomized to bivalirudin plus prasugrel and heparin plus clopidogrel but stopped early due to slow recruitment.

<sup>†</sup>Randomized to bivalirudin, heparin alone, and heparin plus GPI.

<sup>‡</sup>STEMI 56% and NSTEMI 44%.

<sup>§</sup>TIMI major bleeding: intracranial bleeding, overt bleeding with hemoglobin drop of >5 g/dL, fatal bleeding.

<sup>||</sup>BARC bleeding: Type 3: overt bleeding with hemoglobin drop of >3 g/dL or requiring transfusion, cardiac tamponade, bleeding requiring intervention or vasoactive agents, intracranial bleeding; Type 4: CABG-related bleeding within 48 hours; Type 5: fatal bleeding.

Visual estimation of the funnel plot was used to assess potential publication bias for each clinical outcome. *P* values were 2-tailed, reaching statistical level of significance at 0.05.

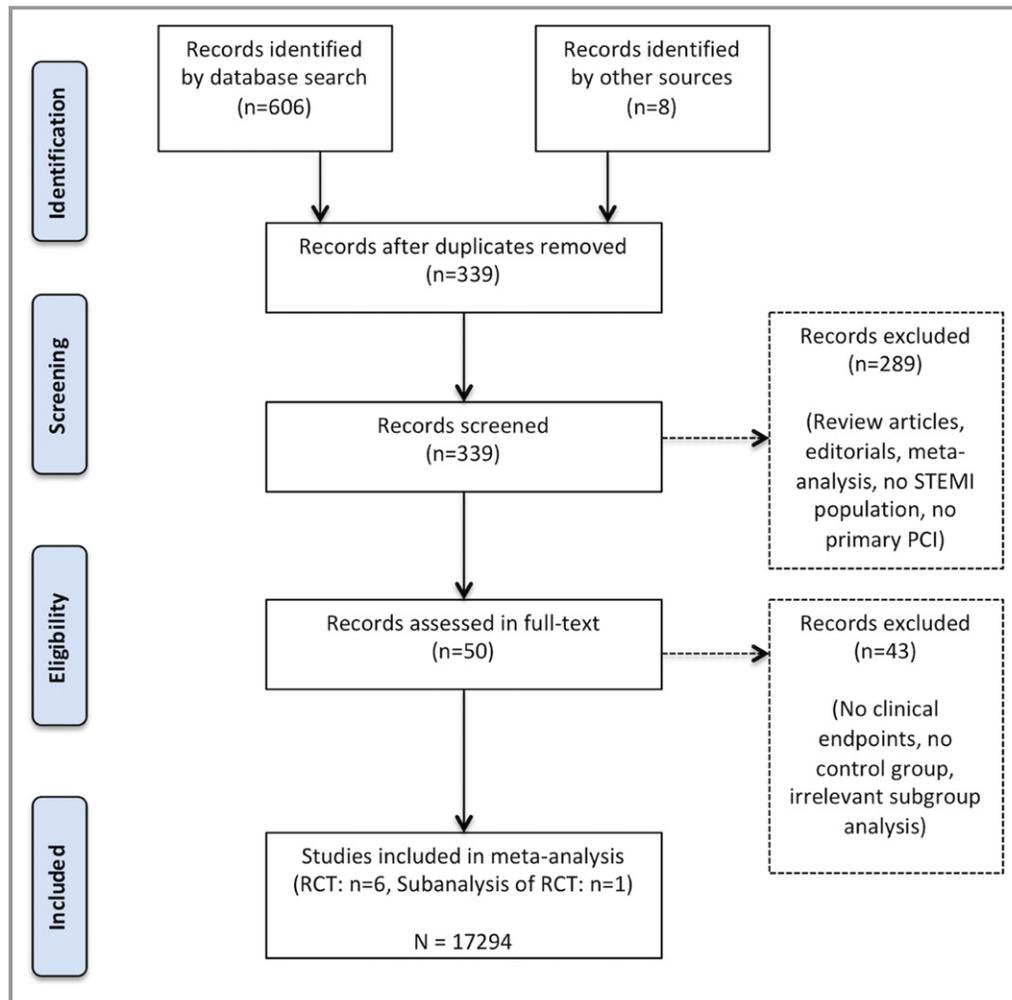
## Results

### Included Studies and Patient Population

The PRISMA statement flowchart describes the process of the literature screening, study selection, and reasons for exclusion (Figure 1). Six hundred fourteen potentially relevant citations were initially identified, of which 50 were retrieved to assess in full-text. Eventually, results from 6 randomized trials were eligible with a total of 17 294 patients included. Study characteristics are highlighted in (Table). The funnel plots suggest no relevant publication bias.

The BRIGHT trial enrolled patients presenting with a non-STEMI; thus, since the outcome data were available separately, we considered only results from the STEMI group.<sup>19</sup> In all studies, bivalirudin was given as initial bolus of 0.75 mg/kg per hour followed by an infusion of 1.75 mg/kg per hour during the procedure. The infusion at PCI-dose was continued in all patients in the BRIGHT<sup>19</sup> trial, as well as partly in the EUROMAX<sup>16</sup> and MATRIX<sup>20</sup> trial, but was stopped immediately after the intervention in the HORIZONS-AMI,<sup>15</sup> HEAT-PPCI,<sup>18</sup> and BRAVE 4.<sup>17</sup> Therefore, 3 studies were considered for the subgroup analysis comparing prolonged PCI-dose bivalirudin with heparin.

The mean age of the included patients was 62 years. Seventy-seven percent were male and 18% had diabetes mellitus. In this meta-analysis, more than 90% of participants underwent PCI.



**Figure 1.** Flow chart of the selection process as per PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) criteria. PCI indicates percutaneous coronary intervention; RCT, randomized clinical trial; STEMI, ST-segment-elevation myocardial infarction.

## Clinical Outcome Comparing Bivalirudin Versus Conventional Antithrombotic Therapy in STEMI Patients

### Major bleeding at 30 days

All 6 randomized trials contributed to the analysis of major bleeding events, with 17 294 patients included (Figure 2A). The rate of major bleeding was significantly reduced in the bivalirudin (1.92% or 160 of 8328) compared with the control (2.93% or 263 of 8966) arm (OR: 0.65, 95% CI: 0.48–0.88,  $P=0.006$ , heterogeneity  $P=0.10$ ,  $I^2=45%$ , random effects model).

### Acute stent thrombosis

Rate of stent thrombosis within 24 hours was reported in 5 studies involving a total of 16 750 patients (Figure 2B). Significant difference emerged between the 2 treatment strategies: 75 of 8059 patients (0.93%) receiving bivalirudin

compared with 29 of 8691 (0.33%) receiving conventional treatment had an acute thrombosis (OR: 2.75, 95% CI: 1.46–5.18,  $P=0.002$ , heterogeneity  $P=0.14$ ,  $I^2=42%$ , random effects model).

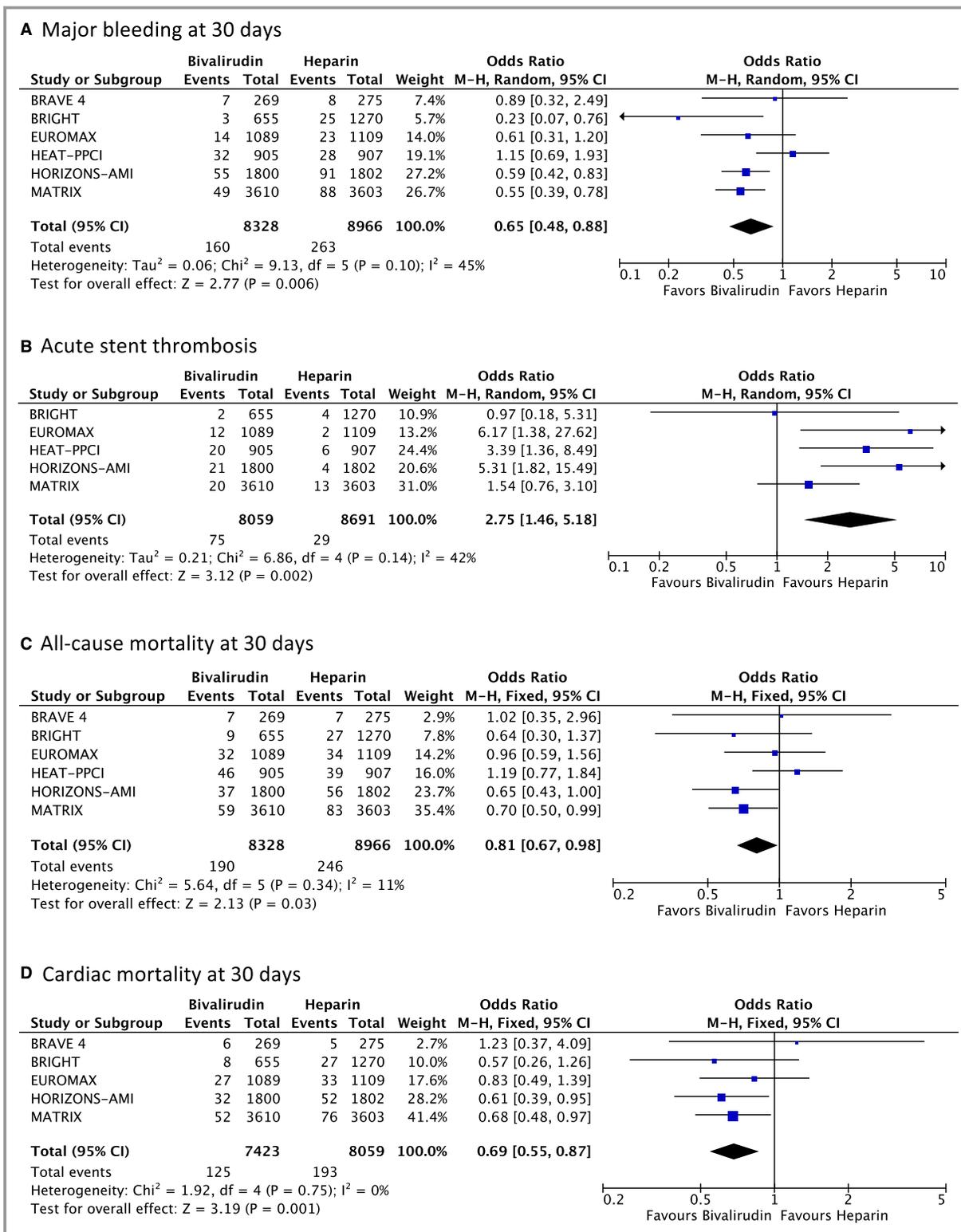
### All-cause mortality at 30 days

All 6 randomized clinical trials, involving 17 294 patients, provided data on overall death (Figure 2C).

The rate of death due to any cause was significantly lower in the bivalirudin (2.28% or 190 of 8328) compared with the standard treatment group (2.74% or 246 of 8966) (OR: 0.81, 95% CI: 0.67–0.98,  $P=0.03$ , heterogeneity  $P=0.34$ ,  $I^2=11%$ , fixed effects model).

### Cardiac mortality at 30 days

Cardiac death was assessed by 5 randomized trials involving a total of 15 482 patients (Figure 2D). There were significantly fewer cardiac deaths with bivalirudin: 1.68% (125 of



**Figure 2.** Forest plot of individual and summarized odds ratios for the comparison of bivalirudin vs heparin in STEMI patients for (A) major bleeding at 30 days, (B) acute stent thrombosis, (C) all-cause mortality at 30 days, and (D) cardiac mortality at 30 days. BRAVE 4, Bavarian Reperfusion Alternatives Evaluation 4; BRIGHT, Bivalirudin in Acute Myocardial Infarction versus Heparin and GPI Plus Heparin; EUROMAX, European Ambulance Acute Coronary Syndrome Angiography; HEAT-PPCI, How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention; HORIZONS-AMI, Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction; MATRIX, Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox; M-H, Mantel-Haenszel; STEMI, ST-segment-elevation myocardial infarction.

7423) compared with conventional treatment: 2.39% (193 of 8059), resulting in a 31% OR reduction (OR: 0.69, 95% CI: 0.55–0.87,  $P=0.001$ , heterogeneity  $P=0.75$ ,  $I^2=0\%$ , fixed effects model).

### Clinical Outcome Comparing Prolonged PCI-Dose Bivalirudin Versus Conventional Antithrombotic Therapy in STEMI Patients

Outcome data on acute stent thrombosis and major bleeding in patients treated with extended high-dose bivalirudin (1.75 mg/kg per hour) are available in 3 of the 6 randomized clinical trials, involving 7337 patients.

#### Acute stent thrombosis and major bleeding at 30 days

The incidence of acute stent thrombosis did not differ in the prolonged PCI-dose bivalirudin (0.26% or 4 of 1517) compared with the standard (0.33% or 19 of 5820) treated arm (OR: 0.81, 95% CI: 0.27–2.46,  $P=0.71$ , heterogeneity  $P=0.64$ ,  $I^2=0\%$ , fixed effects model) (Figure 3A).

The rate of major bleeding events was significantly lower in patient treated with prolonged PCI-dose bivalirudin (0.79% or 12 of 1517) compared with the controlled group (2.92% or 170 of 5820) (OR: 0.28, 95% CI: 0.13–0.60,  $P=0.001$ , heterogeneity  $P=0.24$ ,  $I^2=30\%$ , random effects model) (Figure 3B).

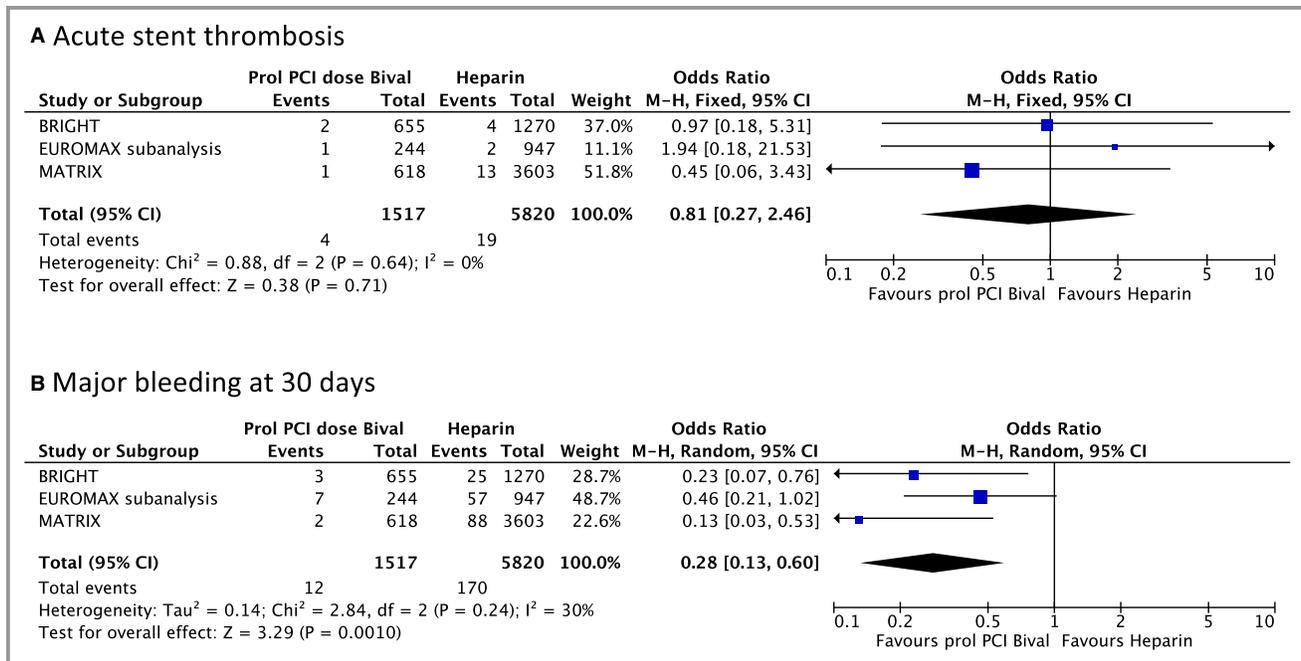
### Discussion

The main findings from our meta-analysis are that bivalirudin (with and without prolonged infusion) compared with conventional antithrombotic therapy in patients undergoing primary PCI reduces “prognostically relevant” major bleeding (TIMI major and BARC 3–5) and death, but increases the rate of acute stent thrombosis. However, prolonging the bivalirudin infusion at the PCI-dose (1.75 mg/kg per hour) for 3 hours after the coronary intervention eliminates the excess of acute stent thrombosis, while maintaining the desired bleeding benefits.

### Debate on Bleeding

The search for the ideal antithrombotic treatment to reduce the rate of thrombotic complications, and minimize bleeding in STEMI patients, was initiated by the HORIZONS-AMI trial.<sup>15</sup> This multicenter trial involved 3602 patients with STEMI undergoing primary PCI who were randomized to bivalirudin alone or UFH plus routine use of glycoprotein IIb/IIIa inhibitor (GPI). In the bivalirudin group, the rates of net adverse clinical events (NACE) were significantly reduced because of a lower rate of major bleeding.

At this time, routine use of GPI in addition to heparin was standard of care, and GPI was administered to more than 90%



**Figure 3.** Forest plot of individual and summarized odds ratios for the comparison of prolonged PCI dose bivalirudin vs heparin in STEMI patients for (A) acute stent thrombosis and (B) major bleeding at 30 days. BRIGHT, Bivalirudin in Acute Myocardial Infarction versus Heparin and GPI Plus Heparin; EUROMAX-ST, European Ambulance Acute Coronary Syndrome Angiography Stent thrombosis; MATRIX, Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox; M-H, Mantel-Haenszel; PCI, percutaneous coronary intervention; STEMI, ST-segment-elevation myocardial infarction.

of patients presenting for primary PCI in Europe and the United States.<sup>27,28</sup> Previous randomized studies in patients with stable angina, unstable angina, and non-STEMI showed a reduction in bleeding complications with similar rates of ischemia after PCI when bivalirudin was used instead of heparin plus GPI.<sup>29,30</sup> This formed the basis for the HORIZONS-AMI study. However, with routine use of dual-antiplatelet therapy, the recommendation to administer GPI in combination with heparin by default was no longer considered as standard of care and the relevance of HORIZONS-AMI on contemporary practice was uncertain.<sup>31</sup>

The EUROMAX trial compared bivalirudin versus heparin in 2218 STEMI patients.<sup>16</sup> This time, the use of GPI was left to the operator's discretion. In addition, bivalirudin was continued for 4 hours post PCI (either in a low or a PCI-dose), and radial access for PCI was used more often. There remained a significant reduction in protocol-defined non-CABG major bleeding with bivalirudin compared with heparin.

However, in the HORIZONS-AMI, BRAVE-4, and EUROMAX trials, any blood product transfusion, even without overt bleeding or significant drop in hemoglobin, was defined as "non-CABG" major bleeding. In these trials, blood transfusions accounted for a large proportion of primary end-point events, though the relationship between transfusion and clinical outcome remains unclear.<sup>32,33</sup> The "prognostically more relevant" TIMI major bleeding (fatal bleeding, intracranial bleeding, or overt bleeding with drop of hemoglobin  $\geq 5$  g/dL) was also reported in HORIZONS-AMI, BRAVE-4, and EUROMAX, but failed to reach statistical significance in the BRAVE-4 and EUROMAX trials.

The use of a nonstandardized "protocol-defined" bleeding definition in earlier ACS trials makes it difficult to interpret relative safety comparisons of different antithrombotic regimens across studies, because results vary according to the definitions used for bleeding. The Bleeding Academic Research Consortium developed the BARC definitions for bleeding end points, providing a consensus for bleeding end points.<sup>24</sup>

This limitation was addressed in the HEAT-PPCI study and the BRIGHT studies, which enrolled patients during 2012 and 2013.<sup>18,19</sup> HEAT-PPCI is a single-center trial that randomly assigned STEMI patients to bivalirudin or UFH, with GPI reserved for selective bailout use (defined as evidence of massive thrombus, slow- or no-reflow, or a thrombotic complication). The multicenter BRIGHT trial randomized patient into 3 study arms including bivalirudin alone, UFH alone, and UFH plus GPI. As in HEAT-PPCI, GPI was reserved only for bailout use in the first 2 study arms. The frequency of GPI use was similar within the study groups. HEAT-PPCI did not demonstrate any difference in bleeding outcomes (BARC 2 and/or 3–5), whereas BRIGHT revealed only a superiority of bivalirudin compared with heparin alone in terms of bleeding requiring medical intervention (BARC 2–5), but not reaching statistical significance for major bleeding (BARC 3–5). PCI in

these later trials were largely performed by radial access, which is associated with a lower rate of major bleeding.<sup>34</sup> Therefore, it is possible that HEAT-PPCI and BRIGHT were underpowered to detect a relevant difference in major bleeding outcome.

The recently published MATRIX trial was designed to address the impact of access route and prolonged bivalirudin infusion.<sup>20</sup> This multicenter trial randomized 7213 patients with an ACS undergoing PCI to bivalirudin or UFH. Thereafter, patients in the bivalirudin group were randomized to stop or continue the infusion at the end of the procedure. The use of GPI was left to the operator's discretion. The study failed to show a difference in the primary composite end point major adverse cardiac event (MACE) (death, myocardial infarction, or stroke) or NACE (major bleeding or major adverse cardiac event) for the comparison between bivalirudin and UFH. However, major bleeding (BARC 3–5) was significantly lower in the bivalirudin compared with the UFH group. This was irrespective of the duration of the bivalirudin infusion.

Our meta-analysis that included all of these trials, involving 17 294 patients, shows a significant reduction of major bleeding (TIMI major and BARC 3–5, rather than non-CABG major bleeding) in patients treated with bivalirudin (1.92%) compared with heparin (2.93%) (OR: 0.65, 95% CI: 0.48–0.88,  $P=0.006$ ).

There is the concern that the imbalanced use of GPI in the 2 study groups may have an influence on bleeding outcome. Two recent meta-analysis of over 25 000 patients undergoing PCI for a range of indications (stable and unstable CAD) with balanced use of GPI confirmed a significant reduction in major bleeding with bivalirudin, suggesting that the beneficial effects on bleeding may be independent of GPI use.<sup>35,36</sup>

## Debate on Stent Thrombosis

Reduction in bleeding is balanced by increased thrombotic complications. The antithrombotic therapy in STEMI patients undergoing primary PCI is especially important since this population has an increased risk of stent thrombosis.<sup>37</sup>

The positive results of the HORIZONS-AMI trial in terms of bleeding and mortality benefit with bivalirudin were compromised by an increase in stent thrombosis.<sup>15</sup> Assignment to bivalirudin, compared with UFH plus GPI, resulted in a 1.0% absolute excess (1.3% versus 0.3%,  $P<0.001$ ) of acute stent thrombosis. This difference in stent thrombosis was present within the first 24 hours and no longer significant at 30 days (2.5% versus 1.9%,  $P=0.30$ ) and 1 year (3.5% versus 3.1%,  $P=0.53$ ).<sup>38</sup>

This increase in early stent thrombosis may be caused by residual thrombin activity after the discontinuation of the short-acting bivalirudin at the end of the procedure and by having low platelet inhibition with oral agents at this time of transition.<sup>39</sup>

Whether the rate of acute stent thrombosis could be diminished by prehospital initiation of novel P2Y<sub>12</sub> blockers and prolonged infusion of bivalirudin at the end of the procedure was assessed in the EUROMAX trial.<sup>16</sup> However, there remained an increased rate of acute stent thrombosis in patients receiving bivalirudin compared with heparin (1.1% versus 0.2%,  $P=0.007$ ).

Dual antiplatelet therapy reduces the risk of stent thrombosis, and the potent third-generation P2Y<sub>12</sub> inhibitors prasugrel and ticagrelor have been shown to reduce stent thrombosis in comparison with clopidogrel in STEMI patients even more.<sup>40,41</sup> However, recent data highlighted that even for novel P2Y<sub>12</sub> inhibitors, the time interval to achieve maximal platelet inhibition is significantly delayed in STEMI patients, not reaching peak pharmacodynamic efficacy for 4 to 6 hours,<sup>42,43</sup> and nor does prasugrel and ticagrelor reduce stent thrombosis in comparison to clopidogrel within the first 24 hours.<sup>44,45</sup> Therefore, unsurprisingly, given that oral antiplatelets in EUROMAX were administered 50 minutes (interquartile range 37–66) before the procedure, the patients did not have P2Y<sub>12</sub> blockade to prevent acute stent thrombosis, which occurred on average 2.3 hours (interquartile range 1.8–2.8) after stent placement.<sup>46</sup> Consequently, stopping the short-lived and rapidly cleared bivalirudin immediately after stent placement compared to longer-acting heparin should result in a substantial increase in acute stent thrombosis, as seen in HEAT-PPCI.<sup>18</sup>

Extending the anticoagulation with bivalirudin during this vulnerable window for stent thrombosis until the pharmacodynamic effects of P2Y<sub>12</sub> blockers become active seems logical, but the exact dosage and duration still need to be defined.

In EUROMAX, all patients received prolonged bivalirudin infusion after the procedure.<sup>16</sup> However, only one fifth were treated at a PCI-dose of 1.75 mg/kg per hour bivalirudin, whereas ≈80% receive a five times lower dose of 0.25 mg/kg per hour. To the best of our knowledge, there are no data showing that anticoagulation with bivalirudin at a dose of 0.25 mg/kg per hour is sufficient to prevent thrombotic complications, especially in a highly thrombotic milieu such as during a myocardial infarction. A post-hoc analysis of the EUROMAX trial revealed that a prolonged bivalirudin infusion at a PCI-dose of 1.75 mg/kg per hour was associated with a significantly lower rate of acute stent thrombosis compared to low-dose bivalirudin and carried the same risk for acute stent thrombosis compared to heparin.<sup>46</sup>

The recently published MATRIX trial showed a borderline increase in stent thrombosis in the bivalirudin group at 30 days (1.0% versus 0.6%,  $P=0.048$ ).<sup>20</sup> Moreover, there was no difference in the rate of stent thrombosis when comparing bivalirudin with a prolonged infusion to bivalirudin without a prolonged infusion. However, this must be interpreted with

some reservation. Prolonged bivalirudin infusion at a PCI-dose of 1.75 mg/kg per hour was given only to one third of patients, whereas the rest received a low dose of 0.25 mg/kg per hour.

The only randomized trial comparing bivalirudin with a prolonged high-dose infusion (1.75 mg/kg per hour for 3 hours) to UFH was the BRIGHT trial.<sup>19</sup> As the post-hoc analysis of the EUROMAX trial had indicated,<sup>46</sup> the BRIGHT trial confirmed that acute stent thrombosis was no more common with bivalirudin followed by prolonged high-dose infusion than heparin.

The results of our meta-analysis suggest that bivalirudin in the overall study population is associated with an increase in acute stent thrombosis compared to heparin (0.93% versus 0.33%, OR: 2.75, 95% CI: 1.46–5.18,  $P=0.002$ ). However, prolonging the bivalirudin infusion at the PCI-dose (1.75 mg/kg per hour) for 3 hours eliminates the excess of acute stent thrombosis (0.26% versus 0.33%, OR: 0.81, 95% CI: 0.27–2.46,  $P=0.71$ ), while maintaining the desired bleeding benefits (0.79% versus 2.92%, OR: 0.28, 95% CI: 0.13–0.60,  $P=0.001$ ).

## Debate on Death

In the HORIZONS-AMI trial, treatment with bivalirudin rather than UFH plus GPI resulted in a significantly lower rate of death after primary PCI at 30 days.<sup>15</sup> The robustness of this finding has been questioned since it was a secondary finding with a broad confidence interval (95% CI=0.44–1.00,  $P=0.047$ ) and moreover, EUROMAX, BRAVE-4, HEAT-PPCI, and BRIGHT failed to reach level of statistical significance.<sup>16–19</sup> However, MATRIX provided further evidence of a reduction in mortality when bivalirudin is compared to UFH.<sup>20</sup>

The consequences of acute stent thrombosis do not appear to impact on the mortality advantage in STEMI patients treated with bivalirudin. The effect on clinical outcome of stent thrombosis that occurs after hospital discharge in patients following elective coronary intervention with well-preserved ventricular function might differ from acute stent thrombosis that affects a recently infarcted territory in patients closely monitored and with the possibility of prompt coronary reintervention.

The relationship between major bleeding after PCI and subsequent death has been confirmed in several trials.<sup>9,10,47,48</sup> The precise mechanism remains unknown, but the mortality benefit seen with bivalirudin may reflect the early prevention of hemorrhagic complications. Nevertheless, HORIZONS-AMI showed a reduction in cardiac mortality not only in bivalirudin-treated patients with major bleeding (5.8% versus 14.6%,  $P=0.025$ ), but also in those without major bleeding (2.6% versus 3.8%,  $P=0.048$ ).<sup>49</sup> Therefore, prevention of bleeding may only partly explain the lower death rate in the bivalirudin group.

Despite the initial higher rate of acute stent thrombosis, treatment with bivalirudin rather than UFH was associated with reduced rates of reinfarction (6.2% versus 8.2%,  $P=0.04$ ).<sup>50</sup> Discontinuation of antiplatelet therapy to control hemorrhage may increase the risk of reinfarction, including subacute and late stent thrombosis,<sup>51–53</sup> which is known to be a major cause of subsequent death after primary PCI,<sup>54,55</sup> and may partially explain this observation.

Our meta-analysis shows a significant reduction in all-cause mortality within 30 days in STEMI patients treated with bivalirudin rather than with heparin (2.28% versus 2.74%, OR: 0.81, 95% CI: 0.67–0.98,  $P=0.03$ ), which is even more pronounced in cardiac death (1.68% versus 2.39%, OR: 0.69, 95% CI: 0.55–0.87,  $P=0.001$ ).

## Limitations

This meta-analysis has several limitations. Firstly, the imbalanced use of GPI in the bivalirudin and heparin group may have influenced the outcome. The Cochrane guidelines do not recommend a meta-regression analysis on confounders if there are fewer than 10 trials in an analysis.<sup>22</sup> However, previous meta-analysis comparing bivalirudin to heparin with balanced GPI use in both groups including more than 25 000 patients undergoing PCI for stable coronary artery disease and ACS showed a significant bleeding benefit in the bivalirudin group.<sup>35,36</sup> Secondly, variation in protocol-defined major bleedings among the included studies makes a direct comparison difficult. Thus, we used the prognostically more relevant TIMI major bleeding (rather than the protocol-defined non-CABG major bleeding) for HORIZONS-AMI, EUROMAX, and BRAVE-4 and the recommended BARC 3–5 major bleeding for HEAT-PPCI, BRIGHT, and MATRIX.<sup>25</sup> This ensures that the bleeding outcome in our meta-analysis is clinically relevant. Thirdly, despite contacting the original investigators, the rates of cardiac death from HEAT-PPCI were not available.<sup>18</sup> However, calculating the summarized OR with a random effect model, assuming that all deaths are caused by cardiac mortality, still resulted in a significant difference in favor of bivalirudin. Fourthly, the MATRIX trial also included non-STEMI patients and outcome for STEMI patients is not available separately.<sup>20</sup> However, this non-STEMI population contributes only 18.5% of the whole study population in our meta-analysis, and the rate of acute stent thrombosis in the MATRIX trial treated with prolonged PCI-dose bivalirudin coincides with the results of the BRIGHT STEMI population, in which all received a prolonged PCI-dose bivalirudin infusion. Therefore, we believe that this is unlikely to have a relevant impact on our overall findings. Fifthly, the bivalirudin infusion at PCI-dose (1.75 mg/kg per hour) was continued in all patients in the BRIGHT trial.<sup>19</sup> However,

prolonging the infusion at the higher dose, rather than a lower dose (0.25 mg/kg per hour), was left to the operators' discretion in the EUROMAX and MATRIX trials.<sup>16,20</sup> Consequently, data for the subgroup analysis are in part not randomized. Nevertheless, these are the best data available to answer this remaining important question.

## Conclusions

Bivalirudin (with and without prolonged infusion) compared with conventional therapy in STEMI patients undergoing primary PCI reduces major bleeding (TIMI major and BARC 3–5) and death, but increases the risk of acute stent thrombosis. However, prolonging the bivalirudin infusion at a PCI-dose (1.75 mg/kg per hour) for 3 hours eliminates the excess of acute stent thrombosis, while maintaining the bleeding benefits.

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## Disclosures

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