EuroIntervention 2015;11:196-203 published online ahead of print August 2014

Bivalirudin versus heparin in patients treated with percutaneous coronary intervention: a meta-analysis of randomised trials

Salvatore Cassese[1], MD; Robert A. Byrne[1]*, MB, BCh, PhD; Karl-Ludwig Laugwitz[2,3], MD; Heribert Schunkert[1,3], MD; Peter B. Berger[4], MD; Adnan Kastrati[1,2,3], MD

1. Deutsches Herzzentrum, Technische Universität München, Munich, Germany; 2. Medizinische Klinik, Klinikum rechts der Isar, Technische Universität München, Munich, Germany; 3. DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany; 4. Geisinger Medical Center, Danville, PA, USA

The references and also the accompanying supplementary data can be found in the online version of this paper at the following website: http://www.pcronline.com/eurointervention/85th_issue/34

KEYWORDS

- anticoagulation
- bivalirudin
- heparin
- meta-analysis
- percutaneous coronary intervention

Abstract

Aims: Current recommendations on the use of bivalirudin in patients treated with percutaneous coronary intervention (PCI) are mostly based on trials comparing bivalirudin versus heparin plus planned glycoprotein IIb/IIIa inhibitor (GPI). Whether bivalirudin is also superior to heparin alone is still not well established. This meta-analysis investigates the efficacy and safety of bivalirudin versus heparin in patients treated with PCI without planned use of GPI.

Methods and results: Scientific databases and websites were searched for randomised controlled trials. The primary efficacy and safety outcomes were the 30-day incidence of death and major bleeding, respectively. The secondary outcomes were the 30-day incidence of myocardial infarction (MI), definite stent thrombosis (ST), urgent target vessel revascularisation (TVR), and overall death at the longest available follow-up. Odds ratio (OR) and 95% confidence interval (95% CI) served as summary statistics. Ten trials were identified including a total of 18,065 PCI patients randomised to bivalirudin (n=9,033) versus heparin (n=9,032). At 30 days, bivalirudin versus heparin showed a comparable risk of death (1.09 [0.83-1.41], p=0.54), and MI (1.10 [0.83-1.46], p=0.50) with a trend towards a higher risk of urgent TVR (1.37 [0.96–1.96], p=0.08). The risk of major bleeding was lower with bivalirudin (0.57 [0.40-0.80], p=0.001) and the bleeding reduction was more evident when high doses of heparin were used as comparator (p for interaction <0.001). The risk of definite ST (2.09 [1.26-3.47], p=0.005) and, in particular, the risk of acute ST (3.48 [1.66-7.28], p<0.001) was increased by bivalirudin.

Conclusions: Patients undergoing PCI randomised to therapy with either bivalirudin or heparin display a similar mortality. Bivalirudin as compared to heparin appears to reduce the risk of major bleeding at the expense of a higher risk of acute ST.

Corresponding author: Deutsches Herzzentrum, Technische Universität München, Lazarettstrasse 36, D-80636 Munich, Germany. E-mail: byrne@dhm.mhn.de

SUBMITTED ON 29/07/2014 - REVISION RECEIVED ON N/A - ACCEPTED ON 29/07/2014

DOI: 10.4244/EIJY14M08_01

Introduction

Antiplatelet and anticoagulant agents represent core adjuvant antithrombotic therapy in patients undergoing percutaneous coronary intervention (PCI). In this context, heparin has for a long time been the dominant anticoagulant available and was the therapy of choice in virtually all settings[1].

Bivalirudin is a synthetic peptide derived from the natural drug hirudin with a direct and reversible thrombin-inhibitor activity. Bivalirudin inhibits both circulating and clot-bound thrombin, as well as thrombin-mediated platelet activation and aggregation, without binding plasma proteins[2]. In patients undergoing PCI, bivalirudin has become an attractive therapeutic option by combining antiplatelet and anticoagulant effects with a predictable antithrombotic response in comparison with heparin[1].

In patients treated with PCI, bivalirudin reduced bleeding-associated complications[3]. In line with this evidence, guideline-writing authorities have assigned to bivalirudin a class I recommendation among anticoagulant agents available for PCI[1,4]. However, most of this supportive evidence has come from earlier comparisons of bivalirudin versus heparin plus planned glycoprotein IIb/IIIa inhibitor (GPI), a strategy which is no longer the standard of care[1,4]. In addition, recent data have pointed to an increased risk of ischaemic complications with bivalirudin[3,5], questioning its role in patients treated with PCI.

This meta-analysis sought to investigate the clinical impact of bivalirudin versus heparin in patients treated with PCI without planned use of GPI.

Methods

SEARCH STRATEGY AND SELECTION CRITERIA

We searched Medline, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), scientific sessions' abstracts and relevant websites (www.cardiosource.com, www.clinicaltrialresults.org, www.escardio.org, www.tctmd.com, www.theheart.org) without restricting language or publication status. Search terms included the keywords and the corresponding Medical Subject Headings for: "anticoagulation", "bivalirudin", "heparin", "percutaneous coronary intervention", "angioplasty", "stent", "trial", and "randomised trial". The references listed in all eligible publications, as well as in prior meta-analyses[6-10] on the same topic, were checked to identify further citations. Inclusion criteria were: (1) randomised design; (2) bivalirudin or heparin administration for elective or urgent PCI; (3) >150 patients enrolled; (4) intention-to-treat analysis. Exclusion criteria were: (1) anticoagulation for elective or urgent PCI other than bivalirudin or heparin; (2) planned GPI use; (3) thrombolysis before randomisation; (4) duplicated data. The final search was performed on 5 July 2014.

DATA COLLECTION AND ASSESSMENT OF RISK OF BIAS

Two investigators (SC and RAB) independently assessed publications for eligibility at title and/or abstract level, with divergences resolved by a third investigator (AK). Studies that met the inclusion criteria were selected for further analysis. Freedom from bias was evaluated for each study by the same investigators, in accordance with The Cochrane Collaboration method[11], based on the following methodological items: adequacy of random sequence generation and allocation concealment, blinding (at participant or outcome assessor level), completeness of reporting outcome data, completeness and adequacy of description of sample size calculation and appropriate disclosure of funding sources. We avoided formal quality score adjudication, which has previously been considered potentially misleading[12].

OUTCOME VARIABLES

The primary efficacy and safety outcomes were the 30-day incidence of death and major bleeding, respectively. The secondary outcomes were the 30-day incidence of myocardial infarction (MI), definite stent thrombosis (ST), urgent target vessel revascularisation (TVR), and the cumulative incidence of death at the longest available follow-up. Endpoints of interest were prospectively defined and were evaluated as per protocol definitions. Where further details were required, we attempted to obtain them from the study investigators directly.

STATISTICAL ANALYSIS

Statistical analysis was performed using the RevMan (Review Manager [RevMan] Version 5.1; The Cochrane Collaboration, Copenhagen, Denmark), and Stata 11.2 (StataCorp, College Station, TX, USA) software packages. Distribution of patient characteristics was presented as median (interquartile range). Odds ratio (OR) and 95% confidence interval (95% CI) served as summary statistics and were calculated for comparison of bivalirudin versus heparin. The Mantel-Haenszel random effects model (DerSimonian and Laird) was used to obtain pooled OR. In case of statistical significance, the number needed to treat (NNT) or the number needed to harm (NNH) with relative (95%) CI was provided. Treatment effects could not be assessed in trials in which no event was reported within the groups. For trials in which only one of the treatment groups had no events of interest, the risk estimates were approximated from 2×2 contingency tables after adding 0.5 to each cell[13]. The Breslow-Day χ^2 test and the I^2 statistic were used to test heterogeneity across the trials. As a guide, I^2 values <25% indicated low, 25-50% moderate, and >50% high heterogeneity[11]. To estimate the additive (between-study) component of variance, the restricted maximum likelihood method (Tau^2) took into account the occurrence of residual heterogeneity. Visual estimation of funnel plots as well as statistical tests assessed possible publication bias for primary outcome, as previously published[14]. Similarly, an influence analysis, in which meta-analysis estimates are computed omitting one trial at a time, was performed for all outcomes. A random effects sensitivity analysis evaluated the extent to which several covariates might have influenced the risk estimates for endpoints showing significant difference. The following covariates were included: the size of the study (under/above median number of patients enrolled), the average of females enrolled (under/above median value), the average of PCI performed with drug-eluting stent (DES, under/above median

value), the average of GPI use in the heparin arm (under/above median value), the dose of heparin (≤70 or >70 IU/kg), the inclusion of patients with ST-elevation myocardial infarction (STEMI), the routine measurement of activated clotting time (ACT) and the presence of industry funding. The same statistical method was used to address the time dependence of risk estimates for definite ST (acute, ≤24 hours; subacute, >24 hours and ≤30 days) associated with bivalirudin versus heparin.

This study was performed in compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement[15]. The PRISMA research checklist has been provided as an **Online Appendix**.

Results

ELIGIBLE STUDIES

The process of study selection is summarised in **Online Figure 1**. Ten studies – eight full-length manuscripts[5,16-22], two meeting presentations[23,24] – totalling 18,065 patients (bivalirudin, n=9,033, versus heparin, n=9,032) were selected for inclusion in the meta-analysis. Seven trials[5,16,17,19-21,23] had a multicentre design. The main characteristics of the trials are described in detail in **Online Table 1**. Briefly, patients with significant stable or unstable coronary artery disease (CAD) scheduled for PCI were randomised to receive bivalirudin versus heparin. Four trials[5,20,22,23] enrolled patients with acute STEMI.

Bivalirudin was administered as a bolus of 0.75 mg/kg, followed by a periprocedural infusion of 1.75 mg/kg/hr and an optional additional infusion of 0.25 mg/kg/hr after PCI in almost all trials. In one trial, a bolus of bivalirudin (1 mg/kg) followed by two-hour infusion at 2.5 mg/kg/hr and a 14- to 20-hour infusion at 0.2 mg/kg/hr was administered[16].

In the control arm, anticoagulation was achieved predominantly with a bolus of unfractionated heparin (UFH) ranging between 60 and 175 IU/kg. In one trial[16], the bolus of UFH was followed by eight to 24-hour infusion of 15 IU/kg. In another trial[5] enrolling patients scheduled for primary PCI, a bolus of 50 IU (0.5 mg)/kg of enoxaparin could be used as an alternative to UFH. Six trials[16,18,20-22,24] administered additional boluses of bivalirudin or heparin according to ACT values. One trial[18] administered protamine sulphate at a dose of 0.5 mg/100 IU of UFH at the end of PCI.

In eight trials[5,18-24], bail-out (in the presence of intracoronary abundant thrombotic material or sustained microvascular obstruction) or provisional (optional) use of GPI was allowed. One trial[23] comprised a third treatment arm in which patients (n=730) were randomly allocated to UHF plus planned GPI administration: these patients were not included in the analysis.

All trials except two[23,24] clearly reported that loading doses of thienopyridines (clopidogrel 300 or 600 mg, prasugrel 30 or 60 mg, ticagrelor 180 mg, oral) as well as aspirin (100 to 325 mg orally or 500 mg i.v.) were administered to all patients before PCI. In one trial[20], enrolling exclusively STEMI patients, participants were randomised to a combination of bivalirudin plus prasugrel versus heparin plus clopidogrel. In all trials, aspirin was recommended indefinitely at a dose of 75 to 200 mg/d, whilst thienopyridines were prescribed for a period of time ranging from one to 12 months according to clinical indication or type of stent implanted during index PCI. In all but one trial[16], the predominant revascularisation strategy consisted of PCI with stent implantation: in the remaining trial only balloon angioplasty was used.

The median number of patients included in each trial was 1,260 (837-2,198). The principal clinical characteristics are shown in **Table 1**. The median age was 63.7 years (61.5-68.9), 25.8% (23.5-30.1) were females, and 24.4% (20.6-43.0) had a diagnosis of diabetes mellitus. More than half of the patients (56.0% [22.8-100]) presented with acute coronary syndrome. The radial artery served as access route for PCI in a small proportion of patients (2.3%

Table 1. Main characteristics of patients enrolled among studies included in the meta-analysis.

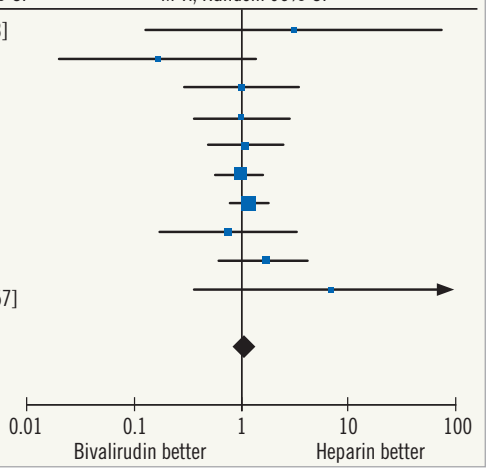
Study	Patients, n	Age, yrs	Females, %	Diabetes, %	ACS at admission, %	Radial access, %	GPI use (bivalirudin arm), %	GPI use (heparin arm), %	DES use, %
ARMYDA-7 BIVALVE[19]	401	70.2	28.5	63.0	29.0	2.0	12.0	14.0	27.5
ARNO[18]	850	68.9	24.0	21.5	26.5	2.0	15.0	28.0	76.5
BAS[16]	4,312	62.5	32.0	21.0	83.0	N/R	N/A	N/A	N/A
BRAVE 4[20]	548	61.4	22.5	43.0	100	0.2	3.0	6.1	95.2
BRIGHT[23]	1,464 (2,194)*	57.6	17.8	20.6	100	78.7	4.4	5.7	N/R
EUROMAX[5]	2,198	61.5	23.8	13.5	100	47.0	11.5	69.1	56.5
HEAT-PPCI[22]	1,829	63.2	27.7	13.8	100	81.1	15.9	18.7	79.8
ISAR-REACT 3[17]	4,570	66.9	23.5	27.4	18.3	N/R	N/A	N/A	87.7
NAPLES III[24]	837	78.0	47.5	44.1	22.8	0.5	0.5	1.3	82.5
REPLACE-1[21]	1,056	64.3	30.1	30.1	N/R	2.6	71.1	72.5	N/A

Overall mean values are reported. ACS: acute coronary syndrome; DES: drug-eluting stent; GPI: glycoprotein IIb/IIIa inhibitor; N/A: not applicable; N/R: not reported; *Including the group of patients randomised to bivalirudin versus heparin plus planned GPI use. Trial acronyms: ARMYDA-7 BIVALVE: Anti-Thrombotic Strategy for Reduction of Myocardial Damage During Angioplasty-Bivalirudin vs Heparin; ARNO: Antithrombotic Regimens aNd Outcome; BAS: Bivalirudin Angioplasty Study; BRAVE 4: Bavarian Reperfusion Alternatives Evaluation; BRIGHT: Bivalirudin vs. Heparin Monotherapy and Glycoprotein IIb/IIIa plus Heparin for Patients with Acute Myocardial Infarction Undergoing Coronary Stenting; EUROMAX: European Ambulance Acute Coronary Syndrome Angiography; HEAT-PPCI: How Effective Are Antithrombotic Therapies in Primary PCI; ISAR-REACT 3: Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment; NAPLES III: Novel Approaches in Preventing or Limiting Events; REPLACE-1: Randomised Evaluation of PCI Linking Angiomax to Reduced Clinical Events

A. Death at 30 days

Study or subgroup	Bivalirudin Events	Bivalirudin Total	Heparin Events	Heparin Total	Weight	Odds ratio M-H, Random, 95% CI
ARMYDA-7 BIVALVE	1	198	0	203	0.7%	3.09 [0.13, 76.33]
ARNO	1	425	6	425	1.5%	0.16 [0.02, 1.37]
BAS	5	2,161	5	2,151	4.5%	1.00 [0.29, 3.44]
BRAVE 4	7	269	7	275	6.2%	1.02 [0.35, 2.96]
BRIGHT	13	728	12	724	11.1%	1.08 [0.49, 2.38]
EUROMAX	32	1,089	34	1,109	29.0%	0.96 [0.59, 1.56]
HEAT-PPCI	46	905	39	907	36.4%	1.19 [0.77, 1.84]
ISAR-REACT 3	3	2,289	4	2,281	3.1%	0.75 [0.17, 3.34]
NAPLES III	10	418	6	419	6.7%	1.69 [0.61, 4.68]
REPLACE-1	3	532	0	524	0.8%	6.93 [0.36, 134.57]
Total (95% CI)		**9,014**		**9,018**	**100.0%**	**1.09 [0.83, 1.41]**
Total events	121		113			

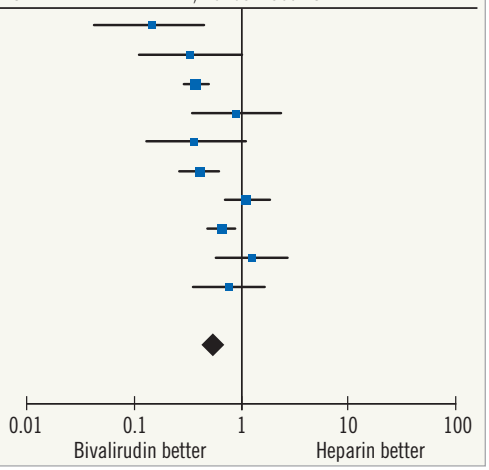
Heterogeneity: Tau²=0.00; Chi²=6.36, df=9 (P=0.70); I²=0%
Test for overall effect: Z=0.61 (P=0.54)



B. Major bleeding

Study or subgroup	Bivalirudin Events	Bivalirudin Total	Heparin Events	Heparin Total	Weight	Odds ratio M-H, Random, 95% CI
ARMYDA-7 BIVALVE	3	198	20	203	5.5%	0.14 [0.04, 0.48]
ARNO	4	425	12	425	6.1%	0.33 [0.10, 1.02]
BAS	79	2,161	199	2,151	15.7%	0.37 [0.28, 0.49]
BRAVE 4	7	269	8	275	7.0%	0.89 [0.32, 2.49]
BRIGHT	4	728	11	724	6.1%	0.36 [0.11, 1.13]
EUROMAX	28	1,089	67	1,109	13.5%	0.41 [0.26, 0.64]
HEAT-PPCI	32	905	28	907	12.6%	1.15 [0.69, 1.93]
ISAR-REACT 3	70	2,289	104	2,281	15.3%	0.66 [0.48, 0.90]
NAPLES III	14	418	11	419	9.1%	1.29 [0.58, 2.87]
REPLACE-1	11	532	14	524	9.1%	0.77 [0.35, 1.71]
Total (95% CI)		**9,014**		**9,018**	**100.0%**	**0.57 [0.40, 0.80]**
Total events	252		474			

Heterogeneity: Tau²=0.19; Chi²=30.75, df=9 (P=0.0003); I²=71%
Test for overall effect: Z=3.18 (P=0.001)



C. Myocardial infarction

Study or subgroup	Bivalirudin Events	Bivalirudin Total	Heparin Events	Heparin Total	Weight	Odds ratio M-H, Random, 95% CI
ARMYDA-7 BIVALVE	20	198	17	203	10.3%	1.23 [0.62, 2.42]
ARNO	11	425	20	425	9.1%	0.54 [0.25, 1.14]
BAS	71	2,161	90	2,151	19.4%	0.78 [0.57, 1.07]
BRAVE 4	4	269	4	275	3.5%	1.02 [0.25, 4.13]
BRIGHT	7	728	9	724	6.1%	0.77 [0.29, 2.08]
EUROMAX	19	1,089	10	1,109	8.8%	1.95 [0.90, 4.22]
HEAT-PPCI	24	905	8	907	8.3%	3.06 [1.37, 6.85]
ISAR-REACT 3	128	2,289	110	2,281	21.0%	1.17 [0.90, 1.52]
NAPLES III	1	418	0	419	0.7%	3.01 [0.12, 74.21]
REPLACE-1	27	532	26	524	12.9%	1.02 [0.59, 1.78]
Total (95% CI)		**9,014**		**9,018**	**100.0%**	**1.10 [0.83, 1.46]**
Total events	312		294			

Heterogeneity: Tau²=0.08; Chi²=17.43, df=9 (P=0.04); I²=48%
Test for overall effect: Z=0.67 (P=0.50)

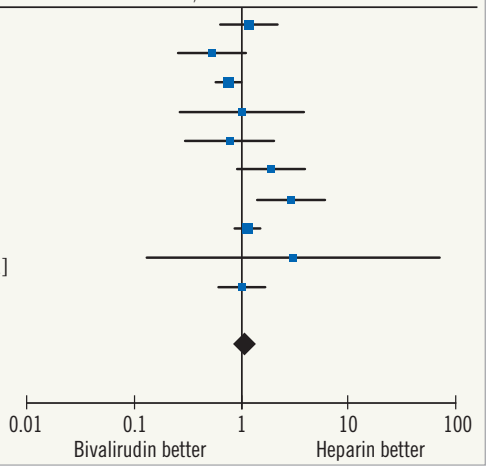


Figure 1. *Risk estimates of primary and secondary outcomes at 30-day follow-up for bivalirudin versus heparin in patients treated with PCI. Plot of odds ratio for primary efficacy (A) and safety outcomes (B) as well as for secondary outcomes (C-E) associated with bivalirudin versus heparin. The diamond indicates the point estimate and the left and the right ends of the line the 95% confidence interval (CI). M-H: Mantel-Haenszel; TVR: target vessel revascularisation*

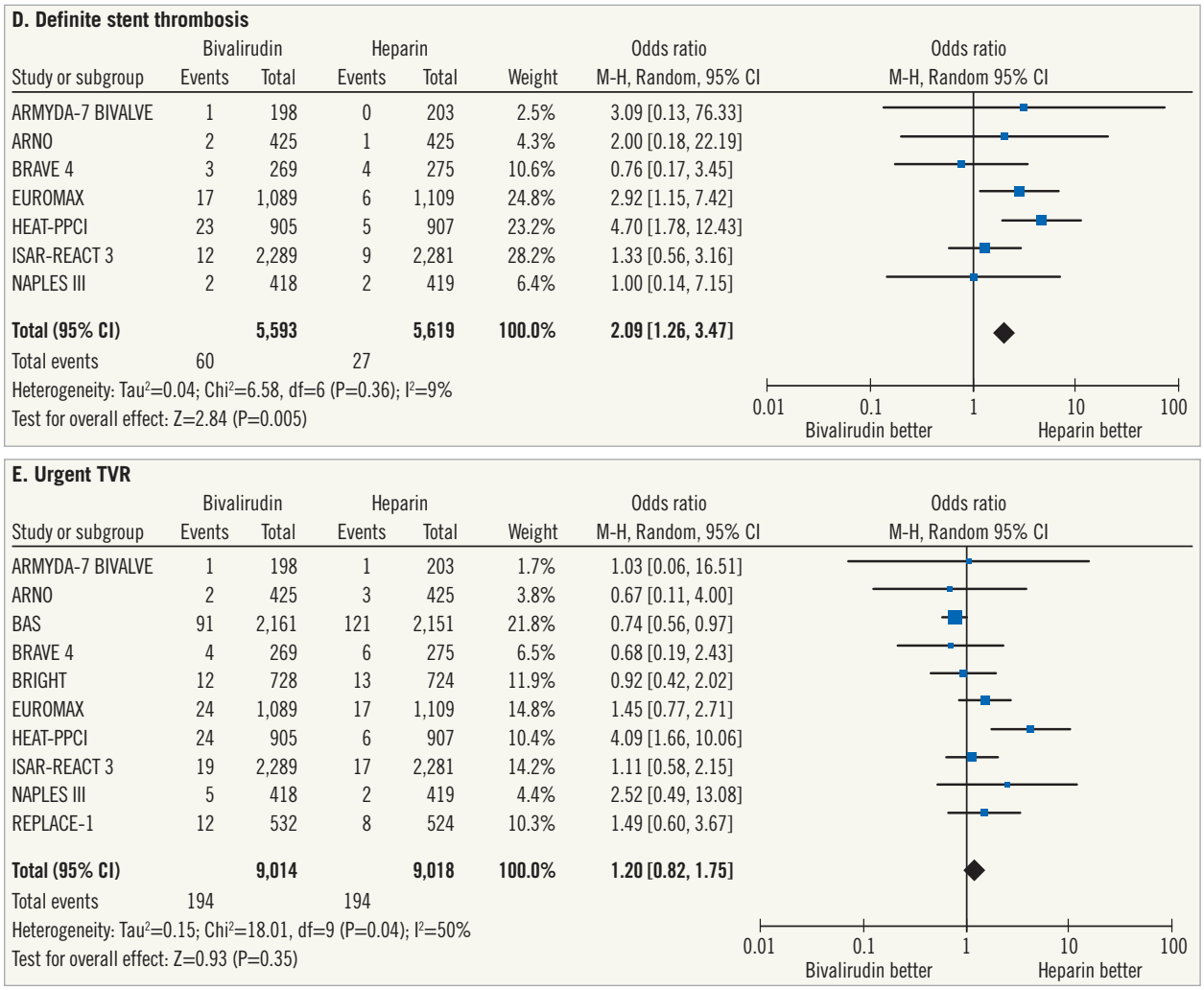


Figure 1 (Continued). *Risk estimates of primary and secondary outcomes at 30-day follow-up for bivalirudin versus heparin in patients treated with PCI. Plot of odds ratio for primary efficacy (A) and safety outcomes (B) as well as for secondary outcomes (C-E) associated with bivalirudin versus heparin. The diamond indicates the point estimate and the left and the right ends of the line the 95% confidence interval (CI). M-H: Mantel-Haenszel; TVR: target vessel revascularisation*

[1.2-62.8]). The predominant type of stent used was DES (79.8% [56.5-87.7]).

An overview of the definitions of the endpoints in the studies is reported in **Online Table 2**. In all trials except two[16,21], the incidence of major bleeding was the primary outcome. Major bleeding was most frequently adjudicated according to the Thrombolysis In Myocardial Infarction (TIMI) definition[25]. Definite stent thrombosis was adjudicated according to Academic Research Consortium criteria[26]. The risk of bias among studies is reported in **Online Table 3**.

CLINICAL OUTCOMES

Among those randomised, a total of 18,032 patients (99.8%; bivalirudin, n=9,014, versus heparin, n=9,018) were available for 30-day outcome assessment.

The incidence of death at 30 days, the primary efficacy outcome, occurred in 234 patients (1.3%) **(Figure 1A)**. Bivalirudin versus heparin showed a comparable risk of death (1.3% versus 1.2%; OR: 1.09 [0.83-1.41], p=0.54; I^2=0%, p for heterogeneity - p_{het}=0.70). Data regarding cardiac cause of death were available for four trials[5,18-20] (n=3,993 patients). In these studies, cardiac death occurred in 88 patients (2.2%): bivalirudin versus heparin showed a comparable risk of cardiac death (1.7% versus 2.1%; OR: 0.85 [0.53-1.34], p=0.47; I^2= 0%, p_{het}=0.43).

Major bleeding, the primary safety outcome, occurred in 726 patients (4.0%). Bivalirudin versus heparin reduced the risk of major bleeding although there was high heterogeneity among studies (2.8% versus 5.2%; OR: 0.57 [0.40-0.80], p=0.001; I^2=71%, p_{het}=0.0003; NNT=41 [33-53]) **(Figure 1B)**. Therefore, the analysis was restricted to those trials[5,17,19,20,24] (n=8,550 patients) in which major bleeding was adjudicated according to TIMI definition. TIMI major bleeding occurred in 116 (1.3%) patients. Bivalirudin versus heparin reduced the risk of TIMI major bleeding without significant heterogeneity (0.8% versus 1.8%; OR: 0.51 [0.30-0.85], p=0.01; I^2=31%, p_{het}=0.21; NNT=108 [70-225]).

MI occurred in 606 patients (3.3%) **(Figure 1C)**. Bivalirudin versus heparin showed a comparable risk of MI although there was

moderate heterogeneity among studies (3.4% versus 3.2%; OR: 1.10 [0.83-1.46], p=0.50; I^2=48%, p_{het}=0.04).

Adjudication of definite ST was available for seven trials[5,17-20,22,24] (n=11,212 patients). Definite ST occurred in 87 patients (0.7%) **(Figure 1D)**. Bivalirudin versus heparin increased the risk of definite ST without significant heterogeneity (1.0% versus 0.5%; OR: 2.09 [1.26-3.47], p=0.005; I^2=9%, p_{het}=0.36; NNH=169 [107-366]). Data regarding the time point of definite ST were available for five trials[5,17,18,20,22] (n=9,954 patients). Acute ST occurred in 43 patients (0.4%): bivalirudin versus heparin increased the risk of acute ST without significant heterogeneity (0.7% versus 0.2%; OR: 3.48 [1.66-7.28], p<0.001; I^2=0%, p_{het}=0.53; NNH=199 [131-408]). Subacute ST occurred in 44 patients (0.4%): bivalirudin versus heparin showed a comparable risk of subacute ST without significant heterogeneity (0.4% versus 0.4%; OR: 1.11 [0.60-2.03], p=0.74; I^2=0%, p_{het}=0.81). The time dependence of definite ST risk for bivalirudin versus heparin was supported by a significant interaction (p for interaction - p_{int}=0.02).

Urgent TVR occurred in 388 patients (2.1%) **(Figure 1E)**. Bivalirudin versus heparin showed a comparable risk of urgent TVR, although there was moderate-to-high heterogeneity among studies (2.1% versus 2.1%; OR: 1.20 [0.82-1.75], p=0.35; I^2=50%, p_{het}=0.04). Therefore, the trial of Bittl et al[16], in which patients received balloon angioplasty only, was excluded. Among 16,720 patients available for further analysis, urgent TVR occurred in 176 patients (1.0%). Bivalirudin versus heparin showed a trend towards an increased risk of urgent TVR without significant heterogeneity (1.5% versus 1.0%; OR: 1.37 [0.96-1.96], p=0.08; I^2=16%, p_{het}=0.30).

Overall, clinical follow-up was reported to 105 days (30-360), with five trials[16-18,23,24] evaluating >30-day outcomes. During this period, death occurred in 400 patients (2.2%) **(Figure 2)**. Bivalirudin versus heparin showed a comparable risk of death without significant heterogeneity (2.3% versus 2.1%; OR: 1.08 [0.89-1.32], p=0.44; I^2= 0%, p_{het}=0.74).

SMALL STUDY EFFECTS, INFLUENCE AND SENSITIVITY ANALYSES

Funnel plot distribution of outcomes of interest was derived from the standard error of the logarithm OR plotted against the OR of outcomes of interest **(Online Figure 2)**. Of note, the absence of bias due to small study effects was confirmed both visually and mathematically. Additionally, the influence analysis demonstrated that no single study significantly altered the summary OR for outcomes of interest (data not shown).

Sensitivity analyses were conducted for those outcomes showing a significant difference **(Table 2)**. The risk of major bleeding was increased by high doses of heparin (p_{int}<0.001). The risk of definite ST was higher with bivalirudin in combination with less frequent DES use (p_{int}=0.02); similarly, bivalirudin showed a higher risk of definite ST in comparison with heparin and more frequent GPI use (p_{int}=0.02). The size of studies, the average proportion of females, the enrolment of STEMI patients, the use of routine ACT measurement and the nature of trial sponsorship did not influence the risk estimates for major bleeding nor for definite ST.

Discussion

We undertook this meta-analysis to investigate the relative efficacy and safety of bivalirudin versus heparin in patients treated with PCI without planned use of GPI. The main findings of this systematic review of randomised trial data are that bivalirudin in comparison with heparin i) does not reduce mortality, ii) decreases the risk of major bleeding, and iii) increases the risk of acute ST.

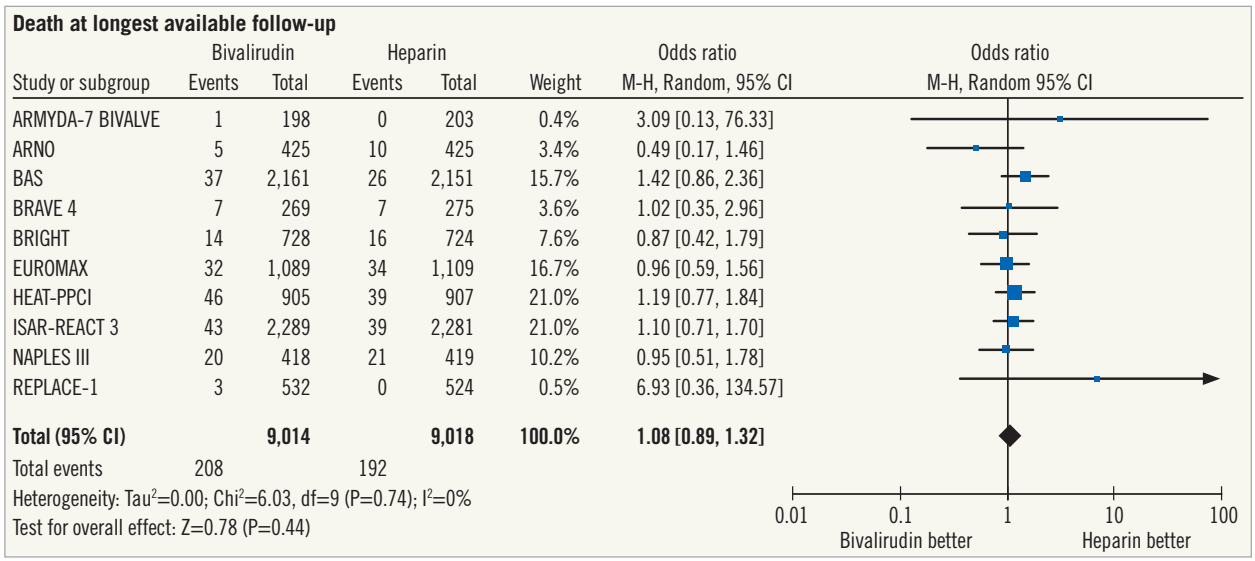


Figure 2. *Risk estimates of overall mortality for bivalirudin versus heparin in patients treated with PCI. Plot of odds ratio for overall mortality associated with bivalirudin versus heparin. The diamond indicates the point estimate and the left and the right ends of the line the 95% confidence interval (CI). M-H: Mantel-Haenszel*

Table 2. Sensitivity analysis for endpoints showing a significant difference.

Variable	Subgroup	Trial, n	Major bleeding OR [95% CI]	p_{int}	Trial, n	Definite ST OR [95% CI]	p_{int}
Trial size, patients	≤1,260	5	0.58 [0.28-1.19]	0.86	5	1.12 [0.41-3.10]	0.19
	>1,260	5	0.54 [0.36-0.83]		4	2.56 [1.49-5.35]	
Average of females, %	≤25.8	5	0.53 [0.39-0.73]	0.71	4	1.68 [0.95-2.97]	0.16
	>25.8	5	0.61 [0.31-1.22]		4	3.44 [1.49-7.98]	
Average of DES, %	≤79.8	4	0.43 [0.19-0.98]	0.19	4	3.49 [1.85-6.60]	0.02
	>79.8	3	0.78 [0.53-1.13]		3	1.14 [0.56-2.29]	
Average of GPI use (heparin arm), %	≤14	5	0.59 [0.33-1.06]	0.90	4	1.19 [0.60-2.36]	0.02
	>14	4	0.62 [0.34-1.14]		4	3.51 [1.84-6.72]	
Heparin dose, IU/kg	≤70	3	1.08 [0.74-1.58]	<0.001	3	2.77 [0.66-11.72]	0.54
	>70	7	0.44 [0.31-0.61]		5	1.71 [0.98-3.00]	
Enrolment of STEMI patients	Yes	4	0.64 [0.34-1.22]	0.60	3	2.56 [1.04-6.28]	0.30
	No	6	0.52 [0.33-0.82]		5	1.39 [0.67-2.89]	
Routine ACT measurement	Yes	6	0.71 [0.40-1.25]	0.18	5	1.93 [0.70-2.59]	0.98
	No	4	0.42 [0.25-0.71]		3	1.95 [1.04-3.63]	
Industry funding	Yes	6	0.57 [0.39-0.83]	0.83	4	2.56 [1.23-5.35]	0.52
	No	4	0.51 [0.19-1.37]		4	1.55 [0.39-6.11]	

Odds ratios (OR) (95% confidence intervals [CI]) are used as summary statistics and were calculated for comparisons of bivalirudin versus heparin; p-values for interaction (p_{int}) between treatment effects (bivalirudin versus heparin) and subgroups of interest are derived using the Mantel-Haenszel random effects model (DerSimonian and Laird). The median values are used to define cut-offs for trial size, average of females, DES and GPI use. A p-value <0.05 is considered significant. ACT: activated clotting time; DES: drug-eluting stent ST: stent thrombosis; STEMI: ST-elevation myocardial infarction

Anticoagulation is an integral part of interventional therapy of coronary lesions in order to avoid intravascular or device-related clot formation. Heparin has, for a long period of time, been the dominant anticoagulant used in PCI and still maintains a class I recommendation for use[1,4]. In the last decade, the use of bivalirudin, a direct thrombin inhibitor, has attracted considerable interest: the lack of protein binding, ensuring a more predictable pharmacokinetic together with both anticoagulant and antiplatelet effects, has supported bivalirudin as a valuable therapy alternative to heparin[2].

Earlier large-scale randomised trials[3,27,28] and meta-analyses[8-10] have shown that bivalirudin significantly reduces bleeding-related complications in patients receiving PCI. According to this evidence, bivalirudin has received a class I recommendation as anticoagulant for PCI[1,4]. Importantly, this recommendation is largely based on trials in which the comparator was the fixed combination of heparin and GPI[27,28]. Since GPI use for patients undergoing PCI is nowadays recommended primarily as a bail-out rather than a planned routine strategy, the applicability of these results in the current era is open to question. Moreover, the impact of the increasing use of more potent oral antiplatelet inhibitors must also be considered. In addition, some recent data have suggested that bivalirudin may increase the risk of ischaemic complications, calling into question the benefit of this direct thrombin inhibitor in patients undergoing PCI[5,22].

The present analysis pooled study-level data from 10 randomised trials including more than 18,000 PCI-treated patients and investigated the efficacy and safety of bivalirudin versus heparin. In contrast to previous meta-analyses on the same topic[7-10,29], but in accordance with recommendations of guideline-writing authorities and current clinical practice, the present study included only randomised trials without planned routine use of GPI[1,4].

The findings of the current report may be considered important for a number of reasons. Firstly, in our analysis bivalirudin versus heparin showed no sign of mortality benefit. In fact, the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial is to date the only large-scale randomised trial in which the use of bivalirudin as compared with heparin plus planned use of GPI for PCI has reduced mortality[3]. Although these results were based on wide confidence intervals and were regarded as hypothesis-generating, the lower mortality associated with bivalirudin was supposed plausible as a consequence of bleeding reduction. Indeed, the higher risk of death in patients who bleed after PCI remains undisputed[30,31]. However, it should be noted that GPI was routinely applied in the control arm of the HORIZONS-AMI trial and that the bleeding-related deaths accounted only in part for the survival difference observed for bivalirudin[32,33].

Secondly, the present meta-analysis reports that bivalirudin versus heparin during PCI significantly reduces the risk of major bleeding at 30-day follow-up. Although this result is consistent with all previous studies and meta-analyses[9,10], a high degree of heterogeneity was observed, mainly due to different protocol definitions of major bleeding across trials. However, in the meta-analysis of those trials adjudicating major bleeding according to the TIMI definition, bivalirudin remains superior to heparin in terms of bleeding reduction in the absence of significant heterogeneity. Additional sensitivity analysis shows that the bleeding reduction with bivalirudin is more evident when high doses of heparin are used as comparator

treatment. This is important, since it has been shown that in PCI patients a low dose as compared with a high dose of heparin reduces bleeding without increasing the risk of thrombotic events[34].

Thirdly, in this analysis bivalirudin versus heparin significantly increased the risk of definite ST at 30 days. The large majority of these events occurred within 24 hours after PCI. This issue potentially represents the major drawback of bivalirudin. Indeed, even in the current era of rapid-onset more potent thienopyridine therapy, full antiplatelet inhibition is not achieved until some hours after the administration of the loading dose[35]. For this reason, insufficient antithrombotic protection in the early phase after revascularisation may expose patients to a higher risk of abrupt vessel closure. Moreover, the sensitivity analysis for definite ST showed that the combination of bivalirudin with less frequent DES use significantly increased the risk of definite ST. The large majority of trials included in this analysis have been performed in the current era of safer DES which have demonstrated a lower risk of ST versus bare metal platforms[36]. In this respect, it might be speculated that the use of bivalirudin may less effectively neutralise the intrinsic thrombotic risk of platforms other than current DES. Moreover, the sensitivity analysis for definite ST showed that bivalirudin is associated with a higher risk of definite ST when compared with heparin and higher percentages of GPI use. Per protocol, the trials included in the present meta-analysis allowed the use of GPI only as bail-out or provisional indication: on the one hand, a higher percentage of GPI use indicates a higher thrombotic risk; on the other hand, the higher antithrombotic potency of the combination of heparin plus GPI cannot be neglected. Unfortunately, the lack of a mechanistic explanation precludes further speculations concerning the efficacy of bivalirudin in preventing ST in those patients at higher risk for this complication. Surprisingly, although the use of bivalirudin increased the risk of acute ST it did not impact on mortality hazard at 30-day follow-up. This is consistent with previous observations[3,5] and is possibly due to the predominant in-hospital occurrence of ST, which is amenable to prompt invasive management.

Finally, at 30-day follow-up, bivalirudin versus heparin increased the risk of urgent TVR in patients receiving stents. However, the risk of MI was not affected. On the one hand, it is intuitive that a higher risk of thrombotic occlusion of the stented vessel carries a parallel increase in the number of urgent (ischaemia-driven) TVR. On the other hand, the moderate heterogeneity reported, due to the different definitions of MI used in the original trials, precludes definitive conclusions.

STUDY LIMITATIONS

The current study has some important limitations. Firstly, this meta-analysis is based on study-level rather than individual patient-level data and shares the limitations of the original trials. Secondly, we elected to include both published and unpublished trials. However, in our opinion the inclusion of "grey literature" is the preferred approach, as prior investigation has suggested that treatment effects may be exaggerated when grey literature is excluded[37]. Thirdly, different thienopyridines have been used among treatment arms and may have been administered at different intervals before PCI; however, a possible influence of antiplatelet regimens on the risk of thrombotic as well as bleeding complications cannot be addressed in the context of this analysis. Fourthly, the majority of the studies included were powered for composite endpoints of ischaemic and bleeding outcomes: for this reason, analysis regarding relatively infrequent adverse events such as ST should be interpreted with caution. Moreover, although the sources of heterogeneity observed in the risk estimates have been investigated thoroughly, unknown sources of heterogeneity cannot be definitively excluded. Finally, the majority of trials included in the present analysis used the femoral route to perform PCI; the widespread adoption of radial access and vascular closure devices makes further evaluation in these settings a relevant undertaking.

Conclusions

In comparison with the currently used standard regimen of heparin, administration of bivalirudin does not reduce mortality in patients undergoing PCI. However, bivalirudin as compared with heparin appears to reduce the risk of major bleeding at the expense of a higher risk of acute stent thrombosis.

Impact on daily practice

The role of bivalirudin in patients undergoing PCI without planned glycoprotein IIb/IIIa inhibitor remains unclear with four recent clinical trials providing conflicting results. This meta-analysis shows that in patients treated with PCI receiving bail-out or provisional use of glycoprotein IIb/IIIa inhibitor, bivalirudin has no advantage over the currently used standard regimen of heparin in terms of mortality. Although lower rates of bleeding are seen with bivalirudin, the rates of stent thrombosis are higher.

Conflict of interest statement

R.A. Byrne has received lecture fees from B. Braun and Biotronik. A. Kastrati has submitted patents in relation to a number of DES technologies and has received consulting or lecture fees from Abbott, Biosensors and Biotronik. The other authors have no conflicts of interest to declare.

References

The references can be found in the online version of the paper.

Online data supplement

Online Appendix. PRISMA research checklist.

Online Figure 1. PRISMA flow chart for the study selection process.

Online Figure 2. Funnel plot distribution of studies included in the meta-analysis according to outcomes of interest.

Online Table 1. Main characteristics of studies included in the meta-analysis.

Online Table 2. Endpoint definitions within studies included in the meta-analysis.

Online Table 3. Assessment of risk of bias.

Online data supplement

References

1. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Nallamothu BK, Ting HH; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; Society for Cardiovascular Angiography and Interventions. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol.* 2011;58:e44-122.

2. Busch G, Steppich B, Sibbing D, Braun SL, Stein A, Groha P, Schomig A, Kastrati A, von Beckerath N, Ott I. Bivalirudin reduces platelet and monocyte activation after elective percutaneous coronary intervention. *Thromb Haemost.* 2009;101:340-4.

3. Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Kornowski R, Hartmann F, Gersh BJ, Pocock SJ, Dangas G, Wong SC, Kirtane AJ, Parise H, Mehran R; HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med.* 2008;358:2218-30.

4. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for Percutaneous Cardiovascular Interventions (EAPCI), Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D. Guidelines on myocardial revascularization. *Eur Heart J.* 2010;31:2501-55.

5. Steg PG, van 't Hof A, Hamm CW, Clemmensen P, Lapostolle F, Coste P, Ten Berg J, Van Grunsven P, Eggink GJ, Nibbe L, Zeymer U, Campo dell' Orto M, Nef H, Steinmetz J, Soulat L, Huber K, Deliargyris EN, Bernstein D, Schuette D, Prats J, Clayton T, Pocock S, Hamon M, Goldstein P; EUROMAX Investigators. Bivalirudin started during emergency transport for primary PCI. *N Engl J Med.* 2013;369:2207-17.

6. Ebrahimi R, Lincoff AM, Bittl JA, Chew D, Wolski K, Wadhan N, Toggart EJ, Topol EJ. Bivalirudin vs heparin in percutaneous coronary intervention: a pooled analysis. *J Cardiovasc Pharmacol Ther.* 2005;10:209-16.

7. De Luca G, Cassetti E, Verdoia M, Marino P. Bivalirudin as compared to unfractionated heparin among patients undergoing coronary angioplasty: A meta-analyis of randomised trials. *Thromb Haemost.* 2009;102:428-36.

8. Bertrand OF, Jolly SS, Rao SV, Patel T, Belle L, Bernat I, Parodi G, Costerousse O, Mann T. Meta-analysis comparing bivalirudin versus heparin monotherapy on ischemic and bleeding outcomes after percutaneous coronary intervention. *Am J Cardiol.* 2012;110:599-606.

9. Tarantini G, Brener SJ, Barioli A, Gratta A, Parodi G, Rossini R, Navarese EP, Niccoli G, Frigo AC, Musumeci G, Iliceto S, Stone GW. Impact of baseline hemorrhagic risk on the benefit of bivalirudin versus unfractionated heparin in patients treated with coronary angioplasty: a meta-regression analysis of randomized trials. *Am Heart J.* 2014;167:401-412.e6.

10. Nairooz R, Sardar P, Amin H, Swaminathan RV, Kim LK, Chatterjee S, Feldman DN. Meta-analysis of randomized clinical trials comparing bivalirudin versus heparin plus glycoprotein IIb/IIIa inhibitors in patients with ST-segment elevation myocardial infarction. *Am J Cardiol.* 2014;114:250-9.

11. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327:557-60.

12. Jüni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *JAMA.* 1999;282:1054-60.

13. Cassese S, Byrne RA, Ott I, Ndrepepa G, Nerad M, Kastrati A, Fusaro M. Paclitaxel-coated versus uncoated balloon angioplasty reduces target lesion revascularization in patients with femoropopliteal arterial disease: a meta-analysis of randomized trials. *Circ Cardiovasc Interv.* 2012;5:582-9.

14. Sterne JA, Egger M, Smith GD. Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. *BMJ.* 2001;323:101-5.

15. Moher D, Liberati A, Tetzlaff J, Altman DG: PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med.* 2009;151:264-9, W64.

16. Bittl JA, Chaitman BR, Feit F, Kimball W, Topol EJ. Bivalirudin versus heparin during coronary angioplasty for unstable or postinfarction angina: Final report reanalysis of the Bivalirudin Angioplasty Study. *Am Heart J.* 2001;142:952-9.

17. Kastrati A, Neumann FJ, Mehilli J, Byrne RA, Iijima R, Buttner HJ, Khattab AA, Schulz S, Blankenship JC, Pache J, Minners J, Seyfarth M, Graf I, Skelding KA, Dirschinger J, Richardt G, Berger PB, Schomig A; ISAR-REACT 3 Trial. Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. *N Engl J Med.* 2008;359:688-96.

18. Parodi G, Migliorini A, Valenti R, Bellandi B, Signorini U, Moschi G, Buonamici P, Cerisano G, Antoniucci D. Comparison of bivalirudin and unfractionated heparin plus protamine in patients with coronary heart disease undergoing percutaneous coronary intervention (from the Antithrombotic Regimens aNd Outcome [ARNO] trial). *Am J Cardiol.* 2010;105:1053-9.

19. Patti G, Pasceri V, D'Antonio L, D'Ambrosio A, Macri M, Dicuonzo G, Colonna G, Montinaro A, Di Sciascio G. Comparison of safety and efficacy of bivalirudin versus unfractionated heparin in high-risk patients undergoing percutaneous coronary intervention (from the Anti-Thrombotic Strategy for Reduction of Myocardial Damage During Angioplasty-Bivalirudin vs Heparin study). *Am J Cardiol.* 2012;110:478-84.

20. Schulz S, Richardt G, Laugwitz KL, Morath T, Neudecker J, Hoppmann P, Mehran R, Gershlick AH, Tölg R, Fiedler KA, Abdel-Wahab M, Kufner S, Schneider S, Schunkert H, Ibrahim T, Mehilli J, Kastrati A; and for the Bavarian Reperfusion Alternatives Evaluation (BRAVE) 4 Investigators. Prasugrel plus bivalirudin vs. clopidogrel plus heparin in patients with ST-segment elevation myocardial infarction. *Eur Heart J.* 2014 May 9. [Epub ahead of print].

21. Lincoff AM, Bittl JA, Kleiman NS, Sarembock IJ, Jackman JD, Mehta S, Tannenbaum MA, Niederman AL, Bachinsky WB, Tift-Mann J 3rd, Parker HG, Kereiakes DJ, Harrington RA, Feit F, Maierson ES, Chew DP, Topol EJ; REPLACE-1 Investigators. Comparison of bivalirudin versus heparin during percutaneous coronary intervention (the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events [REPLACE]-1 trial). *Am J Cardiol.* 2004;93:1092-6.

22. Shahzad A, Kemp I, Mars C, Wilson K, Roome C, Cooper R, Andron M, Appleby C, Fisher M, Khand A, Kunadian B, Mills JD, Morris JL, Morrison WL, Munir S, Palmer ND, Perry RA, Ramsdale DR, Velavan P, Stables RH; for the HEAT-PPCI trial investigators. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. *Lancet.* 2014 Jul 4. [Epub ahead of print].

23. Han Y. BRIGHT: A Prospective, Randomized Trial of Bivalirudin vs. Heparin Monotherapy and Glycoprotein IIb/IIIa plus Heparin for Patients with Acute Myocardial Infarction Undergoing Coronary Stenting. China Interventional Therapeutics Congress, Shanghai, China, March 21 2014.

24. Briguori C. Novel Approaches in Preventing and Limiting Events III Trial (NAPLES III). American College of Cardiology Congress, Washington, DC, USA, March 29 2014.

25. Rao AK, Pratt C, Berke A, Jaffe A, Ockene I, Schreiber TL, Bell WR, Knatterud G, Robertson TL, Terrin ML. Thrombolysis in Myocardial Infarction (TIMI) Trial--phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *J Am Coll Cardiol.* 1988;11:1-11.

26. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344-51.

27. Lincoff AM, Bittl JA, Harrington RA, Feit F, Kleiman NS, Jackman JD, Sarembock IJ, Cohen DJ, Spriggs D, Ebrahimi R, Keren G, Carr J, Cohen EA, Betriu A, Desmet W, Kereiakes DJ, Rutsch W, Wilcox RG, de Feyter PJ, Vahanian A, Topol EJ; REPLACE-2 Investigators. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA.* 2003;289:853-63.

28. Stone GW, McLaurin BT, Cox DA, Bertrand ME, Lincoff AM, Moses JW, White HD, Pocock SJ, Ware JH, Feit F, Colombo A, Aylward PE, Cequier AR, Darius H, Desmet W, Ebrahimi R, Hamon M, Rasmussen LH, Rupprecht HJ, Hoekstra J, Mehran R, Ohman EM; ACUITY Investigators. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med.* 2006;355:2203-16.

29. Lee MS, Liao H, Yang T, Dhoot J, Tobis J, Fonarow G, Mahmud E. Comparison of bivalirudin versus heparin plus glycoprotein IIb/IIIa inhibitors in patients undergoing an invasive strategy: a meta-analysis of randomized clinical trials. *Int J Cardiol.* 2011;152:369-74.

30. Ndrepepa G, Berger PB, Mehilli J, Seyfarth M, Neumann FJ, Schomig A, Kastrati A. Periprocedural bleeding and 1-year outcome after percutaneous coronary interventions: appropriateness of including bleeding as a component of a quadruple end point. *J Am Coll Cardiol.* 2008;51:690-7.

31. Ndrepepa G, Neumann FJ, Richardt G, Schulz S, Tolg R, Stoyanov KM, Gick M, Ibrahim T, Fiedler KA, Berger PB, Laugwitz KL, Kastrati A. Prognostic value of access and non-access sites bleeding after percutaneous coronary intervention. *Circ Cardiovasc Interv.* 2013;6:354-61.

32. Palmerini T, Brener SJ, Mehran R, Dangas G, Genereux P, Riva DD, Mariani A, Xu K, Stone GW. Leukocyte count is a modulating factor for the mortality benefit of bivalirudin in ST-segment-elevation acute myocardial infarction: the HORIZONS-AMI trial. *Circ Cardiovasc Interv.* 2013;6:518-26.

33. Stone GW, Clayton T, Deliargyris EN, Prats J, Mehran R, Pocock SJ. Reduction in cardiac mortality with bivalirudin in patients with and without major bleeding: The HORIZONS-AMI trial (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction). *J Am Coll Cardiol.* 2014;63:15-20.

34. Schulz S, Mehilli J, Neumann FJ, Schuster T, Massberg S, Valina C, Seyfarth M, Pache J, Laugwitz KL, Buttner HJ, Ndrepepa G, Schomig A, Kastrati A; Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 3A Trial Investigators. ISAR-REACT 3A: a study of reduced dose of unfractionated heparin in biomarker negative patients undergoing percutaneous coronary intervention. *Eur Heart J.* 2010;31:2482-91.

35. Parodi G, Valenti R, Bellandi B, Migliorini A, Marcucci R, Comito V, Carrabba N, Santini A, Gensini GF, Abbate R, Antoniucci D. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. *J Am Coll Cardiol.* 2013;61:1601-6.

36. Bangalore S, Kumar S, Fusaro M, Amoroso N, Attubato MJ, Feit F, Bhatt DL, Slater J. Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. *Circulation*. 2012;125:2873-91.

37. McAuley L, Pham B, Tugwell P, Moher D. Does the inclusion of grey literature influence estimates of intervention effectiveness reported in meta-analyses? *Lancet.* 2000;356:1228-31.

Online Appendix. PRISMA research checklist.

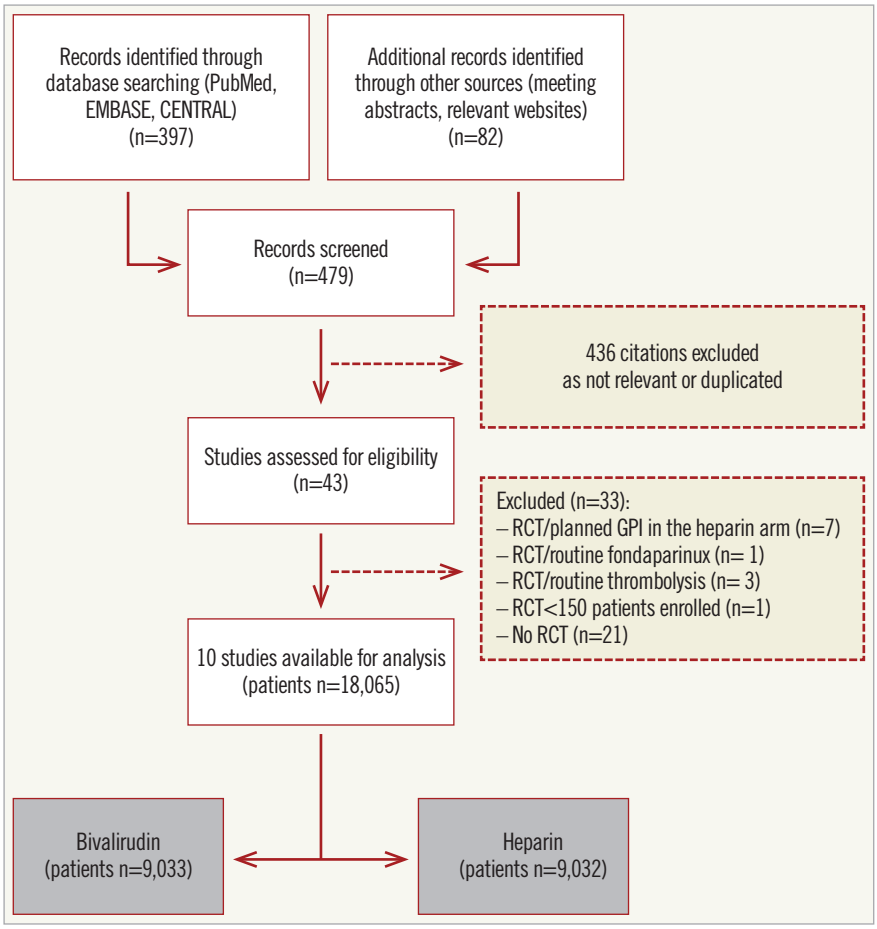
Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	11
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	2
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	2
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	2
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	2
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	2-3
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	12
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see Item 12).	16
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group; (b) effect estimates and confidence intervals, ideally with a forest plot.	4-6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5-6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	16
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7
DISCUSSION			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	6-8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	6-8; 8
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	8

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

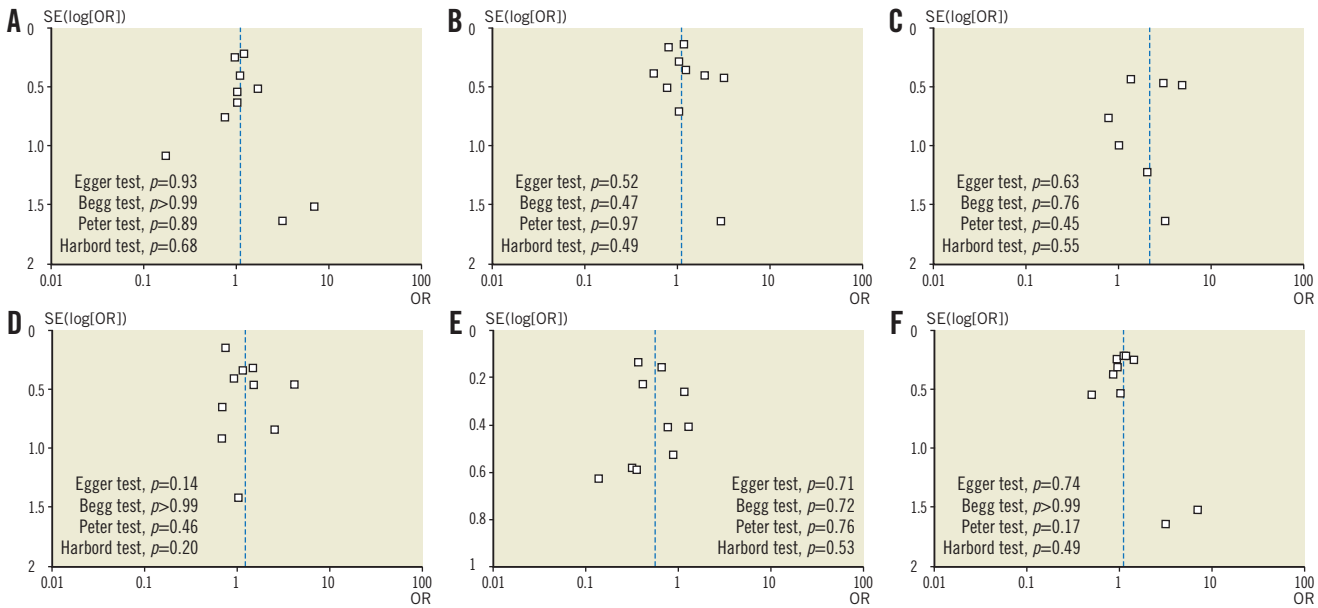
For more information, visit: www.prisma-statement.org.

Search strategy - PubMed

Search[All Fields] AND "anticoagulation"[All Fields] AND "bivalirudin"[All Fields] AND "heparin"[All Fields] AND "percutaneous coronary intervention"[All Fields] AND "angioplasty"[All Fields] AND "stent"[All Fields] AND "trial"[All Fields] AND (randomised[All Fields] AND ("clinical trials as topic"[MeSH Terms] OR ("clinical"[All Fields] AND "trials"[All Fields] AND "topic"[All Fields]) OR "clinical trials as topic"[All Fields] OR "trial"[All Fields]))



Online Figure 1. *PRISMA flow chart for the study selection process. PRISMA: preferred reporting items for systematic reviews and meta-analyses.*



Online Figure 2. *Funnel plot distribution of studies included in the meta-analysis according to outcomes of interest. The standard error (SE) of the logarithm of odds ratio (OR) - SE(log[OR]) - is plotted against the OR at 30-day follow-up of death (A), major bleeding (B), myocardial infarction (C), stent thrombosis (D), urgent target vessel revascularisation (E), as well as against the OR of overall death (F). The absence of publication bias can be evaluated both visually and mathematically. A p-value <0.05 indicates significance.*

Online Table 1. Main characteristics of studies included in the meta-analysis.

Trial	Main inclusion criteria	Main exclusion criteria	Primary endpoints	Secondary endpoints	Protocol	Longest FU
ARMYDA-7 BIVALVE[19]	PCI-suitable CAD and ≥1 of the following: age >75 years, diabetes mellitus, and chronic renal failure	Primary PCI; bleeding diathesis, major bleeding <4 weeks; long-term OAT indication; platelet count <70x109/L; end-stage renal failure	30-day incidence of bleeding event or entry-site complications; 30-day incidence of MACE (cardiac death, MI, TVR, or definite or probable ST)	Post-PCI increase of cardiac markers >ULN (CK-MB and troponin I)	Bivalirudin (bolus 0.75 mg/kg and infusion 1.75 mg/kg/hr during PCI) versus UFH (bolus 75 IU/kg)*	30 days
ARNO[18]	Age >18 years; PCI patients pre-treated with aspirin (325 mg) and 600 mg clopidogrel loading dose ≥6 hours before PCI	STEMI; PCI for CTO; end-stage renal failure or dependence on renal dialysis; life expectancy <1 year; active bleeding; bleeding diathesis; <15-day major surgery; ≤6-week gastrointestinal or genitourinary bleeding; pre-treatment with study medications before PCI; uncontrolled hypertension; platelet count <100x109/L; allergy to the study medications; HIT history	Incidence of in-hospital major bleedings	30-day incidence of all-cause death, MI, unplanned TVR (composite ischaemia); 30-day net clinical outcome (30-day composite ischaemia or 30-day major bleeding); 30-day incidence of minor bleeding; 30-day incidence of entry-site vascular complications; 6-month incidence of all-cause death; 6-month incidence of the composite of death and MI and 6-month incidence of unplanned TVR	Bivalirudin (bolus 0.75 mg/kg and infusion of 1.75 mg/kg/hr during PCI) versus UFH (bolus 100 IU/kg); post-procedural protamine*	6 months
BAS[16]	Age ≥21 years; urgent PCI scheduled	Creatinine >3.0 mg/dl (265 µmol/L); thrombolysis <24 hours; scheduled urgent coronary atherectomy, stenting, or laser angioplasty; scheduled staged PCI; aspirin or heparin intolerance	In-hospital incidence of all-cause death, MI, abrupt vessel closure or rapid clinical deterioration of cardiac origin requiring CABG, IABP or repeated PCI	-	Bivalirudin (bolus 1 mg/kg and 4-hr infusion at 2.5 mg/kg/hr, and 14- to 20-hr infusion at 0.2 mg/kg/hr) versus UFH (bolus 175 IU/kg and 18- to 24-hr infusion at 15 IU/kg/hr)	6 months
BRAVE 4[20]	Age >18 years; urgent PCI scheduled for STEMI ≤24 hours from symptom onset, with chest pain lasting ≥20 minutes and with ≥0.1 mV of ST-segment elevation in ≥2 adjacent limb leads or ≥0.2 mV in ≥2 contiguous precordial leads or new LBBB	Cardiogenic shock; prolonged CPR; active bleeding, bleeding diathesis, coagulopathy ≤2-month; ≤4-week major surgery; history of intracranial bleeding or structural abnormalities; suspected aortic dissection; prior TIA or stroke; HIT; prior administration of thrombolytic, bivalirudin, LMWH, or fondaparinux for the index MI; platelet count <100x109/L; life expectancy <1 year; GFR <30 ml/min and/or dialysis; known allergy to the study medications	30-day incidence of all-cause death, recurrent MI, unplanned TVR, definite ST; stroke, or major bleeding (non-CABG-related)	30-day incidence of all-cause death, recurrent MI, definite ST, unplanned TVR or stroke; 30-day incidence of major bleeding complications; 30-day incidence of cardiac death	Bivalirudin (bolus 0.75 mg/kg and infusion of 1.75 mg/kg/hr [1.4 mg/kg/hr in patients with GFR 30-59 ml/min] during PCI) versus UFH (bolus 70-100 IU/kg)*	30 days
BRIGHT[23]	Age 18 to 80 years; urgent PCI scheduled for STEMI and NSTEMI (STEMI ≤12 hours [or 12 to 24 hours with ongoing chest pain or discomfort and persistent ST-elevation or new LBBB] and NSTEMI ≤72 hours)	Staged PCI ≤30 days after randomisation; thrombolysis ≤72 hours; left main coronary disease; cardiogenic shock; administration of GPI, UFH/LMWH, OAT or bivalirudin ≤48 hours before randomisation; active bleeding or bleeding constitution, bleeding tendency; high probability of vascular lesions; uncontrolled hypertension; platelet count <100x109/L; allergy to the study medications; HIT history; GFR <30 ml/min and/or dialysis; known allergy to the study medications	30-day incidence of NACE (including MACCE [all-cause death, re-MI, TVR and ischaemic stroke] and bleeding events)	1-year incidence of NACE	Bivalirudin (bolus 0.75 mg/kg and infusion of 1.75 mg/kg/hr during PCI) versus UFH (bolus 100 IU/kg)*	6 months
EUROMAX[5]	Age >18 years; urgent PCI scheduled ≤2 hours after first medical contact and ≤24 hours from symptom onset with a presumed diagnosis of STEMI and with any of the following: ≥0.1 mV of ST-segment elevation in ≥2 adjacent limb leads or new LBBB ST-segment elevation, or ST-segment depression ≥0.1 mV in at least two leads in V1-V3 with a positive terminal T wave	Treatment with any injectable anticoagulant before randomisation; OAT; recent surgery; history of bleeding	30-day incidence of the composite of all-cause death or major bleeding (non-CABG-related)	30-day incidence of all-cause death, re-MI or non-CABG major bleeding; 30-day incidence of MACE (death, re-MI, ischaemia-driven TVR or stroke); NACE (MACE and non-CABG major bleeding), ischaemia-driven TVR, ST; 30-day incidence of re-MI, ID-TVR or ST	Bivalirudin (bolus 0.75 mg/kg and infusion of 1.75 mg/kg/hr; during PCI; 4-hr infusion of 0.25 mg/kg/hr after PCI) versus UFH (bolus 70-100 IU/kg) or enoxaparin (bolus 0.5 mg/kg)†	30 days

Online Table 1 (Continued). Main characteristics of studies included in the meta-analysis.

Trial	Main inclusion criteria	Main exclusion criteria	Primary endpoints	Secondary endpoints	Protocol	Longest FU
HEAT-PPCI[22]	Age ≥18 years; STEMI with primary PCI as the proposed index reperfusion strategy	Known intolerance, hypersensitivity or contraindication to any trial medication; active bleeding at presentation; artificial ventilation, reduced conscious level or other factors precluding the administration of oral antiplatelet therapy; physician refusal to administer antiplatelet loading (uncertain diagnosis/risk of bleeding)	28-day incidence of MACE (all-cause death, cerebrovascular accidents, re-MI or additional unplanned TLR; 28-day incidence of major bleeding	28-day incidence of ST, cardiac enzyme release and minor bleeding	Bivalirudin (bolus 0.75 mg/kg and infusion of 1.75 mg/kg/hr during PCI) versus UFH (bolus 100 IU/kg)*	28 days
ISAR-REACT 3[17]	Age >18 years; PCI patients pre-treated with aspirin (325 mg) and a 600 mg loading dose of clopidogrel ≥2 hours before PCI	STEMI <48 hours; troponin T >0.03 µg/L or CK-MB >ULN; cardiogenic shock; ≤2-month active bleeding, bleeding diathesis or coagulopathy; major surgery in the last ≤4 weeks; history of intracranial bleeding or structural abnormalities; suspected aortic dissection; prior TIA or stroke; HIT; prior administration of UFH or LMWH ≤6 hours before PCI or prior administration of bivalirudin ≤24 hours before PCI; staged PCI planned ≤30 days after randomisation; platelet count <100×109/L; life expectancy <1 year; GFR <30 ml/min and/or dialysis; known allergy to the study medications	30-day incidence of all-cause death, MI, ischaemia-driven urgent TVR (CABG or PCI) or in-hospital incidence of major bleeding	30-day incidence of all-cause death, MI, or urgent TVR, minor bleeding, ST	Bivalirudin (bolus of 0.75 mg/kg, and infusion of 1.75 mg/kg/hr) versus UFH (bolus 140 IU/kg)	1 year
NAPLES III[24]	Age ≥18 years; bleeding risk score ≥10; PCI for angiographic evidence of de novo or restenotic lesions; femoral access selected; stable or unstable angina or documented silent ischaemia as clinical indication	Positive markers of myocardial injury; unstable clinical and haemodynamic conditions; STEMI or NSTEMI ≤48 hours before randomisation; stroke ≤6 months; heparin-induced thrombocytopaenia; prior administration of GPI ≤7 days before PCI; platelet count <100×109/L; life expectancy <1 year; GFR <30 ml/min and/or dialysis; known allergy to the study medications	In-hospital incidence of major bleeding	In-hospital incidence of major and minor bleeding; in-hospital, 30-day and 1-year incidence of MACE, (all-cause death, non-fatal MI, TVR); ST	Bivalirudin (bolus 0.75 mg/kg and infusion of 1.75 mg/kg/hr during PCI) versus UFH (bolus 70 IU/kg)*	1 year
REPLACE-1[21]	Age ≥21 years; scheduled for urgent PCI	Acute MI; conditions of elevated bleeding risk; administration of UFH ≤6 hours (unless activated partial thromboplastin time measured ≤2 hours before randomisation was ≤50 seconds), LMWH ≤12 hours, abciximab ≤7 days, or eptifibatide or tirofiban ≤12 hours before randomisation	In-hospital or ≤48-hour incidence of all-cause death, MI or TVR	–	Bivalirudin (bolus 0.75 mg/kg and infusion at 1.75 mg/kg/hr) versus UFH (bolus 60-70 IU/kg)†	2 days

*Provisional/bail-out use of GPI allowed in both arms; † Routine (started before PCI) or bail-out use of GPI allowed in both arms. CABG: coronary artery bypass graft; CAD: coronary artery disease; CK-MB: creatine kinase myocardial band; CPR: cardiopulmonary resuscitation; CTO: chronic total occlusion: FU: follow-up; GFR: glomerular filtration rate; GPI: glycoprotein IIb/IIIa inhibitor; HIT: heparin-induced thrombocytopaenia; IABP: intra-aortic balloon pump; LBBB: left bundle branch block; LMWH: low-molecular weight heparin; MAC(C)E: major adverse cardiac (cerebrovascular) events; MI: myocardial infarction; NACE: net adverse clinical events; OAT: oral anticoagulant therapy; PCI: percutaneous coronary intervention; ST: stent thrombosis; (N)STEMI: (non) ST-elevation myocardial infarction; TIA: transient ischaemic attack; TVR: target vessel revascularisation; UFH: unfractionated heparin; ULN: upper limit of normal. Trial acronyms: ARMYDA-7 BIVALVE: Antiplatelet therapy for reduction of myocardial damage during angioplasty–Bivalirudin vs Heparin; ARNO: Antithrombotic regimens and outcome trial; BAS: Bivalirudin angioplasty study; BRAVE 4: Bavarian reperfusion alternatives evaluation; BRIGHT: Bivalirudin versus Heparin monotherapy and Glycoprotein IIb/IIIa plus Heparin for patients with AMI undergoing coronary stenting; EUROMAX: European ambulance acute coronary syndrome angiography; HEAT-PPCI: how effective are antithrombotic therapies in Primary PCI; ISAR-REACT 3: Intracoronary Stenting and Antithrombotic Regimen: rapid early action for coronary treatment; NAPLES III: Novel Approaches in Preventing or Limiting Events; REPLACE-1: Randomised Evaluation of PCI Linking Angiomax to Reduced Clinical Events

Online Table 2. Endpoint definitions within studies included in the meta-analysis.

Trial	Death	Major bleeding	Myocardial infarction	Definite ST	Urgent revascularisation
ARMYDA-7 BIVALVE[19]	Death due to a cardiac cause	Intracranial or clinically overt bleeding associated with an Hb decrease of >5 g/dl	Post-PCI CK-MB elevation >3×99th percentile of the ULN (normal baseline levels); post-PCI elevation ≥50% of the baseline CK-MB value (NSTEMI)	ARC definition	Any TVR (either CABG or repeat PCI) of the target vessel
ARNO[18]	All-cause death	Intracranial, intraocular, or retroperitoneal haemorrhage, clinically overt bleeding resulting in Hb decrease of >3 g/dl, any Hb decrease of >4 g/dl, or the transfusion of ≥2 units of packed red blood cells or whole blood	ECG changes consistent with MI or cardiac biomarker elevation (CK-MB or troponin I at one measurement >3×ULN) or cardiac biomarker re-elevation in patients with pre-PCI values >ULN ≥50% more than the previous nadir with documentation that the cardiac biomarker levels were decreasing before PCI	ARC definition	Unplanned revascularisation for ischaemia
BAS[16]	All-cause death	Overt bleeding with Hb decrease of ≥3 g/dl, the need for transfusion, intracranial haemorrhage, or retroperitoneal bleeding	Elevation in the total serum CK elevation 2×ULN (with at least 4.0% MB activity), a new two-step Q-wave change, persistent ST-segment or T-wave changes, or a new LBBB, or >30-minute ischaemic chest pain; the diagnosis of re-MI required an elevation of the CK or CK-MB above its previous nadir	N/A	Any CABG or second PCI performed for recurrent myocardial ischaemia
BRAVE 4[20]	All-cause death	Intracranial, intraocular, retroperitoneal bleeding, access-site haemorrhage requiring surgery or a radiologic or interventional procedure, haematoma ≥5 cm in diameter at the puncture site, Hb decrease of ≥4 g/dl without an overt source of bleeding, Hb decrease of ≥3 g/dl with an overt source of bleeding, reoperation for bleeding, or use of any blood product transfusion	ECG changes consistent with MI (new or re-elevation of ST segments ≥0.2 mV in ≥2 contiguous precordial leads, ≥0.1 mV in ≥2 adjacent limb ECG leads, or development of new, abnormal Q-waves considered distinct from the evolution of the index MI) and recurrent ischaemic discomfort lasting ≥20 minutes at rest or ischaemia-triggered haemodynamic instability (cardiac enzymes still rising); either an increase in CK-MB >20% 3 to 6 hours after the second blood sample or new ECG changes consistent with MI (cardiac enzymes falling, but still above ULN)	ARC definition	Any ischaemia-driven CABG or repeat PCI of any lesion of the vessel that supplies the myocardial area of the index MI
BRIGHT[23]	All-cause death	Type 3-5 according to BARC definition	N/R	N/A	Any TVR
EUROMAX[5]	All-cause death	Non-CABG-related bleeding, including intracranial, retroperitoneal, or intraocular bleeding; access-site haemorrhage requiring radiologic or surgical intervention; an Hb decrease >4 g/dl without an overt source of bleeding; an Hb decrease >3 g/dl with an overt source of bleeding; reintervention for bleeding; or use of any blood-product transfusion	≥20-minute chest pain, presumed to be ischaemic in origin and either new ST-segment elevation of ≥1 mm in ≥2 contiguous leads, or presumably new LBBB or angiographic evidence of reocclusion of a previously patent coronary artery or bypass graft (<24 hours); if biomarkers are presumed to be abnormal, a new elevation in biomarkers >20% above the prior documented nadir or if biomarkers are back to normal, according to Thygesen et al (≥24 hours to 7 days); according to Thygesen et al (>7 days)	ARC definition	Any refractory ischaemia-driven repeat PCI or CABG involving any native coronary or pre-existing bypass graft vessel. In the absence of pain, new ST-segment changes indicative of ischaemia, acute pulmonary oedema, ventricular arrhythmias, or haemodynamic instability presumed to be ischaemic in origin, will constitute sufficient evidence of ischaemia. The episode of ischaemia leading to repeat PCI or CABG must occur following completion of the index procedure
HEAT-PPCI[22]	All-cause death (all deaths with a clear cardiovascular or unknown cause are classified as cardiovascular; deaths due to a documented non-cardiovascular cause [i.e., cancer] are classified as non-cardiovascular)	Type 3-5 according to BARC definition	Recurrence of ischaemic type chest discomfort lasting ≥20 minutes or new ECG changes [ST elevation ≥0.1 mV re-occurring in a patient having a lesser degree of ST elevation, new-onset T-wave changes, horizontal ST depression or new pathological Q-waves, in at least 2 consecutive leads] along with either the rise of CK-MB or troponin >3×99th percentile of the ULN and re-elevation >50% from previous baseline following a 25% decrease from the peak value (demonstrating a twin peak effect) or angiographic evidence of new thrombus, vessel occlusion or subtotal occlusion (re-MI during hospitalisation); rise of cardiac enzymes (troponin or CK-MB) with ≥1 value >99th percentile of the ULN together with: symptoms of ischaemia or ECG changes suggestive of new ischaemia (ST-T changes or new-onset LBBB) or development of new pathological Q-waves, in ≥2 consecutive leads (re-MI after discharge)	ARC definition	Any subsequent, unplanned revascularisation of any lesion treated at the index procedure within the original target segment or in the adjacent 5 mm of the distal or proximal vessel. In the case of surgical revascularisation TLR will have occurred if there is the creation of a graft conduit to an epicardial vessel treated at the index procedure

Online Table 2 (Continued). Endpoint definitions within studies included in the meta-analysis.

Trial	Death	Major bleeding	Myocardial infarction	Definite ST	Urgent revascularisation
ISAR-REACT 3[17]	All-cause death	Intracranial, intraocular, or retroperitoneal haemorrhage; clinically overt bleeding resulting in an Hb decrease >3 g/dl; any Hb decrease >4 g/dl; or transfusion of ≥2 units of packed red cells or whole blood	New pathologic Q-waves (≥30 msec and ≥0.1 mV) in ≥2 contiguous precordial leads or ≥2 adjacent limb leads, or an elevation of CK-MB isoenzyme levels (or total CK if measures of CK-MB are unavailable) to ≥2 times the ULN; any CK-MB increase >3×ULN (postprocedural MI)	ARC definition	Urgent TVR (CABG or PCI) due to myocardial ischaemia
NAPLES III[24]	All-cause death (all deaths with a clear cardiovascular or unknown cause are classified as cardiovascular; deaths due to a documented non-cardiovascular cause [i.e., cancer] are classified as non-cardiovascular)	Intracranial, intraocular, or retroperitoneal haemorrhage; clinically overt bleeding resulting in an Hb decrease >3 g/dl; any Hb decrease >4 g/dl; or transfusion of ≥2 units of packed red cells or whole blood	New pathological Q-waves not present at baseline ECG; any CK-MB increase >3×ULN (non-Q-wave MI)	ARC definition	Any TVR due to myocardial ischaemia
REPLACE-1[21]	All-cause death	Intracranial, intraocular, or retroperitoneal haemorrhage or clinically overt bleeding resulting in an Hb decrease >3 g/dl; or transfusion of ≥2 units of packed red cells or whole blood	New significant Q-waves in ≥2 contiguous ECG leads or CK or CK-MB increase >3×ULN	ARC definition	Any TVR due to myocardial ischaemia

(B)ARC: (Bleeding) Academic Research Consortium; CABG: coronary artery bypass graft; CK-MB: creatine kinase myocardial band; LBBB: left bundle branch block; MI: myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; ST: stent thrombosis; TVR: target vessel revascularisation; ULN: upper limit of normal. N/A: not available; N/R: not reported. Trial acronyms: ARMYDA-7 BIVALVE: Anti-Thrombotic Strategy for Reduction of Myocardial Damage During Angioplasty-Bivalirudin vs. Heparin; ARNO: Antithrombotic Regimens aNd Outcome; BAS: Bivalirudin Angioplasty Study; BRAVE 4: Bavarian Reperfusion Alternatives Evaluation; BRIGHT: Bivalirudin vs. Heparin Monotherapy and Glycoprotein IIb/IIIa plus Heparin for Patients with Acute Myocardial Infarction Undergoing Coronary Stenting; EUROMAX: European Ambulance Acute Coronary Syndrome Angiography; HEAT-PPCI: How Effective Are Antithrombotic Therapies in Primary PCI; ISAR-REACT 3: Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment; NAPLES III: Novel Approaches in Preventing or Limiting Events; REPLACE-1: Randomised Evaluation of PCI Linking Angiomax to Reduced Clinical Events

Online Table 3. Assessment of risk of bias.

Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Sample size calculation	Study funding
ARMYDA-7 BIVALVE[19]	Yes (computer-generated)	No	No	Yes	No	Yes (superiority design)	No (investigator-driven)
ARNO[18]	Yes (computer-generated)	No	No	Yes	Yes (flow diagram)	Yes (superiority design)	No (investigator-driven)
BAS[16]	Yes	Yes (no labelling information)	Yes	Yes	No	No	Yes (industry-funded)
BRAVE 4[20]	Yes (computer-generated)	No	No	Yes	Yes	Yes (superiority design)	No (investigator-driven)
BRIGHT[23]	Yes	No	No	Yes	Yes (flow diagram)	Yes (non-inferiority design)	Yes (industry-funded)
EUROMAX[5]	Yes	No	No	Yes	Yes (flow diagram)	Yes (superiority design)	Yes (industry-funded)
HEAT-PPCI[22]	Yes (computer-generated)	No	No	Yes	Yes (flow diagram)	Yes (non-inferiority design)	Yes (industry-funded)
ISAR-REACT 3[17]	Yes (computer-generated)	Yes (no labelling information)	Yes	Yes	Yes	Yes (superiority design)	Yes (industry-funded)
NAPLES III[24]	Yes	No	No	Yes	Yes (flow diagram)	Yes (superiority design)	No (investigator-driven)
REPLACE-1[21]	Yes (telephone system-generated)	No	No	Yes	No	No	Yes (industry-funded)

N/A: not applicable. Trial acronyms: ARMYDA-7 BIVALVE: Antiplatelet therapy for reduction of myocardial damage during angioplasty–Bivalirudin vs Heparin; ARNO: Antithrombotic regimens and outcome trial; BAS: Bivalirudin angioplasty study; BRAVE 4: Bavarian reperfusion alternatives evaluation; BRIGHT: Bivalirudin versus Heparin monotherapy and Glycoprotein IIb/IIIa plus Heparin for patients with AMI undergoing coronary stenting; EUROMAX: European ambulance acute coronary syndrome angiography; HEAT-PPCI: how effective are antithrombotic therapies in Primary PCI; ISAR-REACT 3: Intracoronary Stenting and Antithrombotic Regimen: rapid early action for coronary treatment; NAPLES III: Novel Approaches in Preventing or Limiting Events; REPLACE-1: Randomised Evaluation of PCI Linking Angiomax to Reduced Clinical Events