Original Article

Bivalirudin versus heparin in percutaneous coronary intervention—a systematic review and meta-analysis of randomized trials stratified by adjunctive glycoprotein IIb/IIIa strategy

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Background: Bivalirudin has been shown to be associated with less major bleeding than heparin in patients undergoing percutaneous coronary intervention (PCI); but the confounding effect of concomitant glycoprotein IIb/IIIa inhibitors (GPI) limits meaningful comparison. We performed a systematic review and meta-analysis to compare bivalirudin to heparin, with and without adjunctive GPI in PCI.

Methods: We searched PubMed, Cochrane, EMBASE, CINAHL and WOS from January 2000 to December 2017 for clinical trials comparing bivalirudin to heparin, with and without adjunctive GPI during PCI. Cochrane's Q statistics were used to determine heterogeneity. Random effects model was used.

Results: Twenty-six comparison groups (22 original studies and 4 subgroup analyses) with 53,364 patients were included. Mean follow-up was 192±303 days. There was no difference between the two groups in all-cause mortality [risk ratio (RR: 0.93; 95% CI: 0.82–1.05, P=0.260), target vessel revascularization (TVR) (RR: 1.17; 95% CI: 0.93–1.46, P=0.174) or stroke (RR: 0.91; 95% CI: 0.71–1.18, P=0.490). Major bleeding was lower in the bivalirudin group with concomitant GPI in one or both arms (RR: 0.64; 95% CI: 0.53–0.77, P<0.001) and without (RR: 0.71; 95% CI: 0.51–0.99, P=0.041) provisional or routine GPIs. Bivalirudin appeared to have a higher risk of stent thrombosis (RR: 1.32; 95% CI: 1.04–1.68, P=0.022) and a trend towards more myocardial infarction (RR: 1.12; 95% CI: 0.98–1.28, P=0.098) though without statistical significance. However, exclusion of studies with GPI showed no difference in stent thrombosis or myocardial infarction with bivalirudin.

Conclusions: Bivalirudin is associated with less major bleeding compared to heparin, regardless of GPI use. The lower anticoagulant effect of bivalirudin is linked with higher stent thrombosis and a trend towards more MI, however a confounding effect of GPI use in the heparin arm cannot be excluded.

Keywords: Acute coronary syndromes (ACS); percutaneous coronary intervention (PCI); meta-analysis; systematic review; mortality

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Introduction

Heparin has traditionally been the anticoagulant of choice for percutaneous coronary intervention (PCI). The addition of glycoprotein IIb/IIIa inhibitors (GPIs) to heparin in early trials led to a decrease in ischemic complications, but at the expense of an increase in major bleeding (1-3). Subsequently numerous studies have compared bivalirudin, a direct thrombin inhibitor, with the combination of heparin and GPIs. These trials demonstrated a reduction in major bleeding and more stent thrombosis with bivalirudin compared to heparin, but it is unclear if this is related to the confounding effect of GPI use in the heparin arm. More contemporary trials have aimed to compare bivalirudin to heparin with either no planned GPI use (4-12) or matched GPI use in both arms (8,13-16) but results have been mixed. Therefore, we performed a systematic review and meta-analysis of all randomized controlled clinical trials comparing bivalirudin and heparin, stratified by GPI use strategy.

Methods

Data sources and search strategy

We searched PubMed, EMBASE, Cochrane, CINAHL and Web-of-science databases for randomized clinical trials (RCT) published between January 2000 and December 2017 using the following search terms—"acute coronary syndrome (ACS)", "bivalirudin", "percutaneous coronary intervention (PCI)", "heparin", "glycoprotein inhibitors", "GPI", "mortality" and their combinations. We limited our search to English language and studies including adult population only. We also searched clinicaltrials.gov and reviewed the reference list of relevant articles. The methodology has been validated and published in previous studies (17).

Study selection

To be eligible, studies had to meet the following eligibility criteria: (I) RCT, (II) age >18 years of age, (III) compare bivalirudin to heparin with or without GPI usage (IV) report the estimate of relative risk (RR) with 95% confidence interval (CI), or other measures of RR such as hazard ratio or odds ratio or provide other forms of data from which RR could be computed. The final inclusion group consisted of 22 studies with a total of 26 comparison groups. Our search strategy is displayed in *Figure S1*.

Data extraction

Two reviewers (D Anugula and NR Gujjula) independently reviewed the abstracts, titles of individual studies and all selected full-length articles identified by the above-mentioned search strategy to include/exclude studies. The reviewers also independently abstracted the study characteristics, design, methods, and relevant outcomes. Any discrepancy between the first and second authors was resolved by consensus or consulting with a third reviewer (M Anantha-Narayanan).

Patient selection

Our study included adult patients with PCI who received heparin or bivalirudin with or without GPIs as shown in *Table 1* and the individual trial inclusion/exclusion criteria is shown in *Table 2*. We then analyzed the studies based on GPI usage. When studies had more than two comparison groups, we compared the individual to the common sub-groups. Following the overall analysis, we excluded studies that used GPIs in the heparin or bivalirudin arms and studied their outcomes to enable head-to-head comparison between bivalirudin and heparin. The usage of GPI in the individual trials is mentioned in *Table 3*. We performed a separate analysis of elective PCI and PCI in ACS and reported results for outcomes of interest. We then divided the studies based on radial access. We considered >60% radial access as predominant radial access and studied major bleeding outcomes in these trials.

To assess the effect of ACT in the heparin arm on overall outcomes, we performed a meta regression using the wide range of ACTs used in the trials. We then analyzed studies that reported 30-day and 1-year mortality separately. When 1-year mortality data was not available, we manually extracted these numbers from Kaplan-Meyer curve using methods similar to what was previously described (18).

Outcomes

The primary outcome was major bleeding compared between heparin and bivalirudin, with or without the use of GPI in one or both the arms. Secondary outcomes included all-cause mortality, target vessel revascularization (TVR), stent thrombosis, stroke rates and myocardial infarction at follow-up. All-cause mortality was defined as death from any cause. Major bleeding was defined in the studies as listed in *Table 1*.

Table 1 Randomized controlled clinical trials included in this analysis

Study	Enrollment years	Publication year	Participants	Overall (N)	Heparin (N)	Bivalirudin (N)	Comparison groups	Mean follow-up (days)	Major bleeding definition
ACUITY (bivalirudin + GPI)	2003–2005	2007	UA/NSTEMI	5,170	2,561	2,609	Bivalirudin + GPI *vs.* heparin/ enoxaparin + GPI	30	Intracranial or intraocular bleeding, access site haemorrhage requiring intervention, 5 cm or more diameter haematoma, reduction in haemoglobin of 40 g/L or more without or 30 g/L or more with an overt bleeding source, reoperation for bleeding, or blood product transfusion
ACUITY (bivalirudin)	2003–2005	2007	UA/NSTEMI	5,180	2,561	2,619	Bivalirudin *vs.* heparin/ enoxaparin + GPI	30	Intracranial or intraocular bleeding, access site haemorrhage requiring intervention, 5 cm or more diameter haematoma, reduction in haemoglobin of 40 g/L or more without or 30 g/L or more with an overt bleeding source, reoperation for bleeding, or blood product transfusion
ARMYDA 7 BIVALVE	2009–2011	2012	ACS/stable angina	401	203	198	Bivalirudin + GPI *vs.* heparin + GPI	30	Intracranial bleeding or clinically overt bleeding associated with a decrease in hemoglobin of <5 g/dL, according to the TIMI
ARNO	2006–2008	2009	Elective	850	425	425	Bivalirudin + GPI *vs.* heparin + protamine + GPI	30	Intracranial, intraocular, or retroperitoneal hemorrhage, clinically overt blood loss resulting in a decrease in hemoglobin of 3 g/dL, any decrease in hemoglobin of 4 g/dL, or the transfusion of 2 units of packed red blood cells or whole blood
BRAVE 4	2009–2013	2014	STEMI	548	277	271	Bivalirudin + GPI *vs.* heparin + GPI	30	TIMI
BRIGHT (heparin alone)	2012–2013	2015	STEMI/ NSTEMI	1,464	729	735	Bivalirudin *vs.* heparin	365	BARC
BRIGHT (heparin + GPI)	2012–2013	2015	STEMI/ NSTEMI	1,465	730	735	Bivalirudin *vs.* heparin + GPI (tirofiban)	365	BARC
CACHET	1998–2000	2001	Elective	82	64	18	Bivalirudin + GPI *vs.* heparin + GPI	7	Intracranial, intraocular, or retroperitoneal hemorrhage, blood loss resulting in a decrease in hemoglobin level by 3 g/dL, or clinically overt bleeding leading to transfusion of 2 units of blood

Table 1 (*continued*)

Table 1 (*continued*)

Study	Enrollment years	Publication year	Participants	Overall (N)	Heparin (N)	Bivalirudin (N)	Comparison groups	Mean follow-up (days)	Major bleeding definition
CACHET	1998–2000	2001	Elective	105	64	41	Bivalirudin *vs.* heparin + GPI	7	Intracranial, intraocular, or retroperitoneal hemorrhage, blood loss resulting in a decrease in hemoglobin level by 3 g/dL, or clinically overt bleeding leading to transfusion of 2 units of blood
Deshpande *et al.*	2010	2012	Elective	101	52	49	Bivalirudin + GPI *vs.* heparin + GPI	30	Intracranial, intraocular, or retroperitoneal hemorrhage; clinically overt blood loss resulting in a decrease in hemoglobin of more than 3 g per decilitre any decrease in hemoglobin of more than 4 g per deciliter; or transfusion of 2 or more units of packed red cells or whole blood
EUROMAX	2010–2013	2014	STEMI	1,549	460	1,089	Bivalirudin *vs.* heparin + bailout GPI	30	Intracranial, retroperitoneal, or intraocular bleeding; access-site haemorrhage requiring radiological or surgical intervention; a reduction in the haemoglobin level of more than 4 g/dL (2.5 mmol/L) without an overt source of bleeding; a reduction in the haemoglobin level of 3 g/dL (1.8 mmol/L) with an overt source of bleeding; reintervention for bleeding; or use of any blood- product transfusion
EUROMAX	2010–2013	2014	STEMI	1,738	649	1,089	Bivalirudin *vs.* Heparin + routine GPI	30	Intracranial, retroperitoneal, or intraocular bleeding; access-site haemorrhage requiring radiological or surgical intervention; a reduction in the haemoglobin level of more than 4 g/dL (2.5 mmol/L) without an overt source of bleeding; a reduction in the haemoglobin level of 3 g/dL (1.8 mmol/L) with an overt source of bleeding; reintervention for bleeding; or use of any blood-product transfusion
Feldman *et al.*	NA	2014	Elective	100	50	50	Bivalirudin *vs.* heparin	42	Intracerebral, intraocular, or retroperitoneal hemorrhage, overt hemoglobin loss of more than 3 g/dL, need for a blood transfusion or for surgical or percutaneous intervention to stop blood loss, or groin hematoma with a circumference of more than 6 cm
HEAT PPCI	2012–2013	2014	STEMI	1,812	907	905	Bivalirudin *vs.* heparin	1,095	BARC 3–5
HORIZONS-AMI	2005–2008	2011	STEMI	3,602	1,802	1,800	Bivalirudin *vs.* heparin + GPI	1,095	Intracranial or intraocular haemorrhage; access site bleeding with a haematoma diameter of 5 cm or more or requiring intervention; haemoglobin decrease of 40 g/L or more without an overt bleeding source or 30 g/L or more with an overt bleeding source; reoperation for bleeding; or blood product transfusion

Table 1 (*continued*)

Table 1 (*continued*)

Study	Enrollment years	Publication year	Participants	Overall (N)	Heparin (N)	Bivalirudin (N)	Comparison groups	Mean follow-up (days)	Major bleeding definition
ISAR REACT 3	2005–2008	2010	Stable/UA	4,570	2,281	2,289	Bivalirudin *vs.* heparin	365	TIMI
ISAR REACT 4	NA	2013	NSTEMI	1721	861	860	Bivalirudin *vs.* heparin + GPI	365	TIMI
MATRIX	2011–2014	2015	NSTEMI	7,213	3,603	3,610	Bivalirudin *vs.* heparin	30	BARC 3 or 5
NAPLES 3	2008–2012	2015	Elective	837	419	418	Bivalirudin *vs.* heparin	365	BARC, TIMI
NAPLES	2005–2008	2009	Elective	335	168	167	Bivalirudin *vs.* heparin + planned tirofiban	30	Intracranial, intraocular, or retroperitoneal hemorrhage, clinically overt blood loss resulting in a decrease in hemoglobin than 3 g/dL, any decrease in hemoglobin 4 g/dL, or transfusion of 2 U of packed red blood cells or whole blood
PROTECT TIMI 30	2003–2004	2006	NSTEMI/UA	857	573	284	Bivalirudin *vs.* heparin + eptifibatide	2	TIMI
REPLACE 1	2000–2001	2004	Elective/ urgent	1,056	524	532	Bivalirudin + GPI *vs.* heparin + GPI	2	Intracranial, intraocular, or retroperitoneal hemorrhage or clinically overt bleeding resulting in a decrease in hemoglobin by 3 g/dL or transfusion of 2 U of blood
REPLACE 2	2001–2002	2003	Elective	6,002	3,008	2,994	Bivalirudin *vs.* heparin + GPI	365	TIMI
TENACITY	2011	2011	STEMI/ NSTEMI/UA	383	198	185	Bivalirudin + GPI *vs.* heparin + GPI	30	TIMI
VALIDATE-SWEDEHEART	2014–2016	2017	STEMI/ NSTEMI	6,006	3,002	3,004	Bivalirudin + GPI *vs.* heparin + GPI	180	BARC 2, 3 OR 5
Xiang *et al.*	NA	2013	Elective	217	108	109	Bivalirudin + GPI *vs.* heparin + GPI	30	Massive bleeding or life-threatening hemorrhage; such as intracranial hemorrhage, retroperitoneal bleeding, clinically overt bleeding that resulted in a decrease in hemoglobin more than 30 g/L (or haematocrit (HCT) drop more than 10%), or transfusion of two or more units of packed red blood cells or whole blood

ACS, acute coronary syndrome; GPI, glycoprotein IIb/IIIa inhibitors; MI, myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; UA, unstable angina.

Table 2 Inclusion and exclusion criteria of the included studies

Study	Inclusion criteria	Exclusion criteria
ACUITY	Age >18 years, symptoms of UA for >10 min within the preceding 24 h and at least 1 among: (I) new ST segment depression or transient elevation of 1 mm; (II) raised troponin I, T, or CK-MB isozyme, or (III) known coronary artery disease	STEMI, shock, bleeding diathesis or major bleeding episode <2 weeks; thrombocytopenia, creatinine clearance <30 mL/min, recent administration of abciximab, warfarin, fondaparinux, fibrinolytic agents, bivalirudin, or 2 or more doses of LMWH, allergy to study drugs or iodinated contrast that could not be adequately pre-medicated
ARMYDA 7 BIVALVE	Angiographically documented coronary artery disease suitable for PCI and 1 of the following: age >75 years, diabetes mellitus (defined per American Diabetes Association criteria), and chronic renal failure (defined as creatinine clearance of 30 to 60 mL/min)	Primary PCI for acute myocardial infarction, bleeding diathesis or major bleeding 4 weeks, long-term warfarin therapy, platelet count 70×10^9/L, and end-stage renal failure with creatinine clearance 30 mL/min
ARNO	Undergoing PCI and pretreated with aspirin (325 mg) and a 600-mg loading dose of clopidogrel 6 h before PCI were considered eligible for enrollment	Acute STEMI; PCI for chronic total occlusion; renal insufficiency (creatinine clearance rate 30 mL/min or serum creatinine 3 mg/dL) or dependence on renal dialysis; comorbid conditions with a life expectancy of 1 year; active bleeding, bleeding diathesis, or recent major surgery (15 days); gastrointestinal or genitourinary bleeding within the previous 6 weeks; pretreatment with UFH or low-molecular-weight heparin or bivalirudin before PCI; uncontrolled hypertension 180/110 mmHg unresponsive to therapy; relevant hematologic abnormalities (hemoglobin 10 g/dL or platelet count 100×10^9/L); allergy to the study medications; a history of heparin-induced thrombocytopenia; and age 18 years
BRAVE 4	Patients presenting within 24 h from symptom onset, with chest pain lasting 20 min 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	Age <18 years, cardiogenic shock or prolonged CPR, active bleeding, bleeding diathesis, coagulopathy, history of GI or genitourinary bleeding within the previous 2 months, refusal to receive blood transfusion, major surgery in the last 6 weeks, history of intracranial bleeding or structural abnormalities, suspected aortic dissection, prior TIA, prior stroke, heparin-induced thrombocytopenia, prior administration of thrombolytic, bivalirudin, LMWH, or fondaparinux for the index myocardial infarction, known relevant hematological deviations: hemoglobin <100 g/L, platelet count $<100\times10^9$/L, use of coumadin derivatives within the last 7 d, chronic therapy with NSAIDs (except aspirin), COX-2 inhibitors, prasugrel, ticagrelor , life expectancy <1 year, severe liver disease, renal failure with GFR <30 mL/min and/or dialysis, known allergy to the study medications, previous enrollment in this trial, women who are pregnant, who are of childbearing potential and test positive for pregnancy or are breastfeeding, inability to fully cooperate with the study protocol
BRIGHT	Age 18 to 80 years, STEMI within 12 h of symptom onset, or within 12–24 h if ongoing chest pain, continuous ST elevation or new LBBB, NSTEMI within 72 h of symptom onset, planned emergency PCI	Thrombolysis within 72 h, cardiogenic shock, any anticoagulant agents used within 48 h before randomization, active bleeding or bleeding diathesis, hemoglobin <10 g/L or platelet count $<100\times10^9$/L, creatinine clearance <30 mL/min, known allergy to the study drugs or devices (including heparin induced thrombocytopenia)
CACHET	(I) Elective coronary exam; (II) over 21 years of age	(I) Planned atherectomy; (II) acute MI <24 h; (III) coronary intervention <6 months; (IV) warfarin therapy; (V) stroke within 2 years or with residual neurologic deficit; (VI) intracranial neoplasm, aneurysm, or arteriovenous malformation; (VII) active bleeding or recent surgery or trauma; (VIII) blood pressure >180/100 mmHg

Table 2 (*continued*)

Table 2 (*continued*)

Study	Inclusion criteria	Exclusion criteria
Deshpande	(I) Age >18 and <75 years; (II) elective high risk PCI as defined by patients on chronic antiplatelet therapy with aspirin, clopidogrel for >5 days or received total dose of >300 mg for more than 24 h and had severe coronary artery disease; (III) at least one clinical criterion of: prior stroke, prior peripheral vascular disease, diabetes, documented microalbuminuria, prior MI, unstable angina, ECG changes of ST depression of 1 mm, or elevated cardiac enzymes consistent with Non ST elevation MI	(I) Acute STEMI or shock; (II) bleeding diathesis or major bleeding within 2 weeks; (III) thrombocytopenia; (IV) creatinine clearance <30 mL/min; (V) recent administration of abciximab, warfarin, fondaparinux, fibrinolytic agents, bivalirudin or low molecular weight heparin within 8 h
EUROMAX	Men and nonpregnant women over age 18 years, symptoms with a presumed diagnosis of STEMI <12 h; any of the following conditions: ST-segment elevation 1 mm in 2 contiguous leads on ECG, presumed new LBBB, or ST-segment depression of 1 mm in at least 2 leads in V1–V3 with a positive terminal T wave; intention of performing primary PCI <2 h after first medical contact	Bleeding diathesis or hematological disease or history of intracerebral mass, aneurysm, arteriovenous malformation, hemorrhagic stroke, intracranial hemorrhage, or bleeding <2 weeks, surgery <2 weeks, warfarin (not if international normalized ratio known to be <1.5) UFH, LMWH or bivalirudin before randomization, thrombolytic therapy <48 h, absolute contraindications, or allergy that cannot be premedicated, to iodinated contrast or to any of the study medications, contraindications to angiography, pregnant or nursing mothers creatinine clearance <30 mL/min or dialysis, previous enrollment in this or other studies not available primary PCI-capable hospital estimated body weight of >120 kg
Feldman *et al.*	patients with NSTEMI or angina pectoris and with high risk for bleeding	NA
HEAT PPCI	STEMI patients activating primary PCI pathway	Active bleeding at presentation, factors precluding administration of oral antiplatelet therapy, intolerance/contraindication to trial medication, previous enrolment in this trial
HORIZONS-AMI	Age >18 years, symptom duration of 20 to 720 min, ST-segment elevation >1 mm in 2 or more contiguous leads, new LBBB, or true posterior myocardial infarction	Contraindications to study drugs , previous administration of thrombolytic therapy, bivalirudin, GPI, LMWH, or fondaparinux for the present admission, warfarin use, history of bleeding diathesis, coagulopathy, heparin-induced thrombocytopenia, intracerebral mass, aneurysm, arteriovenous malformation, or previous hemorrhagic stroke, stroke or TIA <6 mo or any permanent neurological deficit, refusal to receive blood transfusions , gastrointestinal or genitourinary bleeding <2 mo, major surgery <6 weeks, known platelet count <100,000/mL or hemoglobin <10 g/L, planned elective surgical procedure, coronary stent implantation <30 d, life expectancy <1 year
ISAR REACT 3	Biomarker negative patients with stable and unstable angina undergoing PCI after pre-treatment with 600 mg clopidogrel at least 2 h prior to the intervention	NA
ISAR REACT 4	Angina >20 min or recurrent episodes within 48 h, increase of cardiac biomarkers, coronary stenosis requiring PCI	Acute myocardial infarction <48 h, cardiogenic shock, pericarditis, malignancy or other comorbid conditions with life expectancy <1 year , active bleeding or a bleeding diathesis or any history of intracranial bleeding or structural intracranial abnormalities, refusal to receive a transfusion, blood pressure >180/110 mmHg despite therapy, planned staged PCI procedure within 30 d or PCI within the prior 30 d, hemoglobin <10 g/L, platelet count $<100\times10^9$ or $>600\times10^9$ cells/L, GFR <30 mL/min or serum creatinine >30 mg/L, allergy or intolerance to any study drug or to stainless steel or to contrast media, pregnancy, coumadin within 7 d, GPI <14 d, UFH within 4 h, LMWH <8 h, and bivalirudin<24 h

Table 2 (*continued*)

Table 2 (*continued*)

Study	Inclusion criteria	Exclusion criteria
MATRIX	For ACS all of the following 3 factors: history consistent with new, or worsening ischemia, occurring at rest or with minimal activity, enrolment within 7 d of the most recent symptoms, planned coronary angiography with indication to PCI; at least 2 of the following: age >60 years; troponin T or I or CK-MB above the upper limit of normal; ECG changes compatible with ischemia, i.e., ST depression of >1 mm in 2 contiguous leads, T-wave inversion >3 mm, or any dynamic ST shifts For STEMI both: chest pain for >20 min with an ST-segment elevation >1 mm or greater in 2 or more contiguous leads, or with a new left bundle branch block or with ST-segment depression of >1 mm in 2 or more of leads V1–V3 with a positive terminal T wave, Admission either within 12 h of symptom onset or between 12 and 24 h after onset with continuing ischemia or previous fibrinolytic treatment	Patients who cannot give informed consent or have a life expectancy <30 d, allergy or intolerance to bivalirudin or UFH, treatment with LMWH within the past 6 h, treatment with any GPI in the previous 3 d, absolute contraindications or allergy, that cannot be premedicated, to iodinated contrast or to any of the study medications, including both aspirin and clopidogrel, contraindications to angiography, including but not limited to severe peripheral vascular disease, If known, a creatinine clearance <30 mL/min or dialysis dependent, previous enrolment in this study PCI in the previous 30 d
NAPLES 3	(I) Age >18 years; (II) bleeding risk score ≥10; (III) procedure planned through the femoral approach; (IV) angiographic evidence of de novo or restenotic lesions requiring revascularization; (V) stable or unstable angina or documented silent ischemia; (VI) negative biomarkers of myocardial injury; (VII) double antiplatelet therapy; (VIII) stable hemodynamic conditions	(I) Bleeding risk score <10; (II) pregnancy; (III) ongoing or recent (48 h) episode of STEMI or NSTEMI; (IV) negative biomarkers of myocardial injury; (V) chronic dialysis and/or history or previous dialysis; (VI) hemodynamic instability requiring inotropic support or IABP; (VII) ongoing or recent treatment with GPI; (VIII) ongoing or recent (6 months) bleeding or bleeding diathesis; (IX) recent (within 6 months) stroke; (X) history of heparin-induced thrombocytopenia; (XI) platelet count <100,000/mm^3
NAPLES	(I) 18 years or older; (II) DM treated with insulin and/or oral agents; (III) de novo coronary lesion in a native coronary artery; (IV) elective PCI	(I) Acute myocardial infarction (MI); (II) pregnancy; (III) previous PCI b 1 month; (IV) restenotic lesion; (V) saphenous venous graft and/or mammary artery lesion intervention; (VI) acute coronary syndrome; (VII) recent (12 weeks) active internal bleeding or bleeding diathesis, surgery, trauma, or bleeding; (VIII) previous intracranial bleeding or structural abnormality; (IX) history of heparin induced thrombocytopenia; (X) serum creatinine levels N 3 mg/dL or dialysis; (XI) warfarin therapy; (XII) administration of UFH within 6 h, low-molecular-weight heparin within 8 h, abciximab within 7 days, or eptifibatide or tirofiban within 12 h before randomization
PROTECT TIMI 30	(I) Age 18 to 80 years of age, (II) hospitalized with unstable angina/NSTEMI with chest discomfort or an angina equivalent at rest >10 min; consistent with acute coronary syndromes, with at least one high-risk feature (i.e., diabetes, a positive cardiac troponin T/I or creatine kinase-myocardial band (CK-MB), ST segment deviation N 0.5 mm, or TIMI risk score; (III) PCI of a native coronary artery	(I) Unresponsive hypertension; (II) ST-segment elevation myocardial infarction (MI) within 24 h; (III) PCI within the previous 2 weeks; (IV) intraventricular conduction defect, pacing, (V) left ventricular hypertrophy or any other electrocardiographic finding that could make continuous electrocardiographic monitoring uninterpretable; (VI) cardiogenic shock; (VII) history of a bleeding diathesis or evidence of active bleeding within 30 days; (VIII) history of a hemorrhagic stroke at any time, stroke or transient ischemic attack of any etiology within 30 days; (IX) platelet count of <100,000/mm^3; (X) major surgery within the previous 6 weeks; (XI) any low-molecular weight heparin within the previous 12 h; (XII) treatment with any GP IIb/IIIa in the previous 30 days or concurrent or anticipated treatment; (XIII) concurrent treatment with warfarin; (XIV) estimated creatinine clearance <30 mL/min; (XV) treatment of in-stent restenosis; or anticipated or staged PCI within 48 h

Table 2 (*continued*)

Table 2 (*continued*)

Study	Inclusion criteria	Exclusion criteria
REPLACE 1	(I) Age >21 years; (II) PCI with approved devices; (III) written, informed consent	(I) Acute MI or conditions of elevated bleeding risk; (II) unfractionated heparin within 6 h (unless activated partial thromboplastin time measured within 2 h before randomization was 50 seconds); (III) low molecular weight heparin within 12 h; (IV) abciximab within 7 days, or eptifibatide or tirofiban within 12 h
REPLACE 2	(I) Age >21 years; (II) PCI with approved devices; (III) written, informed consent	(I) Ongoing warfarin therapy; (II) unfractionated heparin <6 h (unless activated partial thromboplastin time was <50 seconds); (III) low-molecular weight heparin <8 h, (IV) bivalirudin <24 h; (V) abciximab <7 days, or eptifibatide or tirofiban <12 h; (VI) younger than 18 years, (VII) poorly controlled hypertension; (VIII) unprotected left main trunk stenosis; (IX) pregnancy; (X) PCI <1 month or planned; (XI) active internal bleeding or prior intracranial bleeding or structural abnormality; (XII) platelet count less than 100,000/μL; (XIII) serum creatinine >4 mg/dL or dialysis
TENACITY	Moderate-to-high-risk PCI: patients undergoing elective or urgent PCI with current or recent (<1 mo) ACS (including primary but not rescue PCI), current or history of heart failure, depressed ventricular function, peripheral vascular disease, or insulin-dependent diabetes mellitus. Patients could also be included if their PCI included treatment for complex coronary anatomy	Abciximab within 14 d, thrombolytic therapy within 12 h, or 8 tirofiban, eptifibatide, or LMWH within 10 h
VALIDATE-SWEDEHEART	Patients with a diagnosis of NSTEMI as judged by the physician in accordance with current guideline definitions (positive troponin) or patients with a diagnosis of STEMI as defined by chest pain suggestive for myocardial ischemia for at least 30 min before hospital admission, time from onset of symptoms of b24 h, and an ECG with new ST-segment elevation in ≥2 contiguous leads of ≥0.2 mV in leads V2–V3 and/or ≥0.1 mV in other leads or a probable new-onset left bundle-branch block; PCI of culprit lesion is intended (therapeutic PCI, not primarily diagnostic PCI); ability to provide informed consent; Age ≥18 years treated with bolus dose of ticagrelor, prasugrel, or cangrelor before start of PCI	Previous randomization in the VALIDATE-SWEDEHEART trial Known terminal disease with life expectancy <1 year; patients with known ongoing bleeding; patients with uncontrolled hypertension in the opinion of the investigator; patients with known subacute bacterial endocarditis; patients with known severe renal (GFR b 30 mL/min) and/or liver dysfunctions; patients with known thrombocytopenia or thrombocyte function defects; any other contraindication for the study medications; heparin N5,000 U before arriving to PCI laboratory or N3,000 U given in the beginning of the procedure; GPIIb/IIIa inhibitors have been given or are pre planned to be given during the procedure
Xiang *et al.*	(I) Written informed consent; (II) age from 18 to 70 years old; (III) elective PCI 1 week after myocardial infarction, including patients who received a thrombolytic therapy, with stable or unstable angina that proved to be suited for PCI by coronary angiography	(I) Age >70 or <18 years old; (II) prior administration of unfractionated heparin 4 h before PCI, subcutaneous injection of LNWH 12 h before PCI, long-term use of warfarin; (III) thrombolytic therapy within 48 h before PCI; (IV) bleeding tendency: a history of gastrointestinal bleeding within 3 months, cerebral hemorrhage within 6 months, cerebral infarction within 3 months; (V) serious agranulocytosis and thrombocytopenia patients who could not undergo PCI or heparin-induced thrombocytopenia (HIT) patients; (VI) refractory hypertension; (VII) liver or renal function parameters increased to 1.5 times of upper limits; (VIII) patients who had major surgery within 1 month; (IX) history of allergy to heparin or biological products; (X) pregnant, lactating, or female patients who plan to conceive

ACS, acute coronary syndrome; COX-2, cyclo-oxygenase inhibitor-2; CPR, cardiopulmonary resuscitation; GFR, glomerular filtration rate; GPI, glycoprotein IIb/IIIa inhibitors; LMWH, low molecular weight heparin; LBBB, left bundle branch block; NSAIDs, non-steroidal anti-inflammatory drugs; NSTEMI, non ST elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; TIA, transient ischemic attack; UFH, unfractionated heparin.

Table 3 Baseline characteristics of the included studies

STUDY	Heparin age	Bivalirudin age	Heparin male	Bivalirudin male	Heparin/ GPI inhibitor	Bivalirudin/ GPI inhibitor	Heparin DM %	Bivalirudin DM %	Heparin transfemoral	Heparin transradial	Bivalirudin transfemoral	Bivalirudin transradial	Heparin ACT time (sec)	Bivalirudin ACT time (sec)
ACUITY	63	63	1,860	1,919	97	0	28	28	–	–	–	–	239	–
ACUITY	63	62	1,860	1,919	97	53	28	28	–	–	–	–	239	–
ARMYDA 7 BIVALVE	70	70	148	141	14	12	59	69	199	4	193	5	–	–
ARNO	70	69	319	329	25.3	47.7	22	21	415	10	418	7	297	327
BRAVE	61	61	219	205	6.1	3	15	17	277	0	271	0	–	–
BRIGHT	58	57	595	608	0	4.4	137	168	153	576	159	576	263	298
BRIGHT	58	57	599	608	100	4.4	160	168	159	571	159	576	261	298
CACHET	62	65	73	44	100	31	–	–	–	–	–	–	305	346
CACHET	62	65	73	44	100	0	–	–	–	–	–	–	305	348
DESHPANDE	56	55	43.6	43.6	100	100	42.3	36.7	–	–	–	–	264	286
EUROMAX	62	61	356	814	97.5	98.3	17.4	11.7	208	245	558	510	–	–
EUROMAX	61	61	505	814	97.8	98.3	13.7	11.7	374	257	558	510	–	–
FELDMAN	–	–	30	39	–	–	–	87	–	39	–	45	–	–
HEAT PPCI	63	62	663	647	15	13	15	13	161	744	171	727	206	246
HORIZONS AMI	60	60	1,372	1,388	94.5	7.2	17.3	16.5	–	–	–	–	–	–
ISAR REACT 3	67	67	1,751	1,744	0.2	0.2	636	618	–	–	–	–	–	–
ISAR REACT 4	67	67	661	661	100	0	29.8	28.3	–	–	–	–	–	–
MATRIX	65	65	2,764	2,731	2	1	21.8	22.6	1,916	2,094	1,712	1,683	–	–
NAPLES 3	78	78	190.6	207	1.3	0.5	43	45	417	2	416	2	–	–
PROTECT TIMI 30	60	59.7	378	193	99	0	36.5	44.3	–	–	–	–	266	340
REPLACE 1	64	64	369	368	72.5	71.1	28.9	31.4	509	13	516	14	293	359
REPLACE 2	62	62	2,229	2,236	96.5	7.2	26.1	28.1	–	–	–	–	–	–
TENACITY	–	–	–	–	100	100	–	–	–	–	–	–	225	–
Xiang *et al.*	59	57	96	101	0.9	3.7	NA	NA	79	29	84	25	176	166
VALIDATE-SWEDEHEART	68	68	2,177	2,229	2.8	2.4	508	491	–	–	–	–	305	386

ACT, activated clotting time; DM, diabetes mellitus; GPI, glycoprotein inhibitor; NA, not available.

Statistical analyses

Categorical data were pooled using the random effects model; with the pooled effect size represented as risk ratio (RR) with 95% confidence interval (CI) limits. Publication bias was assessed visually using funnel plot. Cochrane's Q-statistics were used to determine the heterogeneity of included studies for each outcome. I^2 values of <25%, 25–50%, and 50–75% were considered as low, moderate, and high heterogeneity, respectively. An exclusion-sensitivity analysis was included for heterogeneity, when necessary. A meta-regression was performed when necessary to analyze the impact of moderator variables on outcomes of interest. A P value of <0.05 was considered statistically significant. Analyses were performed by M Anantha-Narayanan using the Software Comprehensive Meta-Analysis (version 3.3) (19). This study was exempt from Institutional Review Board approval at our institution.

Results

Study characteristics

Initially, there were 23 original studies (4,5,7-16,20-30) but we excluded the BAT/HAS trial (20) as patients in this trial had received only balloon angioplasty without stents. Also, the trial did not meet our inclusion criteria for year. Finally, we had 22 original studies with a total of 26 comparison groups. *Table 1* shows the baseline study characteristics and patients groups used in the analysis.

Patients

The overall study population consisted of 53,364 patients extracted from 26 comparison groups (22 original studies and 4 subgroups) and about 66% were males. Mean follow-up time was 192±303 days with maximum follow-up of 1,095 days. Mean age of the entire cohort was 63±4 years. Concomitant GPI therapy was used in about 44% of the overall patient population, 27% in the bivalirudin arm and 61% in the heparin arm. Inclusion and exclusion criteria of the individual studies are mentioned in *Table 2*. A total of 16 comparison groups had planned GPI usage in the heparin arm and two of the groups used only bailout GPI. Remaining studies did not have GPI in the heparin arm. A total of 17 comparison groups had bivalirudin without GPI or only with bailout GPI whereas 9 groups had bivalirudin with provisional GPI.

Major bleeding-bivalirudin versus heparin

Among the overall patient population, the risk of major bleeding was 36% lower in patients receiving bivalirudin when compared to those assigned to receive heparin (RR: 0.64; 95% CI: 0.53–0.77, P<0.001) (*Figure 1*). After exclusion of GPI usage (both provisional and routine use) in both arms, the risk of major bleeding was still 29% lower in the bivalirudin arm than in the heparin arm (RR: 0.71; 95% CI: 0.51–0.99, P=0.041) (*Figure 2*). Major bleeding was still lower in the bivalirudin arm when we analyzed only studies with GPI usage (provisional and routine) in both arms (RR: 0.58; 95% CI: 0.42–0.81, P=0.001) (not shown). Sensitivity analysis with exclusion of the study (12) with the maximum strength did not alter the results (RR: 0.64; 95% CI: 0.53–0.77, P<0.001). Funnel plot showed minimal bias (*Figure S2*) and heterogeneity within the included studies was high (I^2=65%). Analysis of studies with PCI in ACS showed lower major bleeding with bivalirudin (RR: 0.64; 95% CI: 0.53–0.78, P<0.001) but in elective PCI, the difference became insignificant between the groups (RR: 0.58; 95% CI: 0.28–1.18, P=0.130). We performed a test for interaction dividing the studies in sub groups as studies using >10% GPI (routine or provisional) in both arms and studies using <10% GPI (routine or provisional) in both arms. The overall test for interaction between the sub groups was insignificant, therefore, the statistical heterogeneity in the overall meta-analysis for major bleeding was not explained by the subgroup analyses with respect to GPI usage and there was no significant interaction.

A meta-regression of ACT in heparin arm on incidence of major bleeding (*Figure S3*) was statistically insignificant (P=0.422) indicating different ACT levels in heparin arm does not affect the risk of major bleeding. Analysis of radial access predominant studies (studies with >60% radial access) showed a trend towards lower risk of major bleeding with bivalirudin but was statistically insignificant (RR: 0.76; 95% CI: 0.45–1.26, P=0.285).

All-cause mortality-bivalirudin versus heparin

All-cause mortality was compared from 23 studies. All-cause mortality was not different between the bivalirudin and heparin arms (RR: 0.93; 95% CI: 0.82–1.05, P=0.260) (*Figure 3*). Sensitivity analysis with exclusion of the study (12) with the maximum strength did not change the results of the analysis. Funnel plot showed minimal bias (not shown) and I^2 was 0 (P=0.516). A meta-regression of all-

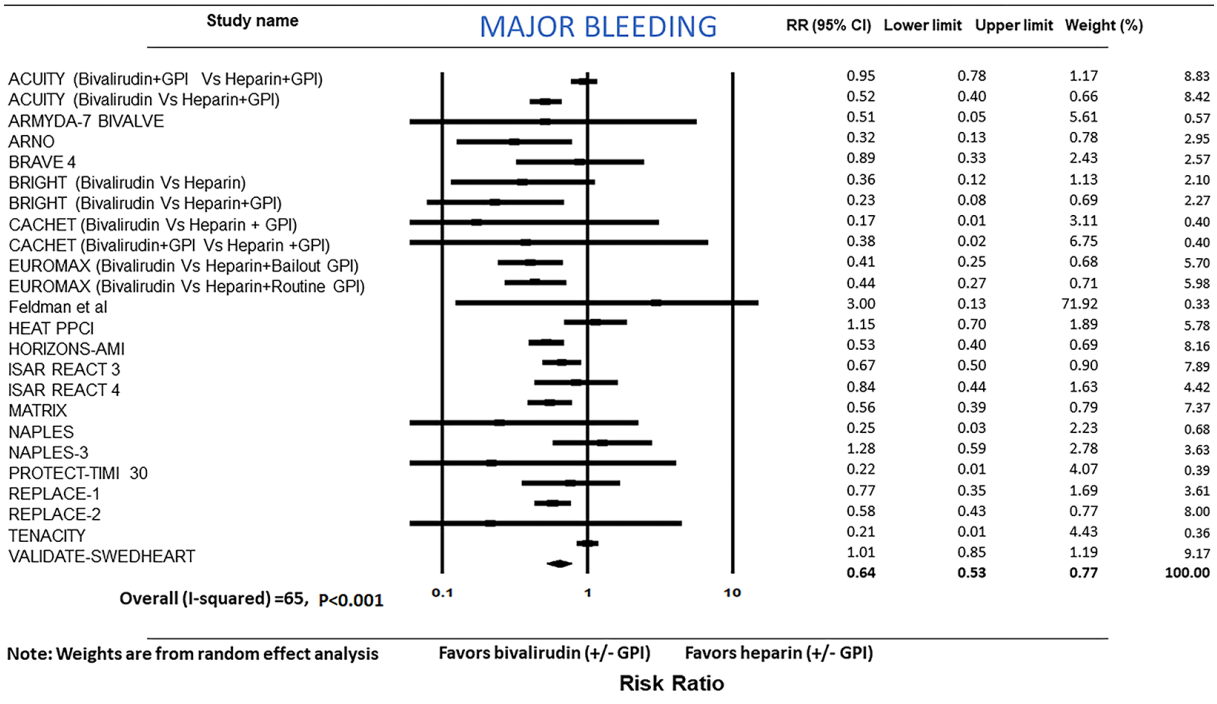

Figure 1 Forest plot and pooled analysis for major bleeding in patients undergoing PCI (heparin versus bivalirudin)*. *, GPI in both arms; RR, relative risk; CI, confidence interval; PCI, percutaneous coronary intervention; GPI, glycoprotein IIb/IIIa inhibitor.

cause mortality on follow-up time period was insignificant (P=0.931). When we excluded provisional and routine GPI in both arms, all-cause mortality was still similar in both groups (RR: 0.98; 95% CI: 0.84–1.15, P=0.823) (not shown).

All-cause mortality was not different between the groups when we divided studies into PCI in ACS (RR: 0.95; 95% CI: 0.83–1.08, P=0.412) and elective PCI (RR: 0.73; 95% CI: 0.46–1.18, P=0.200).

We then separated studies that reported 30-day mortality and 1-year mortality as mentioned in the methods section. Both 30-day (RR: 0.94; 95% CI: 0.79–1.12, P=0.495) and 1-year (RR: 0.83; 95% CI: 0.65–1.07, P=0.160) mortality were not different between the two groups.

Stent thrombosis-bivalirudin versus heparin

Stent thrombosis was reported in 15 studies. Risk of stent thrombosis was higher in the bivalirudin group (RR: 1.32; 95% CI: 1.04–1.68, P=0.022) (*Figure 4*). I^2 was 27% (P=0.157). We then analyzed acute and sub-acute stent thrombosis from the available trials. Acute stent thrombosis was higher in the bivalirudin group (RR: 1.54; 95% CI: 1.07–2.23, P=0.020) whereas sub-acute stent thrombosis showed no difference between bivalirudin and heparin (RR: 1.04; 95% CI: 0.60–1.81, P=0.879). When we excluded studies with GPIs in both arms, the difference became statistically insignificant (RR: 1.40; 95% CI: 0.66–2.97, P=0.379) (not shown). In the PCI group for ACS, stent thrombosis was higher in the bivalirudin group (RR: 1.32; 95% CI: 1.02–1.73, P=0.038), whereas in the elective PCI group, there was no difference in stent thrombosis between the two groups (RR: 1.65; 95% CI: 0.51–5.35, P=0.405).

Myocardial infarction-bivalirudin versus heparin

Myocardial infarction was analyzed from 24 comparison groups comparing bivalirudin to heparin. The risk of myocardial infarction was not different between the two groups (RR: 1.12; 95% CI: 0.98–1.28, P=0.098) (*Figure 5*) and exclusion of GPI in both arms did not alter the difference (RR: 1.08; 95% CI: 0.90–1.30, P=0.392). Sensitivity analysis with exclusion of the study (12) with the maximum strength did not alter the results. Heterogeneity within the included studies was high (I^2=60). When we divided the studies to analyze PCI in ACS, incidence of

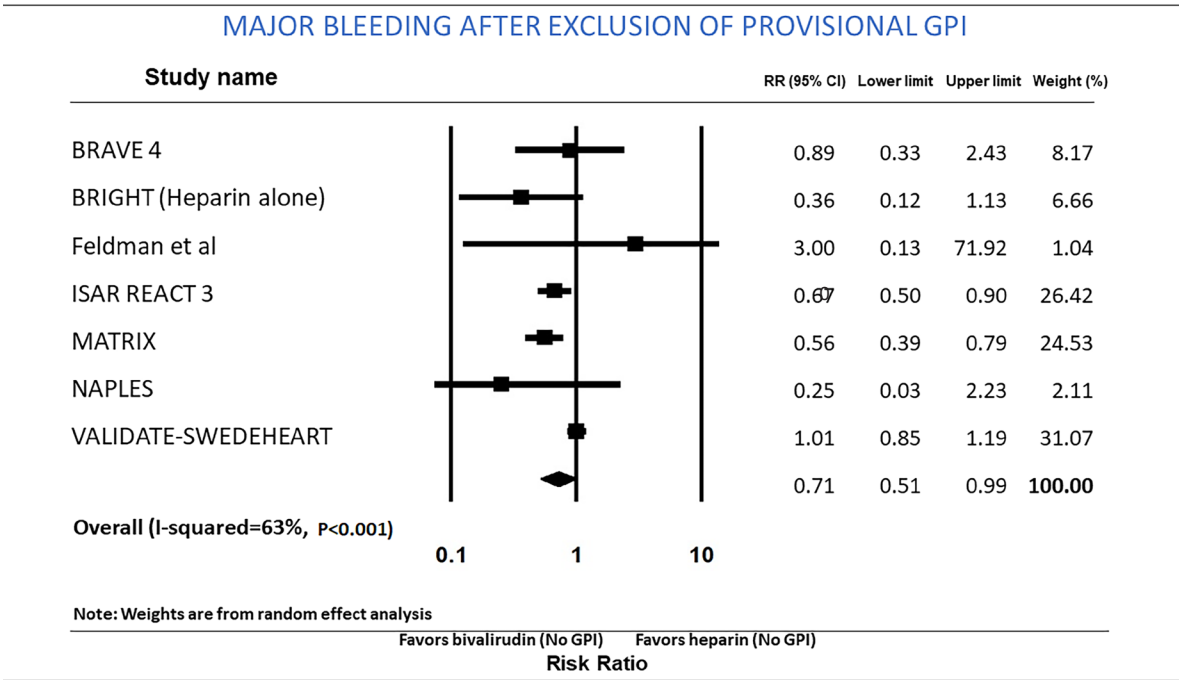

Figure 2 Forest plot and pooled analysis for major bleeding in patients undergoing PCI (heparin versus bivalirudin) after exclusion of GPI in both arms. RR, relative risk; CI, confidence interval; PCI, percutaneous coronary intervention; GPI, glycoprotein IIb/IIIa inhibitor.

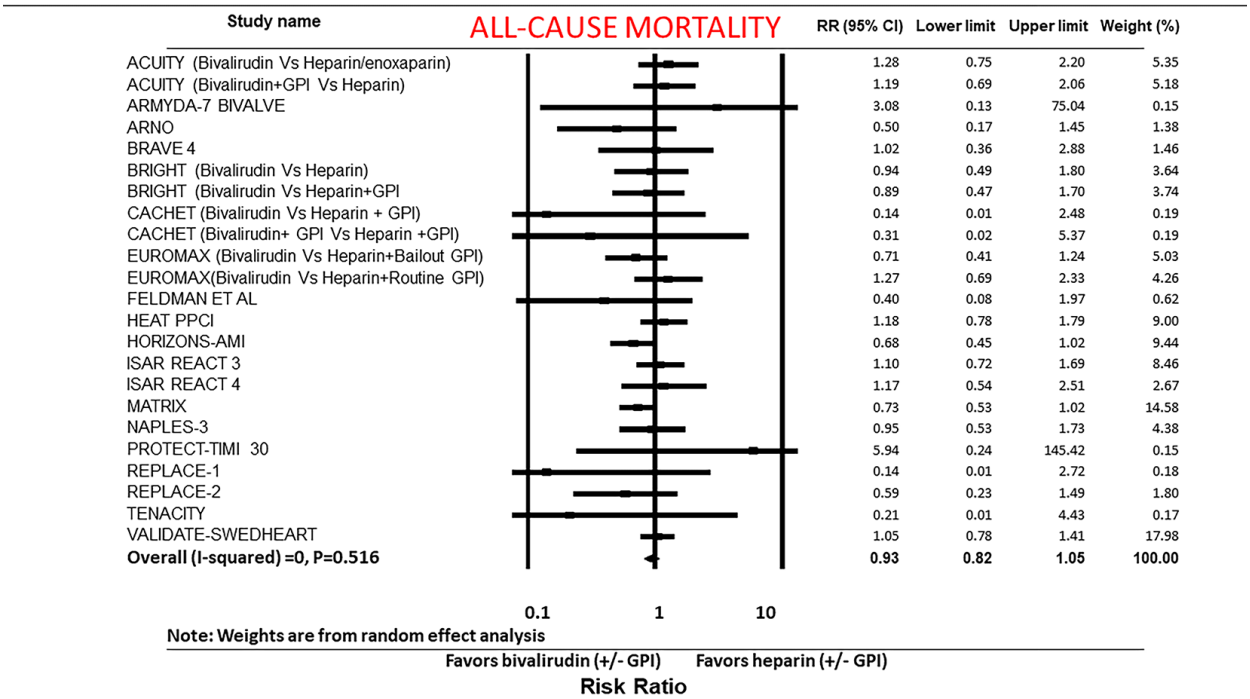

Figure 3 Forest plot and pooled analysis for all-cause mortality in patients undergoing PCI (heparin versus bivalirudin)*. *, GPI in both arms; RR, relative risk; CI, confidence interval; PCI, percutaneous coronary intervention; GPI, glycoprotein IIb/IIIa inhibitor.

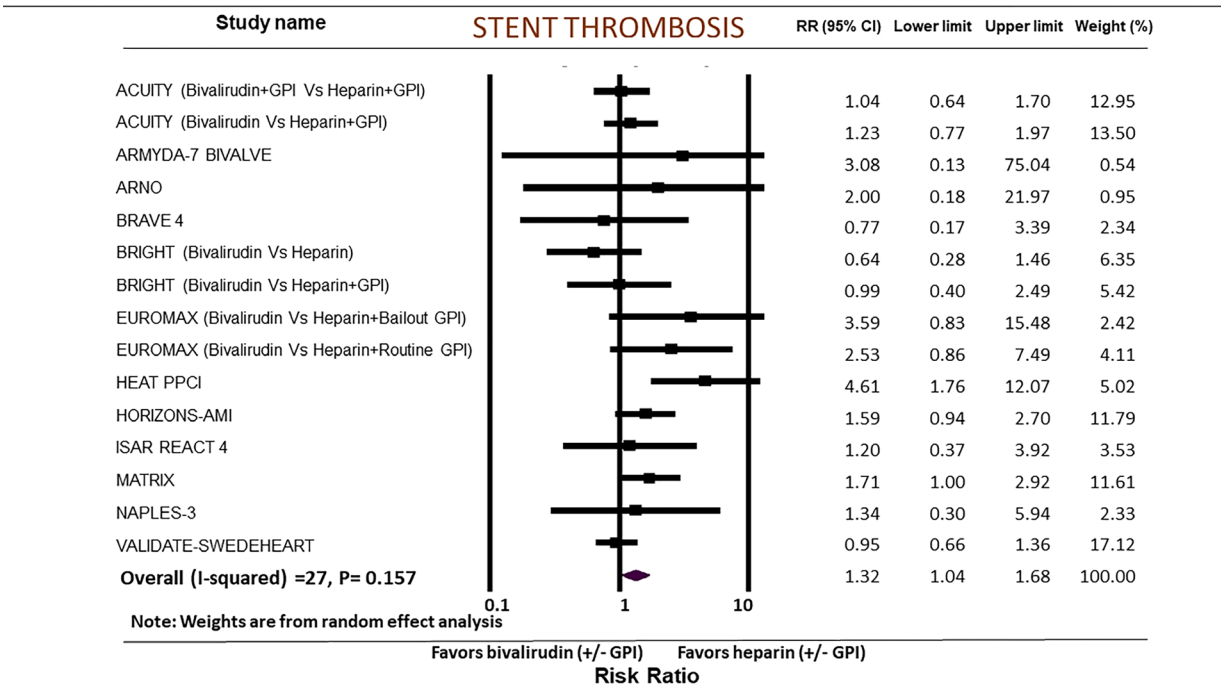

Figure 4 Forest plot and pooled analysis for stent thrombosis in patients undergoing PCI (heparin versus bivalirudin)*. *, GPI in both arms; RR, relative risk; CI, confidence interval; PCI, percutaneous coronary intervention; GPI, glycoprotein IIb/IIIa inhibitor.

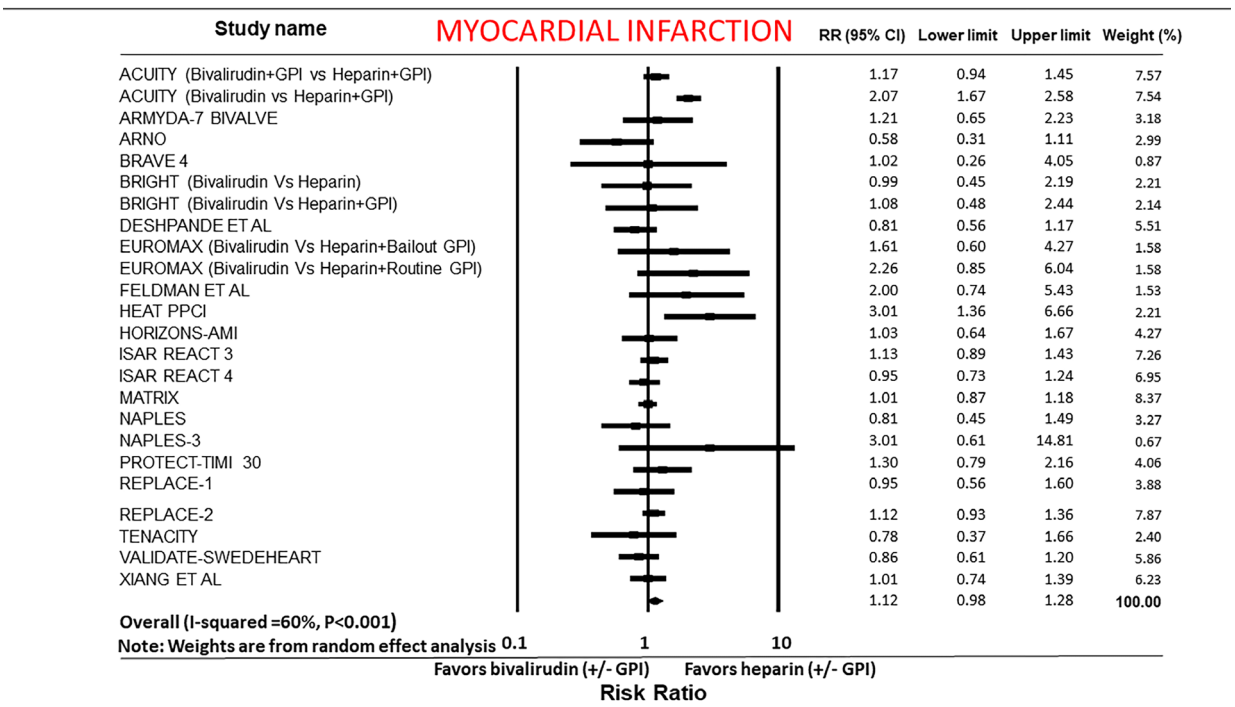

Figure 5 Forest plot and pooled analysis for myocardial infarction in patients undergoing PCI (heparin versus bivalirudin)*. *, GPI in both arms; RR, relative risk; CI, confidence interval; PCI, percutaneous coronary intervention; GPI, glycoprotein IIb/IIIa inhibitor.

myocardial infarction was higher in the bivalirudin group (RR: 1.18; 95% CI: 1.01–1.37, P=0.041) whereas in elective PCI group, there was no difference in myocardial infarction between the two groups (RR: 0.95; 95% CI: 0.74–1.21, P=0.674).

TVR-bivalirudin versus heparin

Incidence of TVR was reported in 17 studies. The risk of TVR was not different between the two groups (RR: 1.17; 95% CI: 0.93–1.46, P=0.174) (*Figure 6*). After exclusion of routine and provisional GPI in both arms, incidence of TVR remained similar between the two groups (RR: 1.21; 95% CI: 0.95–1.54, P=0.118). Sensitivity analysis with exclusion of the study (9) with the maximum strength did not alter the results. Heterogeneity within the included studies was high (I^2=64). In PCI for ACS, there was a trend towards higher incidence of TVR in the bivalirudin group without statistical significance (RR: 1.26; 95% CI: 0.97–1.65, P=0.082). In elective PCI, there was no difference in the incidence of TVR between the bivalirudin and heparin groups (RR: 0.85; 95% CI: 0.60–1.20, P=0.357).

Stroke rates-bivalirudin versus heparin

Stroke rates were not different between bivalirudin and heparin group (RR: 0.91; 95% CI: 0.71–1.18, P=0.490) analyzing 10 comparison groups (*Figure 7*). I^2 was 0 (P=0.849). After exclusion of GPI in both study arms, incidence of stroke was not different between the two groups (RR: 0.92; 95% CI: 0.69–1.21, P=0.541). Dividing the studies into elective PCI (RR: 0.94; 95% CI: 0.59–1.51, P=0.805) and PCI in ACS (RR: 0.91; 95% CI: 0.67–1.24, P=0.565) did not alter the outcomes.

Discussion

Results from our current meta-analysis provide new insight into the role of bivalirudin versus heparin in PCI. Bivalirudin use is associated with lower risk of major bleeding regardless of GPI usage in the heparin arm. This persisted even while retaining studies with GPI use in the bivalirudin arm which would have been expected to bias results towards the null. Although bivalirudin appeared to have a higher rate of stent thrombosis, analysis of studies without GPI usage in both arms showed no significant difference between the two groups. Analysis of studies only with elective PCI showed no difference in major bleeding between heparin and bivalirudin but bivalirudin showed lower bleeding in the ACS setting. Stent thrombosis was higher with bivalirudin in ACS but not in elective PCI. Bivalirudin was similar to heparin with respect to all-cause mortality, recurrent myocardial infarction, TVR or stroke rates.

Bivalirudin has been extensively studied in multiple RCTs as an acute therapy in place of heparin for patients receiving PCI. Whereas unfractionated heparin potentiates anti-thrombin III thereby inactivating thrombin and factor Xa, it has a very limited effect on clot bound thrombin. Heparin also increases platelet activation and can cause heparin induced thrombocytopenia (HIT). Comparatively, bivalirudin is a direct thrombin inhibitor acting on both clot bound and unbound thrombin (31), does not increase platelet activation and does not cause HIT.

The ACUITY (32), EUROMAX (6) and HORIZONS-AMI (27) were large RCTs that showed lower rates of major bleeding with bivalirudin when compared to heparin. However, all of these trials had GPI use in the heparin arm confounding any direct comparisons between heparin and bivalirudin. With the advancement in stent technology along with more potent P2Y12 therapy (ticagrelor and prasugrel), it is generally felt that earlier trials showing the benefit of the addition of GPI with heparin are outdated (1-3). Thus, the question of heparin monotherapy versus bivalirudin monotherapy remained unanswered.

Following these trials supporting bivalirudin, trials began to address the GPI confounding issue in the heparin arms. This resulted in a few negative RCTs. The HEAT PPCI trial (8) was designed to minimize the effect of GPI on outcomes comparing bivalirudin to heparin. In this predominantly radial trial (radial access in 80% bivalirudin and 82% heparin arms), there was no bleeding advantage to bivalirudin, and heparin was actually associated with lower thrombotic events including MI, stent thrombosis and TVR. Similarly, in the BRAVE-4 trial (25), where patients were randomized to bivalirudin plus prasugrel compared to heparin plus clopidogrel, the usage of GPI was much lower in both arms (3% heparin arm, 6.1% bivalirudin arm). The trial showed no benefit with respect to major bleeding or ischemia with bivalirudin but was confounded by the higher potency of prasugrel compared to clopidogrel between the two arms.

As the results of the above trials would suggest, it is unclear whether the bleeding benefit and increase in acute stent thrombosis with a trend towards more TVR and MI seen with bivalirudin is a real finding or as a result of

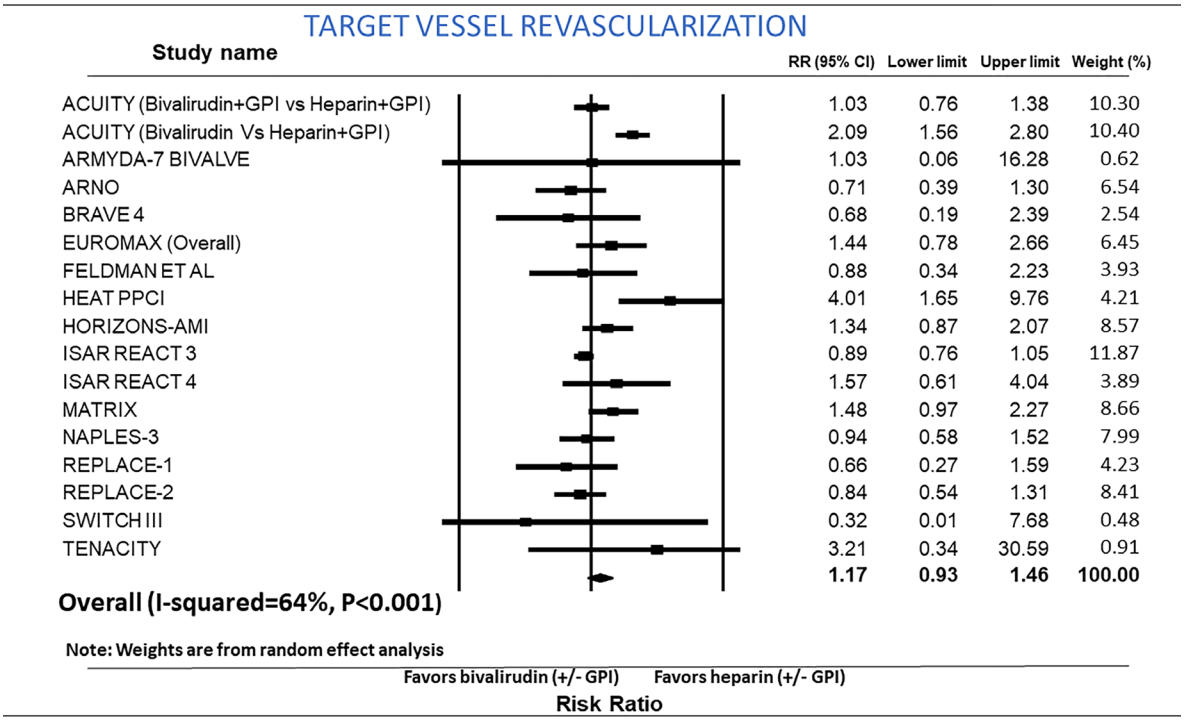

Figure 6 Forest plot and pooled analysis for TVR in patients undergoing PCI (heparin versus bivalirudin)*. *, GPI in both arms; RR, relative risk; CI, confidence interval; PCI, percutaneous coronary intervention; GPI, glycoprotein IIb/IIIa inhibitor.

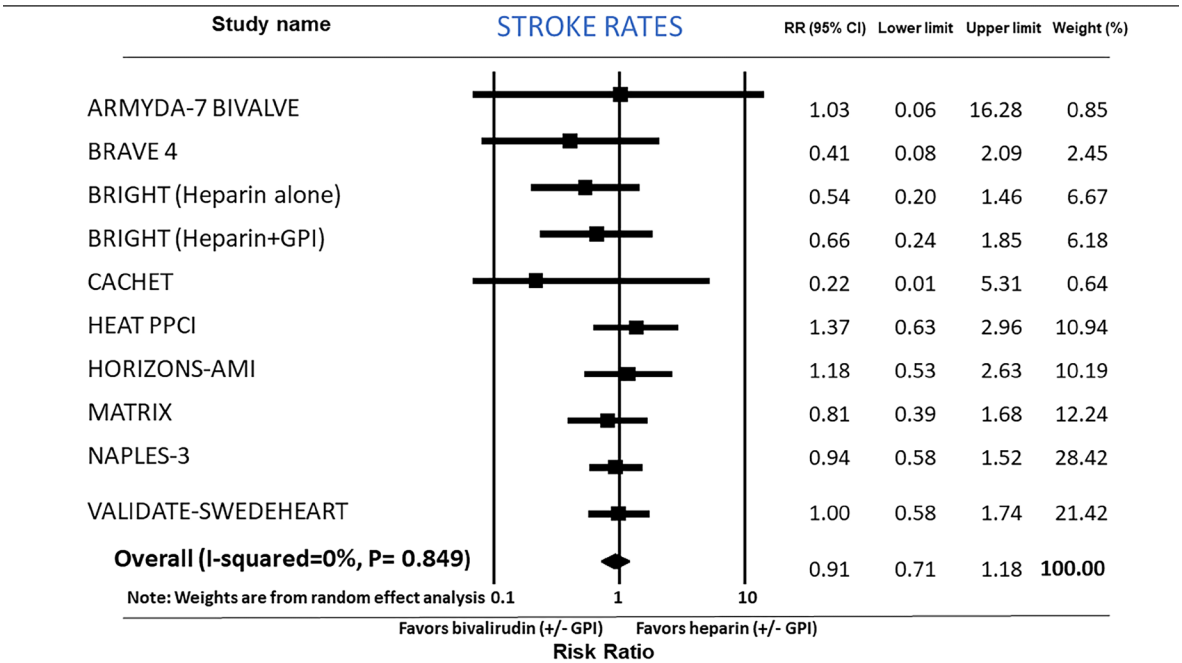

Figure 7 Forest plot and pooled analysis for stroke rates in patients undergoing PCI (heparin versus bivalirudin)*. *, GPI in both arms; RR, relative risk; CI, confidence interval; PCI, percutaneous coronary intervention; GPI, glycoprotein IIb/IIIa inhibitor.

confounding from GPI use in the heparin arm. In our meta-analysis, even after exclusion of trials with concomitant GPI in both arms, there was still a 48% reduction in rates of major bleeding. This increase in major bleeding with heparin did not translate to increased mortality. One could also question whether the bleeding benefit of bivalirudin would exist in the current era with a high utilization of transradial access (33). However, in the contemporary BRIGHT trial, bivalirudin showed a bleeding advantage even though the majority of the patients in the trial (79%) had radial access. Another interesting finding is that bivalirudin showed lower bleeding in the ACS trials but not in elective PCIs. The acute inflammatory state in ACS altering hemostasis increases bleeding risk where bivalirudin demonstrates benefit. In elective PCI, the absence of baseline increased bleeding risk essentially limits us from seeing a meaningful difference between the two groups even if there is truly a small lower biological bleeding risk with bivalirudin. We also sub-stratified patients by studies with radial predominant access and were unable to demonstrate a significant benefit to bivalirudin on bleeding rates in this subgroup, although the point estimate still favored bivalirudin. Whether the potential physiologically lower bleeding rates with bivalirudin are of relevance when radial access is used for PCI is therefore unclear.

Stent thrombosis rates were higher as shown in the previous meta-analysis (34) but with exclusion of concomitant GPI usage, this difference became insignificant suggesting again a confounding effect of GPI use in the heparin arm decreasing acute stent thrombosis. It is also possible that bivalirudin is intrinsically associated with a higher rate of stent thrombosis in the previously published trials that has been overcome by more potent antiplatelet therapy. In addition, other thrombotic complications including recurrent MI and TVR showed a trend towards increase with bivalirudin supporting this hypothesis. Of note, the higher thrombotic events with bivalirudin appears to be of significance not during elective PCI but only in the high risk acute ACS period where the risk-benefit ratio of anticoagulation has an even narrower therapeutic window than usual. It may be that the prothrombotic state of an MI may increase the risk of acute stent thrombosis if bivalirudin is used with its short half-life before adequate platelet inhibition has been achieved with a single dose of an oral P2Y12 inhibitor. This was seen in EUROMAX where bivalirudin was associated with higher rates of stent thrombosis in STEMI patients undergoing PCI (6). It is well known that in STEMI patients, the anticoagulation cascade gets altered and P2Y12 inhibition takes long than usual. In this trial, oral P2Y12 inhibitors were administered at approximately 50 min before PCI but complete P2Y12 inhibition occurred only at 140 min after administration. This effect along with stopping bivalirudin (which has a short half-life) early, leads to an anti-coagulation free period, increasing risk of stent thrombosis as evidenced in the HEAT-PPCI trial (8). Prolonged bivalirudin infusion regimens as used in the BRIGHT trial (4) without an increase in bleeding may be worthy of investigation as methods to reduce this potential acute stent thrombosis risk.

Although a prolonged bivalirudin infusion regimen was used in EUROMAX (6), a lower dose infusion was used which could have potentially contributed to the higher stent thrombus rates seen with bivalirudin post PCI. The higher infusion dose of 1.75 mg/kg/h was used only in one fifth of the patient population whereas the rest of the patients were given a lower dose of 0.25 mg/kg/h. This was confirmed in a post-hoc analysis of EUROMAX (6) which showed higher bivalirudin infusion dose during prolonged infusion significantly reduced the risk of stent thrombus seen with bivalirudin (35). In MATRIX, there was no difference between prolonged and shorted infusion of bivalirudin with respect to stent thrombus but only one third of the patients received a higher dose of infusion (10). If bivalirudin is used, there is currently uncertainly about the need for post procedure infusion, the dosage and duration which requires further investigation. In addition to the above-mentioned mechanisms, the altered hemostasis profile during ACS may also be contributing to bivalirudin's lower potency causing increased stent thrombosis. Our meta-analysis suggests that this may not be applicable to elective PCI where both heparin and bivalirudin appear largely equivalent.

The recently published VALIDATE-SWEDEHEART (12), a large registry-based randomized controlled trial, showed lack of benefit with bivalirudin when compared to heparin in the absence of provisional GPI use. The trial had approximately 3,000 patients in each arm with options for pre-randomization heparin and prolonged bivalirudin infusion along with potent P2Y12 inhibitors including prasugrel, ticagrelor or intravenous cangrelor. However, this trial was also confounded by the use of heparin at a mean dose of 3,470 units in 90% of patients regardless of bivalirudin assignment, essentially comparing bivalirudin plus low dose heparin with heparin monotherapy. This would mitigate the bleeding advantage of bivalirudin monotherapy. The lack of an increase in stent thrombosis

with bivalirudin in that trial is likely also influenced by this concomitant use of low dose heparin in the bivalirudin arm, but also by the use of prolonged bivalirudin infusion in two thirds of patients similar to the BRIGHT trial (36). It should be noted that even after inclusion of the trial in the meta-analysis, bivalirudin still appear to retain benefit with respect to major bleeding events but did carry a higher risk of stent thrombosis.

From the results, it may be seen that tailored anti-coagulation therapy based on individual's risk factors may be beneficial. Advanced age, female gender, history of major bleeding in the past and renal insufficiency are associated with higher bleeding rates and so bivalirudin may be beneficial (37). Stent thrombosis has been shown to be higher in patients with ACS, long segment disease with multiple stents, small vessel diameter, bifurcation lesions and chronic total occlusions (38) and in these patients, heparin without GPIs or judicial use of bivalirudin can be options.

The strength of our meta-analysis is the inclusion of only RCTs to avoid patient selection bias. Another strength of the study is the stratification of results with and without GPIs, and also based on elective versus ACS setting. The results of our meta-analysis are not representation of the real-world registries. The variable definitions used across the studies for major bleeding create bias in comparison of multiple trials. The variable timing and dosage of P2Y12 inhibitors could affect interpretation of results. We did not have patient level data to assess outcomes for sub-groups like radial or femoral access. None of the studies were blinded. BRAVE-4 trial (25) was terminated early due to slow recruitment. Finally, publication bias is an inherent limitation of meta-analysis.

Conclusions

In summary, this systematic review and meta-analysis of published RCTs supports the use of bivalirudin in PCI. Bivalirudin is associated with lower rates of major bleeding independent of the use of GPI with no difference in other clinical outcomes when compared to heparin. The increase in stent thrombosis in earlier trials with bivalirudin is no longer apparent in the elective setting and may have been related to the inflammatory state causing increased thrombosis in ACS and also confounding in the heparin arm from GPI inhibitors lowering stent thrombosis risk. The true benefits of bivalirudin in the current era of radial PCI is an evolving question that will need further exploration.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: Pertinent disclosures are included above. None of the results of this manuscript have been disclosed.

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Supplementary

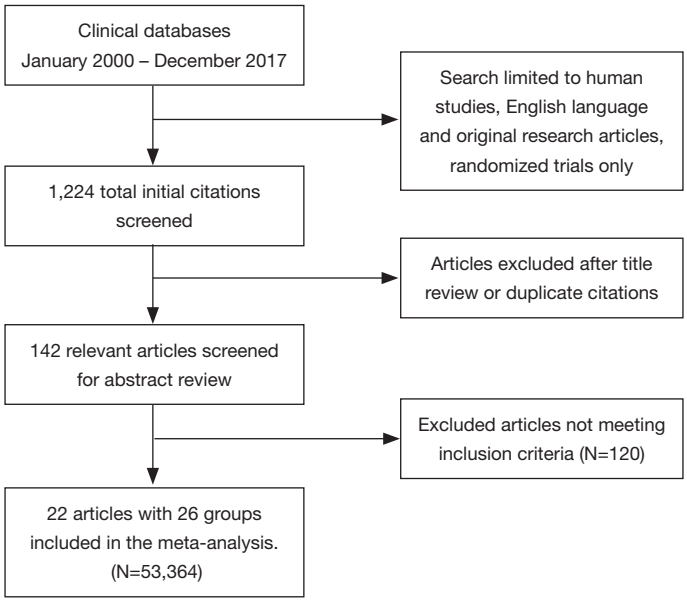

Figure S1 Selection process of clinical studies included in the systematic review and meta-analysis.

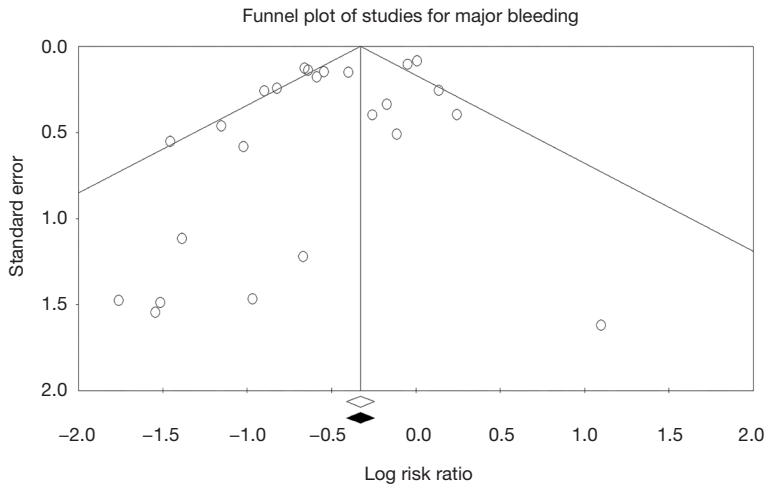

Figure S2 Funnel plot for assessment of publication bias for major bleeding. Each dot represents a study; Y-axis represents the size of the study and the X-axis shows the study results. ACT, activated clotting time.

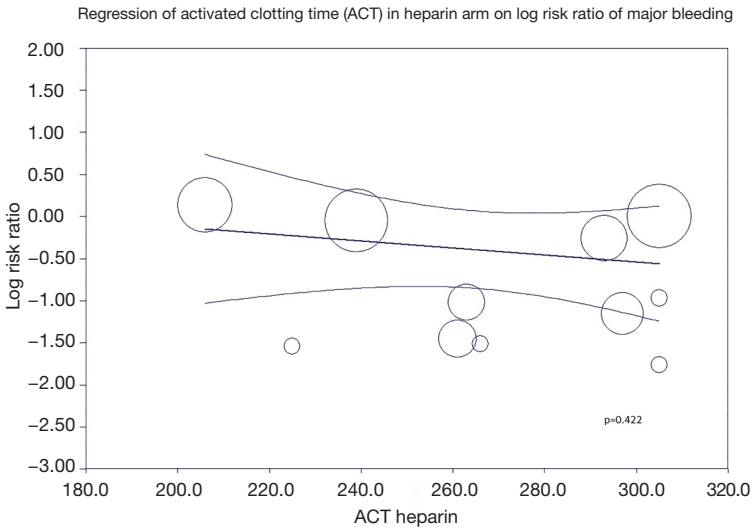

Figure S3 Meta regression of ACT in heparin on major bleeding. Each circle represents a study; Y-axis represents ACT values in heparin arm and X-axis shows log risk ratio of major bleeding. ACT, activated clotting time.