National Institute for Health and Care Excellence

Final

Acute Coronary Syndromes

[D] Evidence review for antithrombin therapy in adults with ST-segment elevation myocardial infarction intended for primary percutaneous coronary intervention

NICE guideline NG185

Intervention evidence review

November 2020

Final

This evidence review was developed by the National Guideline Centre based at the Royal College of Physicians

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1.1 Review question: What is the clinical and cost effectiveness of bivalirudin as adjunctive pharmacotherapy in adults with ST-segment elevation myocardial infarction intended for primary percutaneous coronary intervention?

1.2 Introduction

Systemic anti-coagulation during primary percutaneous coronary intervention (PPCI) for the treatment of ST-segment-elevation myocardial infarction (STEMI) is required to prevent thrombosis of the stent and stent delivery equipment inside the patient's vasculature. Bivalirudin is an intravenous direct thrombin inhibitor that provides systemic anti-coagulation and in 2011 was recommended by NICE technology appraisal 230 'Bivalirudin for the treatment of ST-segment-elevation myocardial infarction':

- Bivalirudin in combination with aspirin and clopidogrel is recommended for the treatment of adults with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention.[33]

This was on the basis of clinical and cost effectiveness evidence submitted by the manufacturer, primarily based on the HORIZONS-AMI RCT.[59, 60] However, since then new studies have been published that could change this recommendation. In particular, following the 2014 publication of the HEAT-PPCI study[47], performed in the UK in an unselected STEMI population bivalirudin use in primary PCI for STEMI has fallen to 1.5% from a high of around 18% in 2013.[28]

This guideline will review the evidence for bivalirudin in STEMI and consider whether the recommendation from TA230 should be changed.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Adults 18 and over with ST-segment elevation myocardial infarction intended for primary percutaneous coronary intervention
Intervention(s)	Bivalirudin with/without GpIIb/IIIa inhibitor (GPI)
Comparison(s)	Heparin (unfractionated or low-molecular-weight) with/without GpIIb/IIIa inhibitor (GPI)
Outcomes	Critical: • All cause mortality – up to 30 days • Cardiac mortality – up to 30 days • New myocardial infarction – up to 30 days • Complications related to bleeding including haemorrhagic stroke – up to 30 days (with hierarchical reporting of bleeding scales as follows: ○ BARC

	○ Author's definition ○ TIMI ○ GUSTO) • Health-related quality of life including EQ5D and SF-36 Important: • All cause mortality at 1 year • Cardiac mortality at 1 year • New myocardial infarction at 1 year • Repeat revascularisation • Stent thrombosis (acute, early or late) • Stroke - up to 30 days • Length of hospital stay
Study design	RCTs and systematic reviews of RCTs

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[32] Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

1.5 Clinical evidence

1.5.1 Included studies

Seven studies (9 papers) were included in the review;[11, 17, 18, 22, 29, 47, 49, 60, 64] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

Comparisons were grouped as (i) bivalirudin with or without bailout glycoprotein inhibitor (GPI) versus heparin (low molecular weight [LMWH] or unfractionated [UFH]) with routine GPI use, whereby 'routine' was agreed by the Guideline Committee as >50% use, and (ii) bivalirudin with or without bailout/selective GPI versus heparin (LMWH or UFH) with or without bailout/selective GPI. Where indicated, both comparisons were further analysed by GPI use in subgroup analyses.

Four studies compared bivalirudin with or without bailout GPI versus heparin with routine GPI use, and four studies compared bivalirudin with or without bailout/selective GPI versus heparin with or without bailout/selective GPI.

Where reported, bleeding scores were analysed as major (BARC 3-5) and minor (TIMI or BARC <3), irrespective of any CABG-related bleeding reported.

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

1.5.2 Excluded studies

See the excluded studies list in appendix I.

1.5.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
BIVAL study (van Geuns 2017[64])	Intervention (n=38): **Bivalirudin** bolus of of 0.75mg/kg and an infusion of 1.75mg/kg/h for the duration of the procedure and for four hours after completion of PPCI. **Bailout GPI** (n=3/28; 11%) Comparison (n=40): **Unfractionated heparin** administered as per standard institutional practice (undefined). In cases where activated clotting time was used to inform UFH dosing, a target value of ≥250 seconds was recommended. **Bailout GPI** (n=3/36; 8%)	n=78 (64 per protocol population) People with ST segment elevation myocardial infarction and undergoing PPCI Age: mean 62.8 (SD 11.8) Male/Female ratio: 52/12 Ethnicity: not reported Netherlands, France	All cause mortality (unclear timepoint)	Setting: hospital Concurrent medication/care: All patients received, as soon as logistically possible, aspirin at an initial dose of 150-325mg orally (or 250-500mg intravenously) and a loading dose of a P2Y12 inhibitor. Administration of UFH at first medical contact or before the angiogram was allowed as per usual practice
EUROMAX trial (Steg 2013[49]; Fabris 2017[11])	Intervention (n=1089): **Bivalirudin** (0.75mg/kg bolus followed immediately by an infusion of 1.75mg/kg/h run continuously until completion of PCI at which time the infusion should be reduced to a dose of 0.25mg/kg/h for at least 4 hours. An optional higher-dose infusion of 1.75mg/kg/h is also permitted for up to 4 hours).	n=2198 People with ST segment elevation myocardial infarction and intended for PPCI Age: Bivalirudin group: mean 61 (range 52-71 years); Heparin group: mean 62 (range 52-72 years)	All cause mortality (30 days) Cardiac mortality (30 days) Non-cardiac mortality (30 days) New myocardial infarction (30 days): reinfarction	Setting: presenting via ambulance or at a centre where PCI is not performed Concurrent medication/care: All patients received aspirin and platelet adenosine diphosphate P2Y12 receptor inhibitor as early as possible after the first medical contact. Decisions regarding access site, performance of

Study	Intervention and comparison	Population	Outcomes	Comments
	Bailout GPI* (n=83/1046; 7.9%; abciximab bolus + 12 hour infusion or eptifibatide double bolus + 12-18 hours infusion or tirofiban bolus followed by an 18 to 24 hour infusion) *Protocol deviation: routine use of GPI occurred in 42/1088; 3.9%) patients in the bivalirudin group Comparison (n=1109): **Unfractionated heparin or low molecular weight heparin** (100 IU/kg with no GPI and 60 IU/kg with a GPI) **With or without routine or bailout GPI** (routine: 649/1109; 58.5%; bailout: 117/460; 25.4%; eptifibatide (two 180 µg/kg boluses with a 10 minute interval followed by an infusion of 2.0 µg/kg/min for 72-96 hours) or tirofiban (25 µg/kg followed by an infusion of 0.15 µg/kg/min for 18 to 24 hours) or abciximab (bolus of 0.25 mg/kg followed by an infusion of 0.125 µg/kg/min for 12-24 hours (maximum dose, 10 µg/min))	Male/Female ratio: 1675/523 Ethnicity: not reported Multiple European countries: France, Netherlands, Germany, Denmark, Austria, Czech Republic, Italy, Poland and Slovenia	Complications related to bleeding (30 days): major and minor All cause mortality (1 year) Cardiac mortality (1 year) Non-cardiac mortality (1 year) Repeat revascularisation (30 days): ischaemia-driven revascularisation Stent thrombosis (≤24hr): definite Stent thrombosis (>24hr to 30 days): definite Stent thrombosis (30 days): probable Stroke (30 days): ischaemic Stroke (30 days): haemorrhagic	thrombus aspiration, and stent type were left to physician preference
He 2016[18]	Intervention (n=129):	n=260	All cause mortality (30 days)	Setting: hospital

Study	Intervention and comparison	Population	Outcomes	Comments
	Bivalirudin first dose-intravenous bolus 0.75mg/kg, then 1.75mg.(kg-h) continuous intravenous infusion until PCI surgery completed; this dose was maintained at least 30 min after surgery, but no more than 4 hours. After the prescribed medication, the doctor may propose intravenous infusion of bivalirudin [0.2 mg/(kg-h)] according to the disease condition, no more than 20 h. **Bailout use of GPI** (n=8/129; 6.2%; tirofiban) Comparison (n=131): **Unfractionated heparin** 100 U/kg **and routine GPI** 10 ug/kg; then intravenous tirofiban 0.15 ug/(kg.min) for 18-36 hours; 100% routine GPI use (n=131/131)	People with acute ST-segment elevation myocardial infarction Age: Bivalirudin group: mean 56.8 (SD 10.1); Heparin group: mean 54.4 (SD 11.8) Male/Female ratio: 127/133 Ethnicity: not reported China	Cardiac mortality (30 days) New myocardial infarction (30 days): reinfarction Complications related to bleeding (30 days): major and minor (BRAC) Repeat revascularisation (30 days): ischaemia-driven revascularisation ((ischaemic target vessel revascularisation) Stent thrombosis (<24 hours): acute Stent thrombosis (1-30 days): subacute Stent thrombosis (30 days): definite Stroke (30 days): any, type not specified	Concurrent medication/care: All patients received dual antiplatelet therapy; if no long-term use of aspirin or clopidogrel, before surgery aspirin (300mg) and clopidogrel (300mg) of loading dose were given. Surgical puncture site, stent type and thrombectomy devices were decided by surgeons
HEAT-PPCI trial (Shahzad 2014[47])	Intervention (n=915): **Bivalirudin** given as a bolus of 0.75mg/kg followed by infusion of 1.75mg/kg/h for the duration of the procedure. A rebolus of	n=1829 People presenting to the PPCI service who were	All cause mortality (28 days)	Setting: hospital Concurrent medication/care: All patients received dual antiplatelet

Study	Intervention and comparison	Population	Outcomes	Comments
	0.3mg/kg was administered if activated clotting time values 5-15 min after the bolus dose or at the end of the procedure were less than 225 seconds. **Selective/ bailout use of GPI** (n=122/905; 13%; abciximab as per the European Society of Cardiology guidelines). The recommended dose was 0.25mg/kg intravenous bolus, followed by a continuous intravenous infusion of 0.125µg/kg/min (to a maximum of 10µg/min for 12h) Comparison (n=914): **Unfractionated heparin** given as a bolus dose of 70 U/kg body weight before the procedure. Additional doses were administered if activated clotting time values 5-15 min after the bolus dose or at the end of the procedure were less than 200 seconds. **Selective/ bailout use of GPI** (n=140/906; 15%; abciximab as per the European Society of Cardiology guidelines. The recommended dose was 0.25mg/kg intravenous bolus, followed by a continuous intravenous infusion of 0.125µg/kg/min (to a maximum of 10µg/kg/min for 12h)	scheduled for emergency angiography and had suspected STEMI Age: Bivalirudin group: median 62.9 (IQR 53.7-74.0); Heparin group: median 63.6 (IQR 54.0-73.8) Male/Female ratio: 1327/502 Ethnicity: White/NonWhite ratio: 1736/93 UK	New myocardial infarction (28 days): new myocardial infarction or reinfarction Complications related to bleeding (28 days): major and minor (BARC) Repeat revascularisation (28 days): unplanned target lesion revascularisation Stent thrombosis (≤24 hours): acute Stent thrombosis (>24 hours to 28 days) subacute Stent thrombosis (28 days): definite Stent thrombosis (28 days): probable	therapy before PPCI as per routine practice at the host institution and its referring emergency departments

Study	Intervention and comparison	Population	Outcomes	Comments
HORIZONS-AMI (Stone 2008[60]; Mehran 2009[29])	Intervention (n=1800): **Bivalirudin** administered as an intravenous bolus of 0.75mg/kg, followed by an infusion of 1.75mg/kg/h. If heparin was administered in a patient in the bivalirudin group, bivalirudin was reported to be started 30 minutes later but in all cases before PCI. Note pre-procedure heparin: 65.8% (1182/1797); during procedure heparin: 2.6% (46/1796). The antithrombin agent was discontinued at the completion of angiography or PCI but could be continued at low doses if they were clinically indicated. **Bailout GPI** (n=129/1792; 7.2%; either abciximab (a bolus of 0.25mg/kg followed by an infusion of 0.125µg/kg/minute; maximum dose, 10µg/kg/min) or double bolus eptifibatide (a bolus of 180µg/kg followed by an infusion of 2.0µg/kg/minute, with a second bolus given 10 minutes after the first; no maximum dose prespecified), adjusted for renal impairment according to the label, permitted at the discretion of the investigator and continued for 12 hours (abciximab) or 12 to 18 hours (eptifibatide)); 7.5%	n=3602 People with ST segment elevation myocardial infarction and intended for PPCI Age: Bivalirudin group: median 59.8 (range 26.0-92.3); Heparin group: median 60.7 (range 21.6-91.6) Male/Female ratio: 2760/842 Ethnicity: not reported Multiple countries	All cause mortality (30 days) Cardiac mortality (30 days) Non-cardiac mortality (30 days): bleeding related death New myocardial infarction (30 days): reinfarction Complications related to bleeding (30 days): major (author's definition) and minor (TIMI) All cause mortality (1 year) Cardiac mortality (1 year) Non-cardiac mortality (1 year) New myocardial infarction (1 year): re-infarction Repeat revascularisation (30 days): ischaemia-driven revascularisation (ischaemic target vessel revascularisation)	Setting: hospital Concurrent medication/care: Aspirin (324mg given orally or 500mg administered intravenously) after which 300 to 325mg was given orally every day during the hospitalisation, and 75 to 81mg every day thereafter indefinitely. A loading dose of clopidogrel (either 300mg or 600mg, at the discretion of the investigator), or ticlopidine (500mg), in the case of allergy to clopidogrel, was administered before catheterisation, followed by 75mg orally every day for at least 6 months (1 year or longer recommended)

Study	Intervention and comparison	Population	Outcomes	Comments
	bailout GPI use at 1 year (n=126/1675) Comparison (n=1802): **Unfractionated heparin** administered as an intravenous bolus of 60 IU/kg of body weight, with subsequent boluses targeted to an activated clotting time of 200 to 250 seconds. The antithrombin agent was discontinued at the completion of angiography or PCI but could be continued at low doses if they were clinically indicated. **Routine GPI** administered before PCI in all patients (either abciximab (a bolus of 0.25mg/kg followed by an infusion of 0.125µg/kg/minute; maximum dose, 10µg/kg/minute) or double bolus eptifibatide (a bolus of 180µg/kg followed by an infusion of 2.0µg/kg/minute, with a second bolus given 10 minutes after the first; no maximum dose prespecified), adjusted for renal impairment according to the label, permitted at the discretion of the investigator and continued for 12 hours (abciximab) or 12 to 18 hours (eptifibatide));		Repeat revascularisation (1 year): ischaemic TVR; ischaemic TLR; ischaemic remote TVR Stent thrombosis (≤24 hours): acute Stent thrombosis (>24 hours to 30 days): subacute Stent thrombosis (30 days): definite Stent thrombosis (30 days): probable Stent thrombosis (1 year): definite Stent thrombosis (1 year): probable stent thrombosis Stroke (30 days): any, type not specified	

Study	Intervention and comparison	Population	Outcomes	Comments
	97.7% routine GPI use at 1 year (n=1625/1664)			
MATRIX trial (Leonardi 2016[22])	Intervention (n=3610; mixed population): **Bivalirudin** given as a bolus of 0.75mg/kg body weight followed immediately by an infusion of 1.75mg/kg body weight hourly until completion of percutaneous coronary intervention. Bivalirudin was then stopped at the end of percutaneous coronary intervention, or prolonged in accordance with the subsequent random assignment. In patients allocated to prolonged treatment, bivalirudin could be administered for up to four hours at the full dose or at a reduced dose of 0.25mg/kg body weight hourly for at least six hours, at the discretion of the treating doctors. **Bailout GPI** (n=121/2012; 6%) Comparison (n=3603; mixed population): **Unfractionated heparin** dosed at 70-100 units/kg body weight in patients not receiving GpIIb/IIIa inhibitors and at 50-70 units/kg body weight in patients receiving GpIIb/IIIa inhibitors. Subsequent heparin dosing	n=7213 (mixed population); n= 4010 (STE-ACS/STEMI subgroup) People with acute coronary syndromes with and without ST segment elevation Age: Bivalirudin group with ST segment elevation: mean 63.9 (SD 12.2); Heparin group with ST segment elevation: mean 63.9 (SD 12.0) Male/Female ratio: 3093/917 (ST segment elevation) Ethnicity: not reported Italy, Netherlands, Spain, Sweden	STE-ACS/STEMI all cause mortality (30 days) STE-ACS/STEMI new myocardial infarction (30 days): re-infarction STE-ACS/STEMI complications related to bleeding (30 days): major (BARC) STE-ACS/STEMI stent thrombosis (30 days): definite stent thrombosis (acute and subacute) STE-ACS/STEMI stent thrombosis (30 days): acute, definite STE-ACS/STEMI stent thrombosis (30 days): subacute, definite STE-ACS/STEMI stent thrombosis (30 days): acute, definite or probable STE-ACS/STEMI stent thrombosis (30 days):	Setting: hospital/'centre' Concurrent medication/care: Use of other drugs was allowed as per guidelines

Study	Intervention and comparison	Population	Outcomes	Comments
	based on activated clotting time was again left to the discretion of the investigator **Selective/ bail out use of GPI** (selective: n=613/1998; 30.7%; bail out: n=86/1998; 4.3%; administered before percutaneous coronary intervention based on investigator judgement)		subacute, definite or probable STE-ACS/STEMI stroke (30 days): any, type not specified	
The BRIGHT trial (Han 2015[17])	Intervention (n=735; mixed population): **Bivalirudin** given as a bolus of 0.75mg/kg followed by infusion of 1.75mg/kg/h during the PCI procedure and for at least 30 minutes but no more than 4 hours afterwards. Following this mandatory infusion, a reduced-dose infusion (0.2mg/kg/h) for up to 20 hours could be administered at physician discretion. An additional bivalirudin bolus of 0.3mg/kg was given if the activated clotting time 5 minutes after the initial bolus was less than 225 seconds. **Bailout (provisional) GPI** (n=32/735; 4.4% of STEMI/NSTEMI patients; tirofiban) Comparison (n=729; mixed population): **Heparin (type**	n=2194 (mixed population); n=1925 (STEMI subgroup) People with acute myocardial infarction including ST segment elevation myocardial infarction and non-ST segment elevation myocardial infarction and undergoing PPCI Age (range): 18-80 years Male/Female ratio: 1605/320 (STEMI) Ethnicity: not reported China	STEMI all cause mortality (30 days) STEMI cardiac mortality (30 days) STEMI new myocardial infarction (30 days): reinfarction STEMI complications related to bleeding (30 days): major and minor (BARC) STEMI all cause mortality (1 year) STEMI cardiac mortality (1 year) STEMI new myocardial infarction (1 year): reinfarction	Setting: hospital Concurrent medication/care: All patients received an oral loading dose prior to PCI of 300mg aspirin if not taking aspirin long-term (100-300mg otherwise) and 300-600mg clopidogrel if not taking long-term clopidogrel. Prasugrel and ticagrelor were not available for use during the trial. Other cardiovascular medications were given in accordance with current guidelines. Decisions regarding selection of access site, use of aspiration and stent type were at the operator discretion pursuant to local standards of care

Study	Intervention and comparison	Population	Outcomes	Comments
	unspecified) only (bolus dose of 100 U/kg administered according to current guidelines. Additional heparin was administered if the post-bolus activated clotting time was less than 225 seconds) **Bail out (provisional) GPI** (n=41/729; 5.6% of STEMI/NSTEMI patients; tirofiban) Comparison (n=730; mixed population): **Heparin (type unspecified) and routine GPI** (heparin 60 U/kg and tirofiban 10µg/kg boluses were given followed by a 0.15µg/kg/min tirofiban infusion for 18 to 36 hours. Additional heparin was administered if the postbolus activated clotting time was less than 200 seconds); 100% routine GPI use		STEMI repeat revascularisation (30 days): ischaemia-driven revascularisation – ischaemic target vessel revascularisation STEMI repeat revascularisation (1 year): ischaemic target vessel revascularisation STEMI stent thrombosis (<24 hours): acute STEMI stent thrombosis (1-30 days): subacute STEMI stent thrombosis (30 days): definite STEMI stent thrombosis (30 days): probable STEMI stent thrombosis (1 year): definite STEMI stent thrombosis (1 year): probable stent thrombosis STEMI stroke (30 days): any, type not specified	

Study	Intervention and comparison	Population	Outcomes	Comments

See appendix D for full evidence tables.

1.5.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Bivalirudin ± bailout glycoprotein inhibitor versus heparin + routine glycoprotein inhibitor

Outcomes and follow up	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with heparin + routine GPI	Risk difference with Bivalirudin ± bailout GPI (95% CI)
All cause mortality – at 30 days	7343 (4 studies)	⨁⨁⨁⊖ MODERATE[1] due to imprecision	RR 0.74 (0.56 to 0.99)	31 per 1000	8 fewer per 1000 (from 0 fewer to 14 fewer)
All cause mortality – at 1 year	7084 (3 studies)	⨁⨁⨁⊖ MODERATE[1] due to imprecision	RR 0.82 (0.65 to 1.02)	48 per 1000	9 fewer per 1000 (from 17 fewer to 1 more)
Cardiac mortality – at 30 days	7343 (4 studies)	⨁⨁⨁⊖ MODERATE[1] due to imprecision	RR 0.68 (0.5 to 0.92)	26 per 1000	8 fewer per 1000 (from 2 fewer to 13 fewer)

Outcomes and follow up	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with heparin + routine GPI	Risk difference with Bivalirudin ± bailout GPI (95% CI)
Cardiac mortality – at 1 year	7084 (3 studies)	⨁⨁⨁⨀ MODERATE[1] due to imprecision	RR 0.71 (0.55 to 0.92)	37 per 1000	11 fewer per 1000 (from 3 fewer to 17 fewer)
Definite and probable stent thrombosis (up to 30 days)	6865 (4 studies)	⨁⨁⨁⨀ MODERATE[1] due to imprecision	RR 1.4 (0.95 to 2.05)	14 per 1000	6 more per 1000 (from 1 fewer to 15 more)
Definite and probable stent thrombosis (up to 1 year)	4886 (2 studies)	⨁⨁⨀⨀ LOW[1] due to imprecision	RR 1.12 (0.79 to 1.59)	19 per 1000	2 more per 1000 (from 4 fewer to 11 more)
Repeat revascularisation (ischaemia-driven revascularisation)- at 30 days	7343 (4 studies)	⨁⨁⨁⨀ MODERATE[1] due to imprecision	RR 1.33 (0.97 to 1.84)	17 per 1000	6 more per 1000 (from 1 fewer to 14 more)
Repeat revascularisation (ischaemic TVR)- at 1 year	4886 (2 studies)	⨁⨁⨁⨀ MODERATE[1] due to imprecision	RR 1.22 (0.96 to 1.56)	37 per 1000	8 more per 1000 (from 1 fewer to 21 more)
Repeat revascularisation (ischaemic TLR) - 1 year	3602 (1 study)	⨁⨁⨁⨀ MODERATE[1] due to imprecision	RR 1.34 (1 to 1.79)	43 per 1000	15 more per 1000 (from 0 more to 34 more)
Repeat revascularisation (ischaemic remote TVR) - 1 year	3602 (1 study)	⨁⨁⨀⨀ LOW[1]	RR 1.15 (0.73 to 1.81)	19 per 1000	3 more per 1000 (from 5 fewer to 15 more)

Outcomes and follow up	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with heparin + routine GPI	Risk difference with Bivalirudin ± bailout GPI (95% CI)
		due to imprecision			
New myocardial infarction (reinfarction) - 30 days	7343 (4 studies)	⨁⨁⨁⊖ MODERATE[1] due to imprecision	RR 1.2 (0.83 to 1.73)	13 per 1000	3 more per 1000 (from 2 fewer to 9 more)
New myocardial infarction (reinfarction)- 1 year	4886 (2 studies)	⨁⨁⨁⊖ MODERATE[1] due to imprecision	RR 0.86 (0.63 to 1.16)	29 per 1000	4 fewer per 1000 (from 11 fewer to 5 more)
Complications related to bleeding (major including BARC 3-5)- 30 days	7355 (4 studies)	⨁⨁⨁⨁ HIGH	RR 0.52 (0.42 to 0.65)	42 per 1000	20 fewer per 1000 (from 15 fewer to 24 fewer)
Complications related to bleeding (minor including TIMI and BARC 2)- 30 days	7343 (4 studies)	⨁⨁⨁⊖ MODERATE[2] due to risk of bias	RR 0.62 (0.49 to 0.78)	46 per 1000	17 fewer per 1000 (from 10 fewer to 23 fewer)
Stroke (any, type not specified) -30 days	5145 (3 studies)	⨁⨁⊖⊖ LOW[1] due to imprecision	Peto OR 1.11 (0.57 to 2.19)	6 per 1000	1 more per 1000 (from 3 fewer to 7 more)
Stroke (ischaemic) -30 days	2198 (1 study) 30 days	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	Peto OR 0.68 (0.25 to 1.88)	8 per 1000	3 fewer per 1000 (from 6 fewer to 7 more)

Outcomes and follow up	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with heparin + routine GPI	Risk difference with Bivalirudin ± bailout GPI (95% CI)
Stroke (haemorrhagic)	2198 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	Peto OR 0.14 (0.01 to 2.2)	2 per 1000	2 fewer per 1000 (from 2 fewer to 2 more)

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 4: Clinical evidence summary: Bivalirudin ± bailout/selective glycoprotein inhibitor versus heparin ± bailout/selective glycoprotein inhibitor

Outcomes and follow up	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with heparin ± bailout/ selective GPI	Risk difference with bivalirudin ± bailout/selective GPI (95% CI)
All cause mortality – at 28-30 days	7118 (3 studies)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.85 (0.65 to 1.12)	31 per 1000	5 fewer per 1000 (from 11 fewer to 4 more)
All cause mortality - unclear timepoint	78 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.05 (0.07 to 16.24)	25 per 1000	1 more per 1000 (from 23 fewer to 381 more)
All cause mortality – at 1 year	1296 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.73 (0.35 to 1.54)	25 per 1000	7 fewer per 1000 (from 16 fewer to 13 more)
Cardiac mortality – at 30 days	1296 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.6 (0.25 to 1.44)	20 per 1000	8 fewer per 1000 (from 15 fewer to 9 more)
Cardiac mortality - at 1 year	1296 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.65 (0.3 to 1.44)	23 per 1000	8 fewer per 1000 (from 16 fewer to 10 more)
Definite and probable stent thrombosis (up to 30 days) - Bailout only GPI	5306 (2 studies)	⨁⨁⊖⊖ LOW[1,2]	RR 1.37 (0.83 to 2.26)	10 per 1000	4 more per 1000 (from 2 fewer to 12 more)

Outcomes and follow up	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with heparin ± bailout/ selective GPI	Risk difference with bivalirudin ± bailout/selective GPI (95% CI)
		due to risk of bias, imprecision			
Definite and probable stent thrombosis (up to 30 days) - Bailout and selective GPI	1379 (1 study)	⨁⨁⨁⊖ MODERATE[1] due to risk of bias	RR 3.91 (1.61 to 9.52)	9 per 1000	26 more per 1000 (from 5 more to 75 more)
Definite and probable stent thrombosis (up to 1 year)	1296 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.62 (0.24 to 1.6)	17 per 1000	6 fewer per 1000 (from 13 fewer to 10 more)
Repeat revascularisation (ischaemic target vessel revascularisation; bailout only GPI)- at 30 days	1296 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.82 (0.35 to 1.87)	19 per 1000	3 fewer per 1000 (from 12 fewer to 17 more)
Repeat revascularisation (unplanned target lesion revascularisation; bailout and selective GPI)- 28 days	1812 (1 study)	⨁⨁⨁⊖ MODERATE[1] due to risk of bias	RR 4.01 (1.65 to 9.76)	7 per 1000	21 more per 1000 (from 5 more to 61 more)
Repeat revascularisation (ischaemic target vessel revascularisation)- at 30 days	1296 (1 study) 1 year	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.98 (0.46 to 2.09)	20 per 1000	0 fewer per 1000 (from 11 fewer to 22 more)

Outcomes and follow up	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with heparin ± bailout/ selective GPI	Risk difference with bivalirudin ± bailout/selective GPI (95% CI)
New myocardial infarction (myocardial infarction/reinfarction)- at 28-30 days	7118 (3 studies)	⨁⊖⊖⊖ VERY LOW[1,2,4] due to risk of bias, inconsistency, imprecision	RR 1.48 (0.8 to 2.76)	13 per 1000	6 more per 1000 (from 3 fewer to 23 more)
New myocardial infarction (reinfarction)- at 1 year	1296 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.07 (0.47 to 2.4)	17 per 1000	1 more per 1000 (from 9 fewer to 24 more)
Complications related to bleeding (major, BARC 3-5)- at 28-30 days	7118 (3 studies)	⨁⊖⊖⊖ VERY LOW[1,2,5] due to risk of bias, inconsistency, imprecision	RR 0.7 (0.38 to 1.29)	27 per 1000	8 fewer per 1000 (from 17 fewer to 8 more)
Complications related to bleeding (minor, BARC 2; bailout only GPI)- at 30 days	1296 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.38 (0.13 to 1.05)	20 per 1000	12 fewer per 1000 (from 17 fewer to 1 more)
Complications related to bleeding (minor, BARC 2; bailout and selective GPI)- at 28 days	1812 (1 study)	⨁⨁⊖⊖ LOW[1,2] due to risk of	RR 0.85 (0.64 to 1.12)	108 per 1000	16 fewer per 1000 (from 39 fewer to 13 more)

Outcomes and follow up	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with heparin ± bailout/ selective GPI	Risk difference with bivalirudin ± bailout/selective GPI (95% CI)
		bias, imprecision			
Stroke (any, type not specified)- at 30 days	5306 (2 studies)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	Peto OR 0.51 (0.25 to 1.04)	8 per 1000	4 fewer per 1000 (from 6 fewer to 0 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
3 Risk difference calculated in Review Manager
4 Downgraded by 1 or 2 increments because heterogeneity, I2= 59%, p= 0.09, unexplained by subgroup analysis
5 Downgraded by 1 or 2 increments because heterogeneity, I2= 65%, p= 0.06, unexplained by subgroup analysis

See appendix F for full GRADE tables.

1.6 Economic evidence

1.6.1 Included studies

One health economic analysis was included that compared bivalirudin +/- bailout/selective GPI versus heparin + routine GPI.[46] Note that this is the analysis undertaken to inform TA230.[33] This is summarised in the health economic evidence profile below (Table 5) and the health economic evidence table in appendix H.

No relevant health economic analyses were identified that compared bivalirudin +/- bailout/selective GPI versus heparin + bailout/selective GPI.

1.6.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G.

1.6.3 Summary of studies included in the economic evidence review

Table 5: Health economic evidence profile: bivalirudin +/- selective/bailout GPIs versus heparin + routine GPIs in STEMI

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Schwenkglenks 2012[46] (UK) *Analysis informed NICE TA230[33]*	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Decision tree based on within trial analysis of 1 year / 3 year clinical event data and resource use from HORIZONS-AMI RCT; followed by Markov model to extrapolate. • Cost utility analysis (QALYs) • Population: acute STEMI (majority PPCI) • Comparators ○ Heparin + routine GPI (95.3%) ○ Bivalirudin (bailout GPI use allowed, 7.6%) • Time horizon: lifetime	***1 year trial data*** -£267[(c)] ***3 year trial data*** -£250[(c)]	***1 year trial data*** 0.09 QALYs ***3 year trial data*** 0.11 QALYs	***1 year trial data*** Bivalirudin dominant ***3 year trial data*** Bivalirudin dominant	***1 year trial data*** Probability bivalirudin cost effective (£20K/30K threshold): 99.2%/NR (and cost saving 95.0%). ICER in sensitivity analyses: bivalirudin dominant to £5,428. ***3 year trial data*** Probability bivalirudin cost effective (£20K/30K threshold): NR/NR (noted as similar to the main analysis)

Abbreviations: GPI = glycoprotein inhibitor; ICER = incremental cost-effectiveness ratio; NR = not reported; PPCI = primary percutaneous coronary intervention; QALY = quality-adjusted life years; RCT = randomised controlled trial

(a) Comparator is heparin + GPI (95% use) - heparin plus lower GPI use (bailout only or selective use) not included in analysis. International resource use from 2005-2007 and UK 2009/10 unit costs may not reflect the current UK context. Note that in this analysis differences in radial access in the UK at the time compared to in the study were attempted to be accounted for through modelling. Length of stay data from the study was also adjusted to account for lower UK length of stay. Differences in the type of GPI used in the UK compared to the trial were also accounted for in cost calculations.

(b) Analysis based on a single study (HORIZONS-AMI) and so does not reflect full body of available evidence for this area (4 RCTs included in clinical review comparing bivalirudin with bailout GPIs and heparin with routine GPIs – overall mortality and MI effect size estimates from the meta-analysis in the clinical review for this comparison were slightly less favourable than in the HORIZONS-AMI RCT individually; revascularisation effect sizes were very similar; bleeding effect sizes were generally similar or slightly more favourable). Study funded by The Medicines Company.

(c) Cost components included: bivalirudin, GPIs, initial hospital length of stay, procedures (angiography, PCI, CABG), event costs (reinfarction, stroke, major and minor bleeds), long term annual cardiovascular treatment costs for survivors. The cost of heparin was considered insignificant and was omitted from the model.

No relevant health economic analyses were identified that compared bivalirudin +/- bailout/selective GPI versus heparin + bailout/selective GPI.

1.6.4 Health economic modelling

This area was not prioritised for new cost-effectiveness analysis.

1.6.5 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness. Table 6 summarises unit costs for bivalirudin, heparin and GPIs.

Table 6: UK unit costs of bivalirudin, heparin and GPIs

Drug	Cost per vial	
	List price	Average NHS cost
Bivalirudin		
Bivalirudin 250mg powder for concentrate for solution for infusion vials (Accord Healthcare Ltd)	£175.00	n/a
Heparin[(a)]		
Heparin sodium 5,000units/5ml solution for injection vials (LEO Pharma)	£1.65	£1.67
Heparin sodium 25,000units/5ml solution for injection vials (LEO Pharma)	£4.50	£2.39
GPIs		
Abciximab		
ReoPro 10mg/5ml solution for injection vials (Janssen-Cilag Ltd)	£250.24	n/a
Eptifibatide		
Eptifibatide 20mg/10ml solution for injection vials (Accord Healthcare Ltd)	£5.14	£12.24
Integrilin 20mg/10ml solution for injection vials (GlaxoSmithKline UK Ltd)	£13.61	
Eptifibatide 75mg/100ml solution for infusion vials (Accord Healthcare Ltd)	£17.14	£38.44
Integrilin 75mg/100ml solution for infusion vials (GlaxoSmithKline UK Ltd)	£42.79	
Tirofiban		
Tirofiban 12.5mg/250ml infusion bags (Aspire Pharma Ltd)	£160.72	£84.97
Tirofiban 12.5mg/250ml infusion bags (Bowmed Ibisqus Ltd)	£159.00	

Source: List prices are the NHS indicative prices are from the BNF accessed July 2018[20]; NHS average costs are from eMIT (based on average of costs March to June 2017)[6]
(a) Unfractionated heparin is generally used in PPCI in UK practice. Many different preparations and manufacturers are available; these are example costs.

Comparative cost calculations

Table 7 summarises comparative drug costs for bivalirudin and heparin based strategies taking account of GPI use with each. This includes the costs used in the HORIZONS-AMI cost effectiveness analysis included above and then also presents updated costs using current drug costs, current GPI usage data and different GPI use scenarios. It includes the following four cost calculations:

1. **HORIZONS-AMI analysis costing.** Drug costs as used in the HORIZONS-AMI cost effectiveness analysis included above.[46] In this drug costs alone are lower with bivalirudin (bailout GPI use allowed) than with a heparin + routine GPI strategy by around £150. Heparin costs were not included as they were considered 'insignificant'.[46] See discussion after table below regarding heparin costs.
2. **Updated unit costs and latest UK data about types of GPIs used; other inputs as in HORIZONS-AMI costing.** Drug unit costs have been updated to current costs where unit costs have generally reduced. The relative usage of different GPIs has also been updated

to reflect current audit data; primarily that use of abciximab has reduced and tirofiban increased; eptifibatide use is also slightly higher. Other data is the same as used in scenario 1, that is all the GPI usage data is the same as in the AMI-HORIZONS cost effectiveness analysis. The aim of this scenario is to try and look at a comparison that better reflects current UK costs. In this the cost of bivalirudin with bailout GPI use is similar to the cost of heparin with routine GPI use.

3. **Updated unit costs and latest UK GPI usage data.** Drug unit costs and relative GPI usage inputs have been updated as in scenario 2 and GPI usage in the heparin + GPI group has also been changed to reflect current UK practice where not everyone gets a GPI when using heparin; latest audit data (2016) reported 38% of PPCI used a GPI. The aim of this scenario is to try and look at a comparison that better reflects a true to life comparison of drug costs not just what happened in the trial. In this the cost of bivalirudin with bailout GPI use is higher than the cost of heparin with selective GPI use by around £140.
4. **Updated unit costs and heparin with bailout GPI use only**. Drug unit costs and GPI usage split have been updated as in scenarios 2 and 3 and GPI usage in the heparin + GPI group has also been changed to reflect a scenario where only bailout GPI use occurs; audit data show a downward trend in GPI use and so current use may be lower than in 2016 and this is the scenario analysed in the UK HEAT RCT included in the clinical review. GPI usage in the bivalirudin arm has also been updated to match that in the HEAT RCT. GPI vial usage has also been changed in the heparin arm so it is the same as in the bivalirudin arm where bailout GPI is also used. In this the cost difference with bivalirudin increased to around £200.

Table 7: Comparative drug cost calculations for bivalirudin and heparin based strategies (including GPI use) in STEMI; underlined values indicate changes compared to the previous scenario

Description	% usage	Mean vials	Cost per vial	Cost per person
1. HORIZONS-AMI analysis costing (2009/10 unit costs)[a]				
Bivalirudin (bailout GPI use allowed)				
Bivalirudin	97%	1.23	£310.00	£369
GPI	8%			£41
• *Abciximab 10mg*	*73%*	*2.8*	*£250.00*	
• *Eptifibatide 20mg*	*8%*	*1.64*	*£14.00*	
• *Tirofiban 12.5mg*	*19%*	*1*	*£161.00*	
TOTAL				**£411**
Heparin + routine GPI				
Heparin				Not included[e]
GPI	95%			£565
• *Abciximab 10mg*	*73%*	*3.07*	*£250.00*	
• *Eptifibatide 20mg*	*8%*	*1.88*	*£14.00*	
• *Tirofiban 12.5mg*	*19%*	*1*	*£161.00*	
TOTAL				£565
Difference with bivalirudin (bailout GPI use allowed) compared to heparin + routine GPI				**-£154**
2. Updated unit costs and latest UK data about type of GPIs used; GPI usage as in HORIZONS AMI costing[b]				
Bivalirudin (bailout GPI use allowed)				
Bivalirudin	97%	1.23	£175.00	£209
GPI	8%			£15

• *Abciximab 10mg*	*22%*	*2.8*	*£250.24*	
• *Eptifibatide 20mg*	*20%*	*1.64*	*£5.14*	
• *Tirofiban 12.5mg*	*58%*	*1*	*£84.97*	
TOTAL				**£224**
Heparin + routine GPI				
Heparin				Not included[e]
GPI	95%			£208
• *Abciximab 10mg*	*22%*	*3.07*	*£250.24*	
• *Eptifibatide 20mg*	*20%*	*1.88*	*£5.14*	
• *Tirofiban 12.5mg*	*58%*	*1*	*£84.97*	
TOTAL				**£208**
Difference with bivalirudin (bailout GPI use allowed) compared to heparin + routine GPI				**£16**
3. Updated unit costs and latest UK data on type of GPIs used and GPI usage alongside heparin[c]				
Bivalirudin (bailout GPI use allowed)				
Bivalirudin	97%	1.23	£175.00	£209
GPI	8%			£15
• *Abciximab 10mg*	*22%*	*2.8*	*£250.24*	
• *Eptifibatide 20mg*	*20%*	*1.64*	*£5.14*	
• *Tirofiban 12.5mg*	*58%*	*1*	*£84.97*	
TOTAL				**£224**
Heparin + bailout/selective use				
Heparin				Not included[e]
GPI	38%			£82
• *Abciximab 10mg*	*22%*	*3.07*	*£250.24*	
• *Eptifibatide 20mg*	*20%*	*1.88*	*£5.14*	
• *Tirofiban 12.5mg*	*58%*	*1*	*£84.97*	
TOTAL				**£82**
Difference with bivalirudin (bailout GPI use allowed) compared to heparin + bailout/selective GPI				**£142**
4. Updated unit costs and heparin with bailout GPI use only (as in HEAT RCT)[d]				
Bivalirudin (bailout GPI use allowed)				
Bivalirudin	97%	1.23	£175.00	£209
GPI	13%			£26
• *Abciximab 10mg*	*22%*	*2.8*	*£250.24*	
• *Eptifibatide 20mg*	*20%*	*1.64*	*£5.14*	
• *Tirofiban 12.5mg*	*58%*	*1*	*£84.97*	
TOTAL				**£235**
Heparin (bailout GPI use allowed)				
Heparin				Not included[e]
GPI	15%			£30
• *Abciximab 10mg*	*22%*	*2.8*	*£250.24*	
• *Eptifibatide 20mg*	*20%*	*1.64*	*£5.14*	
• *Tirofiban 12.5mg*	*58%*	*1*	*£84.97*	
TOTAL				**£30**

Difference with bivalirudin (bailout GPI use allowed) compared to heparin (bailout GPI use allowed)				**£205**

(a) The HORIZONS-AMI cost effectiveness analysis used usage of bivalirudin and GPIs from the study combined with UK specific data regarding the relative use of abciximab, eptifibatide and tirofiban.[46] Average vial usage was estimated from the trial. Costs are those used at the time of the analysis (2009/10 cost year).The total costs vary slightly from those reported in the study report presumably because inputs were reported rounded but used unrounded.

(b) Unit costs have been updated using average NHS costs from the eMIT database (based on average of costs March to June 2017)[6] where available and NHS indicative prices from the BNF (11th July 2018) where not[20]; however, if eMIT cost data is available but the average is higher than the current generic indicative price, this is used. Relative use of abciximab, eptifibatide and tirofiban has been updated based on usage in PCI from 2016 audit data, PPCI specific data was not reported.[28] Other inputs are the same as in the HORIZONS-AMI cost-effectiveness analysis.

(c) Unit costs and relative GPI usage have been updated as in scenarios 2 and 3. Overall GPI usage has also been updated to reflect current UK usage based on 2016 audit data in PPCI suggesting more selective use of GPIs.[28]

(d) Unit costs and relative GPI usage have been updated as in scenarios 2 and 3. GPI usage in the heparin + GPI group has also been changed to reflect a scenario where only bailout GPI use occurs; audit data show a downward trend in GPI use and so current use may be lower than in 2016 and this is the scenario analysed in the UK HEAT RCT included in the clinical review. GPI vial usage also changed in the heparin arm so it is the same as in the bivalirudin arm where bailout GPI is also used.

(e) Heparin costs were not included in the HORIZONS-AMI cost effectiveness analysis as they were considered 'insignificant' and so have been excluded here also.[46] Cost of heparin is discussed below.

Cost of heparin

Unfractionated heparin is generally used in PPCI in UK practice. Heparin is low cost and so has been excluded from the costing above in line with the approach taken in the published cost effectiveness analysis which reports the costs as 'insignificant'.[46]

An initial bolus of heparin is injected. There is no standard dose but an example dose is 70U/kg as used in the UK-based HEAT RCT.[47] Using this dose, a bodyweight of 80kg and the unit cost of £2.39 for a 25,000units/5ml solution for injection vial (assuming multiuse vial so no wastage) this would be a cost of £0.88. Additional heparin may also be required although this will depend on unpredictable factors including individual patient response to heparin and the duration of the procedure.

People react differently to heparin and generally activated clotting time will be monitored during the PPCI procedure to determine whether additional heparin boluses are required. The number of ACT measurements required during a PPCI procedure will depend on unpredictable factors including individual patient response to heparin and the duration of the procedure. It was noted in the NICE technology appraisal report that "bivalirudin may require less monitoring"; however, this cost was not incorporated into the cost effectiveness analysis and so is considered likely to result in only a small difference in cost.[33]

1.7 Evidence statements

1.7.1 Clinical evidence statements

Bivalirudin ± bailout glycoprotein inhibitor versus heparin + routine glycoprotein inhibitor

- Four studies compared bivalirudin with/without bailout use of a glycoprotein inhibitor (4.4-7.9%) against heparin with/without routine use (including >50% routine use) of a glycoprotein inhibitor (GPI).

- There was a clinically important benefit in favour of bivalirudin with/without bailout use of a GPI compared to heparin with routine GPI for all cause mortality and cardiac mortality at 30 days (7343 participants in 4 studies, modrate quality evidence) and for all cause

and cardiac mortality at 1 year (7084 participants in 3 studies, moderate quality evidence).

- There was also a clinically important benefit in favour of bivalirudin with/without bailout use of a GPI compared to heparin with routine GPI for the outcome of complications related to bleeding (major including BARC 3-5) (7355 participants in 4 studies, high quality evidence).

- There was no clinically important difference in new myocardial infarction at 30 days (7343 participants in 4 studies, moderate quality evidence) and 1 year (4886 participants in 2 studies, moderate quality evidence), complications related to bleeding (minor including TIMI and BARC 2) (7343 participants in 4 studies, modrate quality evidence), repeat revascularisation (up to 7343 participants in 4 studies, low to moderate quality evidence, stent thrombosis (up to 6865 participants in 4 studies, low to moderate quality evidence) and stroke at 30 days (up to 5145 participants in 3 studies, very low to low quality evidence).

- The main reasons for downgrading evidence included imprecision and risk of bias.

Bivalirudin ± bailout/selective glycoprotein inhibitor versus heparin ± bailout/selective glycoprotein inhibitor

- Four studies compared bivalirudin with/without bailout and selective use of a GPI (4.4-13%) against heparin with/without bailout and selective use of a GPI (5.6-35%).

- There was a clinically important benefit in favour of bivalirudin with/without bailout use of a GPI compared to heparin with or without selective/bailout GPI for all cause mortality at 30 days (7118 participants in 3 studies, very low quality evidence) and at 1 year; and for cardiac mortality at 30 days and 1 year (1296 participants in 1 study, very low quality evidence) .

- There was a clinically important harm in definite and probable stent thrombosis at 30 days (1379 participants in 1study, moderate quality evidence) and for repeat revascularisation (unplanned TLR; 1812 participants in 1 study, moderate quality evidence) when using bivalirudin with bailout and selective use of a GPI compared to heparin with or without selective/bailout GPI.

- There was no clinically important difference in definite and probable stent thrombosis with bailout GPI (5306 participants in 2 studies, low quality evidence), definite and probable stent thrombosis at 1 year (1296 participants in 1 study, very low quality evidence), repeat revascularisation at 30 days (up to 1812 participants in 1 study, very low to moderate quality evidence).

- There was no clinically important difference in new MI and complications related to major bleeing (BARC 3-5) at 30 days (7118 participants in 3 studies, very low quality evidence), new MI at 1 year and complications related to minor bleeding (BARC 2) with bailout only GPI 30 days (1296 participants in 1 study, very low quality evidence) and complications related to minor bleeding (BARC 2) with bailout and selective GPI at 30 days (1812 participants in 1 study, low quality evidence) .

- There was no clinically important difference in stroke at 30 days (5306 participants in 2 studies, very low quality evidence) .
- The main reasons for downgrading evidence included risk of bias, imprecision and inconsistency.

1.7.2 Health economic evidence statements

- One cost-utility analysis found that bivalirudin (bailout GPI use allowed, 8%) was cost effective compared to heparin + routine GPI use (bivalirudin had lower costs and higher QALYs). This analysis was assessed as partially applicable with potentially serious limitations.
- No relevant published economic evidence was identified that compared bivalirudin +/- bailout/selective GPI versus heparin +/- bailout/selective GPI.

1.8 The committee's discussion of the evidence

1.8.1 Interpreting the evidence

1.8.1.1 The outcomes that matter most

The committee agreed that outcomes critical for decision making were mortality up to 30 days (all-cause and cardiac), new myocardial infarction up to 30 days, complications related to bleeding, and health-related quality of life.

Mortality at 1 year (all-cause and cardiac), new myocardial infarction at 1 year, repeat revascularisation, stent thrombosis, stroke up to 30 days and length of hospital stay were also considered important outcomes.

1.8.1.2 The quality of the evidence

The quality of the evidence ranged from a GRADE rating of very low to high. The main reasons for downgrading the quality of the evidence were risk of bias, imprecision and inconsistency. The presence of selection bias in terms of lack of adequate randomisation and allocation concealment commonly resulted in a high or very high risk of bias rating but this is unlikely to have systematically favoured one intervention over the other.

Evidence was reported for mortality (all-cause and cardiac) at 28-30 days and 1 year, new myocardial infarction at 28-30 days and 1 year, complications related to bleeding, repeat revascularisation, stent thrombosis, and stroke at 30 days. There was no evidence for health-related quality of life. There was no clinical evidence on length of hospital stay.

For the purposes of this review, bleeding scores were considered 'major' or 'minor' according to author and bleeding scale definitions. Where studies reported bleeding on multiple scales, the most relevant available scale was used in the meta-analysis based on a hierarchy as per the protocol.

No data were found comparing bivalirudin and heparin with routine GPI use in both arms. However, studies were available comparing bivalirudin and heparin with bailout GPI use, and this is more relevant to current clinical practice.

1.8.1.3 Benefits and harms

The committee considered the evidence for bivalirudin with or without bailout GPI compared with heparin with routine GPI use. This was the comparison that was considered relevant at the time of TA230 as GPIs were widely used routinely during PPCI. They noted that bivalirudin was associated with lower mortality (all-cause and cardiac at 30 days and 1 year), and that there was a convincing benefit of bivalirudin in reducing major bleeding complications (within 30 days). There was no clinical difference between interventions for new myocardial infarction (at 30 days and 1 year).

The committee considered the evidence for bivalirudin with or without bailout/selective GPI compared with heparin with or without bailout/selective GPI use. The committee agreed that this comparison is most relevant to current UK practice; 2016 audit data reported GPI use as 38% during PPCI and the committee noted that there has been a downward trend in usage of GPI over the past 10 years (from a high of 80% in 2007) and agreed that it is likely that current usage is even lower. They noted there was evidence in favour of bivalirudin with or without bailout/selective GPI for mortality (all-cause mortality and cardiac at 30 days and 1 year) but conversely, evidence in favour of heparin with or without bailout/selective GPI for all-cause mortality at an unspecified time point. Although any mortality difference is potentially important, the committee noted that the differences between treatment arms were very imprecise and consequently they were not confident about applying these mortality data to recommendations.In addition the committee observed that in the UK HEAT RCT the mortality effect actually favoured heparin with bailout GPI. While this study is accounted for in the 30 day mortality meta-analysis, the committee highlighted a number of aspects to this study that make it particularly relevant for UK decision making. Firstly it was a UK study and directly reflects UK practices, for example use of radial versus femoral access which varies between country settings. In the UK radial access is widely used and is associated with lower bleeding rates which may affect the potential for bivalirudin to show a benefit (see next paragraph). In addition, the study was non-selective meaning that, unusually for an RCT, it reflects the full range of PPCI cases seen in the UK. Taking all these factors into account the committee concluded that there was not clear evidence of a mortality benefit for bivalirudin with bailout GPI when compared with heparin with bailout/selective GPI. They noted moderate quality evidence in favour of heparin with or without bailout/selective GPI for unplanned target lesion revascularisation and for definite and probable stent thrombosis. There was no difference between the treatments for complications related to bleeding or new myocardial infarction (at 28-30 days and 1 year). The direction of effect for major bleeding was in favour of bivalirudin but there was imprecision, and it was also noted that in the UK HEAT RCT the direction of effect for major bleeding was in favour of heparin.

In interpreting this evidence the committee considered the importance of the access site for coronary intervention. In the past femoral artery puncture was standard, and sometimes this is still necessary, but in the UK and many other countries a radial approach is now preferred based on a definite reduction in bleeding risk. The committee therefore reasoned that differences in bleeding risk in those studies in which the femoral approach was used would have been less if the procedure was carried out via the radial artery. The BRIGHT study contradicts this argument as it showed the largest bleeding difference (favouring bivalirudin) despite 78.5% of procedures using radial access. However, this is a non-UK study with a number of differences to the UK context including giving a higher weight-adjusted dose of heparin to patients of lower weight, and the committee were not persuaded that it outweighed the other data and their own experience. After allowing for this, the committee considered that the benefit of using bivalirudin would be less than suggested by the overall meta-analysis of study data, except in those few cases in which a femoral artery approach has to be employed.

The committee concluded that heparin is probably superior to bivalirudin in preventing stent thrombosis and reducing the need for unplanned revascularisation procedures, whereas

there is an unconvincing benefit of bivalirudin in reducing bleeding complications as long as the radial artery approach is used.

1.8.2 Cost effectiveness and resource use

One published cost-effectiveness analysis was identified comparing bivalirudin with bailout GPI and heparin with routine GPI use. This was based on the HORIZONS-AMI RCT that was included in the clinical evidence review. This analysis using 2009/10 costs found that bivalirudin with bailout GPI had lower costs and higher QALYs and so was cost effective compared to heparin with routine GPI. Costs were lower with bivalirudin with bailout GPI in this analysis primarily due to lower drug costs (the cost savings from reduced GPI use were greater than the increased cost of using bivalirudin by around £150) and reduced length of stay in ICU that was attributed to reduced bleeding events. QALYs were higher with bivalirudin primarily due to a reduction in mortality. It was noted that drug costs have changed since the analysis was undertaken and when recalculated using current unit costs and UK data about type of GPI used in practice the cost of bivalirudin with bailout GPI use is now similar to the cost of heparin with routine GPI use. This would reduce the cost savings with bivalirudin reported in the published analysis. It was also noted that there are also now other RCTs comparing bivalirudin with bailout GPI and heparin with routine GPI. Estimates of effect size from the meta-analysis of all available studies were mostly similar or worse than in the HORIZONS-AMI study alone. In particular the relative effect size for mortality was slightly reduced which would reduce QALY gains. The major bleeding effect size was however slightly greater. No additional length of stay data was identified.

As noted in the previous section the committee highlighted that GPIs are no longer used routinely in the UK. This therefore limits the relevance of the published cost effectiveness analysis discussed above.

No published economic evaluations were identified comparing bivalirudin with bailout GPI and heparin with bailout or selective GPI use. The committee therefore considered estimates of the drug costs for bivalirudin with bailout GPI compared with heparin with selective or bailout GPI use. Drug costs were higher with bivalirudin by around £140 to £200 depending on the GPI usage scenario alongside heparin. No length of stay data was identified for this comparison to allow assessment of whether savings would still be seen due to reduced length of stay with bivalirudin. The committee however concluded that there was not clear evidence of a reduction in bleeding – given this, saving from reductions in length of stay may also have diminished or disappeared. Overall the committee concluded that bivalirudin would result in higher costs without clear evidence of clinical benefit when compared to heparin with bailout/selective GPI and so was not considered cost effective.

The committee agreed that it was feasible that bivalirudin with bailout GPI may be cost effective for people where femoral access is required. Use of femoral access is associated with higher bleeding risk and there is therefore greater potential for a benefit in terms of bleeding reduction – given this it could be that cost savings would be seen that could offset additional drug costs. For example due to reduced length of stay as in the published cost effectiveness analysis discussed above. In addition, it is feasible that a QALY gain would be seen if this results in reduced mortality.

The latest audit data report usage of bivalirudin in PCI for STEMI was 0.7% in 2017. GPI use was reported as 37.4% although the committee noted that there has been a downward trend in usage over the past 10 years (from a high of 80% in 2007) and agreed that it is likely that current usage is lower. They agreed that bailout GPI use is now the most common practice. They therefore concluded that a recommendation for heparin with bailout GPI use would not be a change in practice and would not result in a substantial resource impact to the NHS in the England. They also agreed that a recommendation to consider bivalirudin with bailout

GPI use when femoral access is required was also unlikely to change practice greatly or result in a substantial resource impact to the NHS in England as recent audit data shows that approximately 85.8% of PCIs for STEMI were undertaken using radial access, therefore only 14.2% used femoral access.

1.8.3 Other factors the committee took into account

The committee considered there to be a potential impact on outcomes of greater clinician experience and familiarity with use of heparin over bivalirudin in the UK. Those who had used bivalirudin commented that it is more complicated to administer than heparin, and that there is more scope for error.

One committee member expressed uncertainty regarding the availability of bivalirudin and noted that the Medicines Company no longer market it. Bivalirudin is however listed in the current BNF with costs from Accord Healthcare Ltd.

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Appendices

Appendix A: Review protocols

Table 8: Review protocol: Bivalirudin in STEMI

ID	Field	Content
0.	PROSPERO registration number	CRD42019131795
1.	Review title	What is the clinical and cost effectiveness of bivalirudin as adjunctive pharmacotherapy in adults with STEMI undergoing primary percutaneous coronary intervention?
2.	Review question	What is the clinical and cost effectiveness of bivalirudin as adjunctive pharmacotherapy in adults with STEMI undergoing primary percutaneous coronary intervention?
3.	Objective	The aim of this review is to compare the clinical effectiveness of bivalirudin against other anti-thrombins in patients with STEMI who undergo primary PCI
4.	Searches	The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Searches will be restricted by: English language Human studies Letters and comments are excluded. Other searches: Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Acute coronary syndromes
6.	Population	Inclusion: Adults 18 years and over with ST-segment elevation myocardial infarction intended for primary percutaneous coronary intervention.

ID	Field	Content
		Exclusion: None
7.	Intervention/Exposure/Test	Bivalirudin in combination with aspirin and an antiplatelet including clopidogrel, prasugrel or ticagrelor with or without glycoprotein IIb/IIIa inhibitors
8.	Comparator/Reference standard/Confounding factors	Heparin (unfractionated orlow molecular weight) with or without Glycoprotein IIb/IIIa Inhibitors in combination with aspirin and an antiplatelet
9.	Types of study to be included	Randomised Controlled Trials (RCT) Systematic Reviews (SR) of RCTs Non-randomised studies will be excluded.
10.	Other exclusion criteria	Randomised cross over trials Studies with UA/NSTEMI unless they report populations separately Studies which exclusively included patients undergoing elective PCI Non-English language studies Abstracts will be excluded as it is expected there will be sufficient full text published studies available
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	All-cause mortality – up to 30 days (specify if in hospital) Cardiac mortality – up to 30 days New myocardial infarction – up to 30 days Complications related to bleeding including haemorrhagic stroke – up to 30 days (access bleeding and non-access bleeding need to be differentiated)- the following hierarchy of bleeding scales will be used: BARC Author's definition TIMI GUSTO Where possible, bleeding outcomes will be categorised into: Major bleeding (including BARC 3-5 and as reported by author) Minor bleeding (including BARC 2, TIMI and as reported by author). Health-related quality of life including EQ5D and SF-36.
13.	Secondary outcomes (important outcomes)	All-cause mortality at 1 year Cardiac mortality at 1 year- Non-cardiac mortality at 1 year New myocardial infarction at 1 year

ID	Field	Content
		Repeat revascularisation Stent thrombosis (acute, early or late) Stroke - up to 30 days Length of hospital stay
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB (2.0) Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be

ID	Field	Content
		conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.
17.	Analysis of sub-groups	Use of GPI Type of antiplatelet (clopidogrel, prasugrel, ticagrelor) Number of stents Thrombus burden Ejection fraction Renal function (GFR- higher risk of bleeding)
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	19/06/18
22.	Anticipated completion date	14/05/20
23.	Stage of review at time of this submission	Review stage: Started / Completed Preliminary searches: ☐ / ☑ Piloting of the study selection process: ☐ / ☑ Formal screening of search results: ☐ / ☑

ID	Field	Content		
		against eligibility criteria		
		Data extraction	☐	☑
		Risk of bias (quality) assessment	☐	☑
		Data analysis	☐	☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail Acutecoronarysyndromes@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Dr Bernard Higgins [Guideline lead] Dr Saoussen Ftouh/Ms Sedina Lewis/ Miss Sophie Carlisle Ms Katherine Jones [Senior Systematic Reviewers; Systematic Reviewer] Ms Annabelle Davies/Ms Kate Lovibond [Health economist; Health economists lead] Ms Agnes Cuyas/Ms Jill Cobb [Information specialists]		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].		
29.	Other registration details			
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=131795		

ID	Field	Content	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Acute coronary syndrome, STEMI, bivalirudin	
33.	Details of existing review of same topic by same authors	N/A	
34.	Current review status	☐	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	N/A	
36.	Details of final publication	www.nice.org.uk	

Table 9: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2003 that were included in the previous guidelines will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[32]

Inclusion and exclusion criteria

- If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile.
- If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.
- If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2003 or later (including any such studies included in the previous guideline(s)) but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'.
- Studies published before 2003 (including any such studies included in the previous guidelines) will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.
- The following will be rated as 'Very serious limitations' and excluded: economic analyses undertaken as part of clinical studies that are excluded from the clinical review; economic models where relative treatment effects are based entirely on studies that are excluded from the clinical review.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[32]

For more information, please see the Methods report published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 10: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 22 July 2019	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 22 July 2019	Exclusions Randomised controlled trials Systematic review studies Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2019 Issue 7 of 7 CENTRAL to 2019 Issue 7 of 7	None

Medline (Ovid) search terms

1.	Acute Coronary Syndrome/ or Angina Pectoris/ or Angina, Unstable/ or Coronary Thrombosis/ or exp Myocardial Infarction/
2.	Heart Arrest/
3.	(acute coronary adj2 syndrome*).ti,ab.
4.	((myocardial or heart) adj infarct*).ti,ab.
5.	(heart adj (attack* or event*)).ti,ab.
6.	((heart or cardiac) adj arrest*).ti,ab.
7.	(coronary adj2 thrombos*).ti,ab.
8.	(stemi or st-segment or st segment or st-elevation or st elevation).ti,ab.
9.	"non-ST-segment elevation".ti,ab.
10.	(non-STEMI or NSTEMI or nonSTEMI).ti,ab.
11.	"Q wave myocardial infarction".ti,ab.
12.	"non Q wave MI".ti,ab.
13.	(NSTE-ACS or STE-ACS).ti,ab.
14.	(subendocardial adj3 infarct*).ti,ab.
15.	((unstable or variant) adj2 angina*).ti,ab.
16.	(unstable adj2 coronary).ti,ab.

17.	or/1-16
18.	letter/
19.	editorial/
20.	news/
21.	exp historical article/
22.	Anecdotes as Topic/
23.	comment/
24.	case report/
25.	(letter or comment*).ti.
26.	or/18-25
27.	randomized controlled trial/ or random*.ti,ab.
28.	26 not 27
29.	animals/ not humans/
30.	exp Animals, Laboratory/
31.	exp Animal Experimentation/
32.	exp Models, Animal/
33.	exp Rodentia/
34.	(rat or rats or mouse or mice).ti.
35.	or/28-34
36.	17 not 35
37.	limit 36 to English language
38.	exp Adrenergic beta-Antagonists/
39.	(Acebutolol or Atenolol or Bisoprolol or Carvedilol or Celiprolol or Esmolol or Labetalol or Metoprolol or Nadolol or Nebivolol or Oxprenolol or Propranolol or Pindolol or Sotalol or Timolol).ti,ab.
40.	(beta adj3 block*).ti,ab.
41.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) adj (block* or antagonist*)).ti,ab.
42.	(b adj3 block*).ti,ab.
43.	(beta adj2 antagonist*).ti,ab.
44.	or/38-43
45.	37 and 44
46.	randomized controlled trial.pt.
47.	controlled clinical trial.pt.
48.	randomi#ed.ti,ab.
49.	placebo.ab.
50.	randomly.ti,ab.
51.	Clinical Trials as topic.sh.
52.	trial.ti.
53.	or/46-52
54.	Meta-Analysis/
55.	exp Meta-Analysis as Topic/
56.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
57.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
58.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.

59.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
60.	(search* adj4 literature).ab.
61.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
62.	cochrane.jw.
63.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
64.	or/54-63
65.	Epidemiologic studies/
66.	Observational study/
67.	exp Cohort studies/
68.	(cohort adj (study or studies or analys* or data)).ti,ab.
69.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
70.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
71.	Controlled Before-After Studies/
72.	Historically Controlled Study/
73.	Interrupted Time Series Analysis/
74.	(before adj2 after adj2 (study or studies or data)).ti,ab.
75.	exp case control study/
76.	case control*.ti,ab.
77.	Cross-sectional studies/
78.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
79.	or/65-78
80.	45 and (53 or 64 or 79)

Embase (Ovid) search terms

1.	acute coronary syndrome/ or angina pectoris/ or unstable angina pectoris/ or coronary artery thrombosis/ or exp heart infarction/
2.	heart arrest/
3.	(acute coronary adj2 syndrome*).ti,ab.
4.	((myocardial or heart) adj infarct*).ti,ab.
5.	(heart adj (attack* or event*)).ti,ab.
6.	((heart or cardiac) adj arrest*).ti,ab.
7.	(coronary adj2 thrombos*).ti,ab.
8.	(stemi or st-segment or st segment or st-elevation or st elevation).ti,ab.
9.	"non-ST-segment elevation".ti,ab.
10.	(non-STEMI or NSTEMI or nonSTEMI).ti,ab.
11.	"Q wave myocardial infarction".ti,ab.
12.	"non Q wave MI".ti,ab.
13.	(NSTE-ACS or STE-ACS).ti,ab.
14.	(subendocardial adj3 infarct*).ti,ab.
15.	((unstable or variant) adj2 angina*).ti,ab.
16.	(unstable adj2 coronary).ti,ab.
17.	or/1-16
18.	letter.pt. or letter/

19.	note.pt.
20.	editorial.pt.
21.	Case report/ or Case study/
22.	(letter or comment*).ti.
23.	or/18-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animal/ not human/
27.	Nonhuman/
28.	exp Animal Experiment/
29.	exp Experimental animal/
30.	Animal model/
31.	exp Rodent/
32.	(rat or rats or mouse or mice).ti.
33.	or/25-32
34.	17 not 33
35.	limit 34 to English language
36.	exp *beta adrenergic receptor blocking agent/
37.	(Acebutolol or Atenolol or Bisoprolol or Carvedilol or Celiprolol or Esmolol or Labetalol or Metoprolol or Nadolol or Nebivolol or Oxprenolol or Propranolol or Pindolol or Sotalol or Timolol).ti,ab.
38.	(beta adj3 block*).ti,ab.
39.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) adj (block* or antagonist*)).ti,ab.
40.	(b adj3 block*).ti,ab.
41.	(beta adj2 antagonist*).ti,ab.
42.	or/36-41
43.	35 and 42
44.	random*.ti,ab.
45.	factorial*.ti,ab.
46.	(crossover* or cross over*).ti,ab.
47.	((doubl* or singl*) adj blind*).ti,ab.
48.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
49.	crossover procedure/
50.	single blind procedure/
51.	randomized controlled trial/
52.	double blind procedure/
53.	or/44-52
54.	systematic review/
55.	meta-analysis/
56.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
57.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
58.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
59.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.

60.	(search* adj4 literature).ab.
61.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
62.	((pool* or combined) adj2 (data or trials or studies or results)).ab.
63.	cochrane.jw.
64.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
65.	or/54-64
66.	Clinical study/
67.	Observational study/
68.	family study/
69.	longitudinal study/
70.	retrospective study/
71.	prospective study/
72.	cohort analysis/
73.	follow-up/
74.	cohort*.ti,ab.
75.	73 and 74
76.	(cohort adj (study or studies or analys* or data)).ti,ab.
77.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
78.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
79.	(before adj2 after adj2 (study or studies or data)).ti,ab.
80.	exp case control study/
81.	case control*.ti,ab.
82.	cross-sectional study/
83.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
84.	or/66-72,75-83
85.	43 and (53 or 65 or 84)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Acute Coronary Syndrome] this term only
#2.	MeSH descriptor: [Angina Pectoris] this term only
#3.	MeSH descriptor: [Angina, Unstable] this term only
#4.	MeSH descriptor: [Coronary Thrombosis] this term only
#5.	MeSH descriptor: [Myocardial Infarction] explode all trees
#6.	(or #1-#5)
#7.	MeSH descriptor: [Heart Arrest] this term only
#8.	(acute coronary near/2 syndrome*):ti,ab
#9.	((myocardial or heart) next infarct*):ti,ab
#10.	(heart next (attack* or event*)):ti,ab
#11.	((heart or cardiac) next arrest*):ti,ab
#12.	(coronary near/2 thrombos*):ti,ab
#13.	(stemi or st-segment or st segment or st-elevation or st elevation):ti,ab
#14.	non-ST-segment elevation:ti,ab
#15.	(non-STEMI or NSTEMI or nonSTEMI):ti,ab

#16.	Q wave myocardial infarction:ti,ab
#17.	non Q wave MI:ti,ab
#18.	(NSTE-ACS or STE-ACS):ti,ab
#19.	(subendocardial near/3 infarct*):ti,ab
#20.	((unstable or variant) near/2 angina*):ti,ab
#21.	(unstable near/2 coronary):ti,ab
#22.	(or #6-#21)
#23.	MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees
#24.	(Acebutolol or Atenolol or Bisoprolol or Carvedilol or Celiprolol or Esmolol or Labetalol or Metoprolol or Nadolol or Nebivolol or Oxprenolol or Propranolol or Pindolol or Sotalol or Timolol):ti,ab
#25.	(beta near/3 block*):ti,ab
#26.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) next (block* or antagonist*)):ti,ab
#27.	(b near/3 block*):ti,ab
#28.	(beta near/2 antagonist*):ti,ab
#29.	(OR #23-#28)
#30.	#22 AND #29

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a search relating to acute coronary syndromes population combined with terms for interventions in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase using a filter for health economics studies.

Table 11: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	01 January 2014 – 18 June 2019	Exclusions Health economics studies
Embase	01 January 2014 – 18 June 2019	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - 2003 – 31 March 2018 NHSEED - 2003 to 31 March 2015	None

Medline (Ovid) search terms

1.	Acute Coronary Syndrome/ or Angina Pectoris/ or Angina, Unstable/ or Coronary Thrombosis/ or exp Myocardial Infarction/
2.	Heart Arrest/
3.	(acute coronary adj2 syndrome*).ti,ab.
4.	((myocardial or heart) adj infarct*).ti,ab.
5.	(heart adj (attack* or event*)).ti,ab.
6.	((heart or cardiac) adj arrest*).ti,ab.

7.	(coronary adj2 thrombos*).ti,ab.
8.	(stemi or st-segment or st segment or st-elevation or st elevation).ti,ab.
9.	"non-ST-segment elevation".ti,ab.
10.	(non-STEMI or NSTEMI or nonSTEMI).ti,ab.
11.	"Q wave myocardial infarction".ti,ab.
12.	"non Q wave MI".ti,ab.
13.	NSTE-ACS.ti,ab.
14.	(subendocardial adj3 infarct*).ti,ab.
15.	((unstable or variant) adj2 angina*).ti,ab.
16.	(unstable adj2 coronary).ti,ab.
17.	or/1-16
18.	letter/
19.	editorial/
20.	news/
21.	exp historical article/
22.	Anecdotes as Topic/
23.	comment/
24.	case report/
25.	(letter or comment*).ti.
26.	or/18-25
27.	randomized controlled trial/ or random*.ti,ab.
28.	26 not 27
29.	animals/ not humans/
30.	exp Animals, Laboratory/
31.	exp Animal Experimentation/
32.	exp Models, Animal/
33.	exp Rodentia/
34.	(rat or rats or mouse or mice).ti.
35.	or/28-34
36.	17 not 35
37.	limit 36 to English language
38.	Economics/
39.	Value of life/
40.	exp "Costs and Cost Analysis"/
41.	exp Economics, Hospital/
42.	exp Economics, Medical/
43.	Economics, Nursing/
44.	Economics, Pharmaceutical/
45.	exp "Fees and Charges"/
46.	exp Budgets/

47.	budget*.ti,ab.
48.	cost*.ti.
49.	(economic* or pharmaco?economic*).ti.
50.	(price* or pricing*).ti,ab.
51.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
52.	(financ* or fee or fees).ti,ab.
53.	(value adj2 (money or monetary)).ti,ab.
54.	or/38-53
55.	37 and 54
56.	*Angiography/
57.	Angiocardiography/
58.	Coronary Angiography/
59.	Angiograph*.ti.
60.	Arteriograph*.ti.
61.	Angiocardiograph*.ti,ab.
62.	Coronary Angiograph*.ti,ab.
63.	Angiogram*.ti,ab.
64.	Cardioangiograph*.ti,ab.
65.	Angiocardiogram.ti,ab.
66.	Angio Cardiograph*.ti,ab.
67.	Coronary Arteriogra*.ti,ab.
68.	Coronarograph*.ti,ab.
69.	*Myocardial Revascularization/
70.	Angioplasty, Balloon, Coronary/
71.	(Myocardial adj revasculari?ation).ti,ab.
72.	PCI.ti,ab.
73.	Percutaneous coronary intervention.ti,ab.
74.	Percutaneous Transluminal Coronary Angioplasty.ti,ab.
75.	PTCA.ti,ab.
76.	exp Angioplasty/
77.	Blunt microdissection.ti,ab.
78.	((laser or patch) adj angioplasty).ti,ab.
79.	Percutaneous Transluminal Angioplasty.ti,ab.
80.	Transluminal Coronary Angioplasty.ti,ab.
81.	(Balloon adj3 coronary).ti,ab.
82.	(Balloon adj3 angioplasty).ti,ab.
83.	exp STENTS/
84.	stent*.ti,ab.
85.	Or/56-84
86.	aspirin/
87.	(aspirin or acetylsalicylic acid).ti,ab.
88.	(clopidogrel or plavix).ti,ab.
89.	(ticagrelor or brilique).ti,ab.
90.	(prasugrel or efient or effient or prasita).ti,ab.

91.	Prasugrel Hydrochloride/
92.	platelet aggregation inhibitors/
93.	(Glycoproteins IIb-IIIa or GPIIb-IIIa Receptors or Integrin alpha-IIb beta-3 or Integrin alphaIIbbeta3 or GPIIB IIIA).ti,ab.
94.	exp Platelet Glycoprotein GPIIb-IIIa Complex/
95.	exp Receptors, Fibrinogen/
96.	(Abciximab or Reopro or Eptifibatide or Integrelin or Integrilin or Intrifiban or Tirofiban or Aggrastat).ti,ab.
97.	exp adrenergic beta-antagonists/
98.	(propranolol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim).ti,ab.
99.	propranolol/ or acebutolol/ or atenolol/ or bisoprolol/ or celiprolol/ or labetalol/ or metoprolol/ or nadolol/ or nebivolol/ or oxprenolol/ or pindolol/ or sotalol/ or timolol/
100.	(beta adj3 block*).ti,ab.
101.	(b adj3 block*).ti,ab.
102.	(beta adj2 antagonist*).ti,ab.
103.	Antithrombins/
104.	Antithrombin*.ti,ab.
105.	(thrombin adj3 inhibitor*).ti,ab.
106.	Hirudins/
107.	Hirudin*.ti,ab.
108.	Hirulog.ti,ab.
109.	Bivalirudin.ti,ab.
110.	Or/86-109
111.	55 and (85 or 110)

Embase (Ovid) search terms

1.	acute coronary syndrome/ or angina pectoris/ or unstable angina pectoris/ or coronary artery thrombosis/ or exp heart infarction/
2.	heart arrest/
3.	(acute coronary adj2 syndrome*).ti,ab.
4.	((myocardial or heart) adj infarct*).ti,ab.
5.	(heart adj (attack* or event*)).ti,ab.
6.	((heart or cardiac) adj arrest*).ti,ab.
7.	(coronary adj2 thrombos*).ti,ab.
8.	(stemi or st-segment or st segment or st-elevation or st elevation).ti,ab.
9.	"non-ST-segment elevation".ti,ab.
10.	(non-STEMI or NSTEMI or nonSTEMI).ti,ab.
11.	"Q wave myocardial infarction".ti,ab.
12.	"non Q wave MI".ti,ab.
13.	NSTE-ACS.ti,ab.

14.	(subendocardial adj3 infarct*).ti,ab.
15.	((unstable or variant) adj2 angina*).ti,ab.
16.	(unstable adj2 coronary).ti,ab.
17.	or/1-16
18.	letter.pt. or letter/
19.	note.pt.
20.	editorial.pt.
21.	Case report/ or Case study/
22.	(letter or comment*).ti.
23.	or/18-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animal/ not human/
27.	Nonhuman/
28.	exp Animal Experiment/
29.	exp Experimental animal/
30.	Animal model/
31.	exp Rodent/
32.	(rat or rats or mouse or mice).ti.
33.	or/25-32
34.	17 not 33
35.	limit 34 to English language
36.	health economics/
37.	exp economic evaluation/
38.	exp health care cost/
39.	exp fee/
40.	budget/
41.	funding/
42.	budget*.ti,ab.
43.	cost*.ti.
44.	(economic* or pharmaco?economic*).ti.
45.	(price* or pricing*).ti,ab.
46.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
47.	(financ* or fee or fees).ti,ab.
48.	(value adj2 (money or monetary)).ti,ab.
49.	or/36-48
50.	35 and 49

51.	angiography/
52.	angiocardiography/
53.	coronary angiography/
54.	Angiograph*.ti.
55.	Arteriograph*.ti.
56.	Angiocardiograph*.ti,ab.
57.	Coronary Angiograph*.ti,ab.
58.	Angiogram*.ti,ab.
59.	Cardioangiograph*.ti,ab.
60.	Angiocardiogram.ti,ab.
61.	Angio Cardiograph*.ti,ab.
62.	Coronary Arteriogra*.ti,ab.
63.	Coronarograph*.ti,ab.
64.	*heart muscle revascularization/
65.	transluminal coronary angioplasty/
66.	(Myocardial adj revasculari?ation).ti,ab.
67.	PCI.ti,ab.
68.	Percutaneous coronary intervention.ti,ab.
69.	Percutaneous Transluminal Coronary Angioplasty.ti,ab.
70.	PTCA.ti,ab.
71.	*angioplasty/
72.	Blunt microdissection.ti,ab.
73.	((laser or patch) adj angioplasty).ti,ab.
74.	Percutaneous Transluminal Angioplasty.ti,ab.
75.	Transluminal Coronary Angioplasty.ti,ab.
76.	(Balloon adj3 coronary).ti,ab.
77.	(Balloon adj3 angioplasty).ti,ab.
78.	exp STENTS/
79.	stent*.ti,ab.
80.	Or/51-79
81.	acetylsalicylic acid/
82.	(aspirin or acetylsalicylic acid).ti,ab.
83.	(clopidogrel or plavix).ti,ab.
84.	(ticagrelor or brilique).ti,ab.
85.	(prasugrel or efient or effient or prasita).ti,ab.
86.	prasugrel/
87.	antithrombocytic agent/

88.	(Glycoproteins IIb-IIIa or GPIIb-IIIa Receptors or Integrin alpha-IIb beta-3 or Integrin alphaIIbbeta3 or GPIIB IIIA).ti,ab.
89.	exp fibrinogen receptor/
90.	(Abciximab or Reopro or Eptifibatide or Integrelin or Integrilin or Intrifiban or Tirofiban or Aggrastat).ti,ab.
91.	abciximab/ or eptifibatide/ or tirofiban/
92.	exp beta adrenergic receptor blocking agent/
93.	(propranolol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim).ti,ab.
94.	propranolol/ or acebutolol/ or atenolol/ or bisoprolol/ or bisoprolol fumarate/ or carvedilol/ or celiprolol/ or esmolol/ or labetalol/ or metoprolol/ or nadolol/ or nebivolol/ or oxprenolol/ or pindolol/ or sotalol/ or timolol/ or timolol maleate/
95.	(beta adj3 block*).ti,ab.
96.	(b adj3 block*).ti,ab.
97.	(beta adj2 antagonist*).ti,ab.
98.	antithrombin/
99.	Antithrombin*.ti,ab.
100.	(thrombin adj3 inhibitor*).ti,ab.
101.	hirudin derivative/
102.	Hirudin*.ti,ab.
103.	Hirulog.ti,ab.
104.	Bivalirudin.ti,ab.
105.	Or/81-104
106.	50 and (80 or 105)

NHS EED and HTA (CRD) search terms

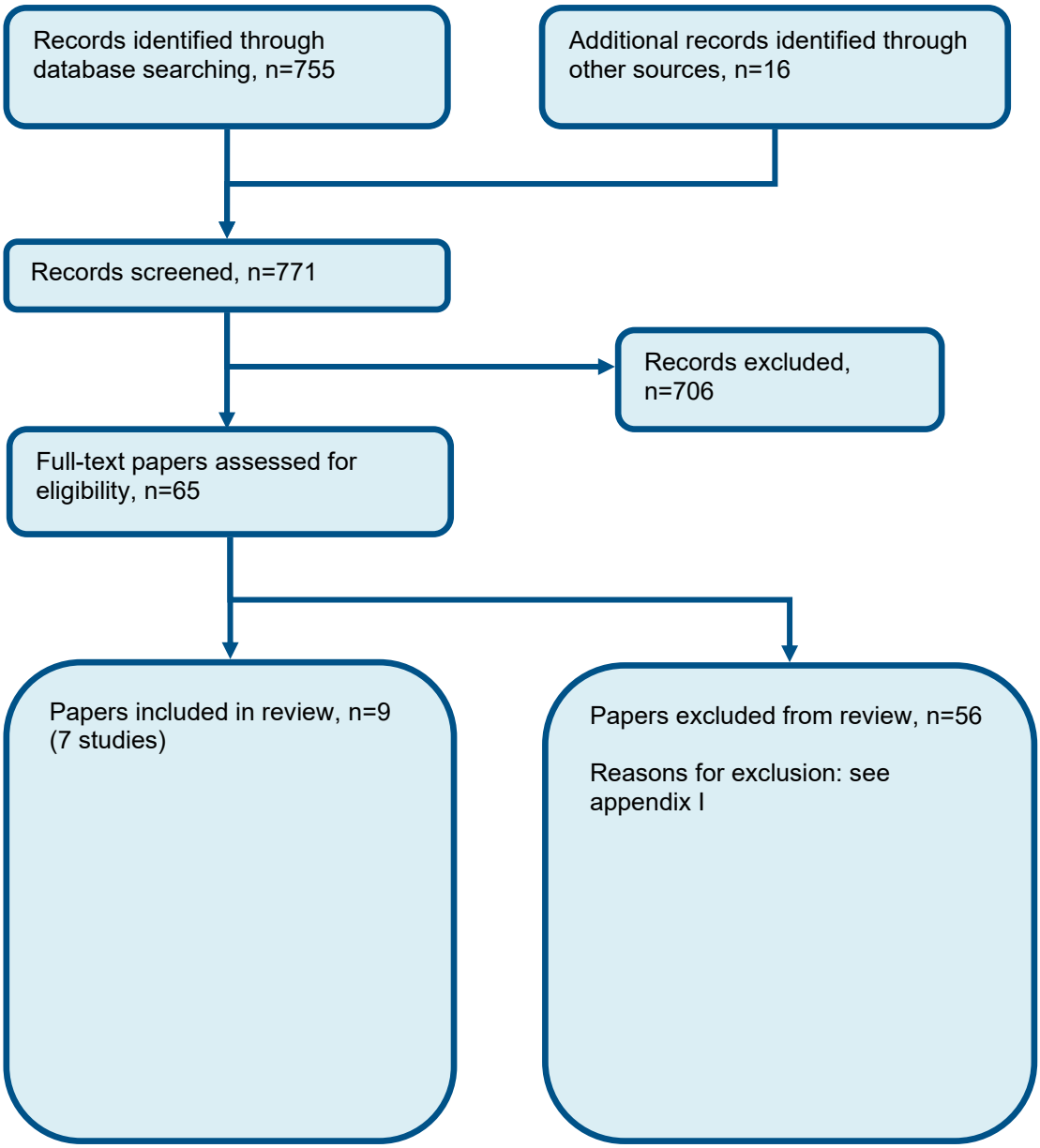
#1.	MeSH DESCRIPTOR Acute Coronary Syndrome
#2.	(MeSH DESCRIPTOR angina pectoris)
#3.	(MeSH DESCRIPTOR Angina, Unstable)
#4.	(MeSH DESCRIPTOR Coronary Thrombosis)
#5.	MeSH DESCRIPTOR Myocardial Infarction EXPLODE ALL TREES
#6.	#1 OR #2 OR #3 OR #4 OR #5
#7.	(MeSH DESCRIPTOR Heart Arrest)
#8.	((acute coronary adj2 syndrome*))
#9.	(((myocardial or heart) adj infarct*))
#10.	((heart adj (attack* or event*)))
#11.	(((heart or cardiac) adj arrest*))
#12.	((coronary adj2 thrombos*))
#13.	((stemi or st-segment or st segment or st-elevation or st elevation))
#14.	("non-ST-segment elevation")

#15.	((non-STEMI or NSTEMI or nonSTEMI))
#16.	("Q wave myocardial infarction")
#17.	("non Q wave MI")
#18.	(NSTE-ACS)
#19.	(STE-ACS)
#20.	(((subendocardial adj3 infarct*)))
#21.	((((unstable or variant) adj2 angina*)))
#22.	(((unstable adj2 coronary)))
#23.	(#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22)
#24.	(MeSH DESCRIPTOR Angiography)
#25.	(MeSH DESCRIPTOR Angiocardiography)
#26.	((MeSH DESCRIPTOR Coronary Angiography))
#27.	((Angiograph*))
#28.	((Arteriograph*))
#29.	((Angiocardiograph*))
#30.	((Coronary Angiograph*))
#31.	((Angiogram*))
#32.	((Cardioangiograph*))
#33.	((Angiocardiogram))
#34.	((Angio Cardiograph*))
#35.	((Coronary Arteriogra*))
#36.	((Coronarograph*))
#37.	(MeSH DESCRIPTOR Myocardial Revascularization)
#38.	(MeSH DESCRIPTOR Angioplasty, Balloon, Coronary)
#39.	(((Myocardial adj revasculari?ation)))
#40.	((PCI))
#41.	((Percutaneous coronary intervention))
#42.	((Percutaneous Transluminal Coronary Angioplasty))
#43.	((PTCA))
#44.	(MeSH DESCRIPTOR Angioplasty EXPLODE ALL TREES)
#45.	((Blunt microdissection))
#46.	((((laser or patch) adj angioplasty)))
#47.	((Percutaneous Transluminal Angioplasty))
#48.	((Transluminal Coronary Angioplasty))
#49.	(((Balloon adj3 coronary)))
#50.	((Balloon adj3 angioplasty))
#51.	(MeSH DESCRIPTOR Stents EXPLODE ALL TREES)
#52.	((stent*))
#53.	(#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52)
#54.	(MeSH DESCRIPTOR Aspirin)
#55.	((aspirin or acetylsalicylic acid))
#56.	((clopidogrel or plavix))
#57.	((ticagrelor or brilique))

#58.	((prasugrel or efient or effient or prasita))
#59.	MeSH DESCRIPTOR Prasugrel Hydrochloride
#60.	MeSH DESCRIPTOR Platelet Aggregation Inhibitors
#61.	((Glycoproteins IIb-IIIa or GPIIb-IIIa Receptors or Integrin alpha-IIb beta-3 or Integrin alphaIIbbeta3 or GPIIB IIIA))
#62.	MeSH DESCRIPTOR Platelet Glycoprotein GPIIb-IIIa Complex EXPLODE ALL TREES
#63.	MeSH DESCRIPTOR Receptors, Fibrinogen EXPLODE ALL TREES
#64.	((Abciximab or Reopro or Eptifibatide or Integrelin or Integrilin or Intrifiban or Tirofiban or Aggrastat))
#65.	MeSH DESCRIPTOR Adrenergic beta-Antagonists EXPLODE ALL TREES
#66.	((propranolol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim))
#67.	(MeSH DESCRIPTOR propranolol)
#68.	(MeSH DESCRIPTOR acebutolol)
#69.	(MeSH DESCRIPTOR atenolol)
#70.	(MeSH DESCRIPTOR bisoprolol)
#71.	(MeSH DESCRIPTOR celiprolol)
#72.	(MeSH DESCRIPTOR labetalol)
#73.	(MeSH DESCRIPTOR metoprolol)
#74.	(MeSH DESCRIPTOR nadolol)
#75.	(MeSH DESCRIPTOR nebivolol)
#76.	(MeSH DESCRIPTOR oxprenolol)
#77.	(MeSH DESCRIPTOR pindolol)
#78.	(MeSH DESCRIPTOR sotalol)
#79.	(MeSH DESCRIPTOR timolol)
#80.	((beta adj3 block*))
#81.	((b adj3 block*))
#82.	((beta adj2 antagonist*))
#83.	MeSH DESCRIPTOR Antithrombins
#84.	(Antithrombin*)
#85.	((thrombin adj3 inhibitor*))
#86.	MeSH DESCRIPTOR Hirudins
#87.	(Hirudin*)
#88.	(Hirulog)
#89.	(Bivalirudin)
#90.	#54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89
#91.	(#23 AND (#53 OR #90))

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of bivalirudin as adjunctive pharmacotherapy in adults with STEMI intended for primary percutaneous coronary intervention



Appendix D: Clinical evidence tables

Study	BIVAL trial: Van Geuns 2017[64]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=78)
Countries and setting	Conducted in France, Netherlands; Setting: Hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 90 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Adults with STEMI who presented >20 minutes and <12 hours after symptom onset, who fulfilled angiographic criteria
Stratum	Overall: People with ST-segment elevation myocardial infarction (STEMI), stratified by duration of symptom onset to randomisation (<6 hrs versus ≥6 hrs) and site
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with STEMI who presented >20 minutes and <12 hours after symptom onset, who fulfilled angiographic criteria: Thrombolysis In Myocardial Infarction (TIMI) 0 or 1 flow in the infarct-related artery; angiographic score ≥21 (sizeable infarction, based on initial angiogram) according to the APPROACH score; and eligible for PPCI. Use of glycoprotein IIb/IIIa inhibitors was permitted only as bail-out therapy for the treatment of no-reflow phenomenon or giant thrombus, defined as >2 times the diameter of the vessel. Full study criteria listed elsewhere
Exclusion criteria	Patients with a history of Q-wave myocardial infarction or who had received antithrombotic therapy other than UFH at first medical contact
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Bivalirudin group: 62.9 (10.6); Heparin group: 62.8 (12.8) per protocol population. Gender (M:F): 52/12 (per protocol population). Ethnicity: Not reported
Further population details	1. Renal function: Not stated / Unclear
Indirectness of population	No indirectness

Study	BIVAL trial: Van Geuns 2017[64]
Interventions	(n=38) Intervention 1: Bivalirudin . A bivalirudin bolus of 0.75 mg/kg and an infusion of 1.75 mg/kg/hr for the duration of the procedure and for four hours after completion of PPCI to maintain consistent thrombin inhibition. Use of glycoprotein IIb/IIIa inhibitors was permitted only as bail-out therapy for the treatment of no-reflow phenomenon or giant thrombus, defined as >2 times the diameter of the vessel. Bail out GPI occurred in 3/28 (11%). Duration 90 days. Concurrent medication/care: All patients received, as soon as logistically possible, aspirin at an initial dose of 150-325 mg orally (or 250-500 mg intravenously) and a loading dose of a P2Y12 inhibitor. Administration of UFH at first medical contact or before the angiogram was allowed as per usual practice. Indirectness: No indirectness Further details: 1. Drug dose: Not stated / Unclear 2. Number of stents: Not stated / Unclear 3. Type of antiplatelet: Not stated / Unclear 4. Use of GpIIb/IIIa : Not stated / Unclear (n=40) Intervention 2: Heparin - UFH. Unfractionated heparin was administered at a dose as per standard institutional practice. In cases where activated clotting time was used to inform UFH dosing, a target value of ≥250 seconds was recommended. Use of glycoprotein IIb/IIIa inhibitors was permitted only as bail-out therapy for the treatment of no-reflow phenomenon or giant thrombus, defined as >2 times the diameter of the vessel. Bail out GPI occurred in 3/36 (8%). Duration 90 days. Concurrent medication/care: All patients received, as soon as logistically possible, aspirin at an initial dose of 150-325 mg orally (or 250-500 mg intravenously) and a loading dose of a P2Y12 inhibitor. Administration of UFH at first medical contact or before the angiogram was allowed as per usual practice. Indirectness: No indirectness Further details: 1. Drug dose: Not stated / Unclear 2. Number of stents: Not stated / Unclear 3. Type of antiplatelet: Not stated / Unclear 4. Use of GpIIb/IIIa : Not stated / Unclear
Funding	Study funded by industry (The study and editorial support for this study were funded by The Medicines Company)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BIVALIRUDIN versus UFH

Protocol outcome 1: Mortality at 1 year at at 1 year
- Actual outcome: All cause mortality at Unclear; Group 1: 1/38, Group 2: 1/40; Comments: Results reported for ITT population. In the per protocol population there was 1 death in the UFH group (1/36) versus no deaths in the bivalirudin group (0/28)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - 6/38 patients from the bivalirudin group did not complete the study (5 withdrew consent and 1 died); 3/40 patients from the heparin group did not complete the study (1 withdrew and 1 died); Indirectness of outcome: No indirectness ; Baseline details: Per protocol baseline characteristics only. Statistically higher proportion of UFH group had never smoked and lower proportion of UFH group started prasugrel before PCI. None of bivalirudin group had previous cerebrovascular event, MI or diabetes versus 25% of UFH group; Blinding details: Open label study; Group 1 Number missing: ; Group 2

Study	BIVAL trial: Van Geuns 2017[64]
Number missing:	
Protocol outcomes not reported by the study	Quality of life ; Myocardial infarction at up to 30 days ; Cardiac mortality at up to 30 days ; Complications related to bleeding; Non-haemorrhagic stroke; Need for revascularisation at at 1 year; Early and late stent thrombosis; Re-infarction at at 1 year; Length of hospital stay; All cause mortality at up to 30 days

Study	EUROMAX trial: Fabris 2017[11]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2198)
Countries and setting	Conducted in Multiple countries; Setting: The protocol specifies inclusion of subjects presenting via ambulance or to a centre where PCI is not performed
Line of therapy	Unclear
Duration of study	Intervention + follow up: 1-year follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ST-segment elevation myocardial infarction
Stratum	Overall: People with ST-segment elevation myocardial infarction (STEMI)
Subgroup analysis within study	Unclear: renal function; type of P2Y12 inhibitor. The protocol reports that sub-analysis will be completed for ST segment resolution only, and that primary randomisation will be stratified based on the enrolling centre (approximately 50 centres in Europe)
Inclusion criteria	The protocol reports that the decision to randomise patients must be made by a qualified physician or paramedic who is present at the time. Subjects may be included in the study if they present either via ambulance or to a centre where PCI is not performed and meet all of the following criteria: be aged ≥18 years at the time of randomisation; have a presumed diagnosis of a STE-ACS with onset of symptoms of >20 minutes and <12 hours with one or more of the following: ST segment elevation of ≥1mm in ≥2 contiguous leads, presumably new left bundle branch block, an infero-lateral MI with ST segment depression of ≥1mm in ≥2 of leads V1-3) with a positive terminal T wave; all patients must be scheduled for angiography +/- PCI (if indicated) <2 hours after first medical contact
Exclusion criteria	The protocol reports that subjects will be excluded from the study if any of the following exclusion criteria apply prior to randomisation: any bleeding diathesis or severe haematological disease or history of intra-cerebral mass, aneurysm, arterio-venous malformation, haemorrhagic stroke, intra-cranial haemorrhage or

Study	EUROMAX trial: Fabris 2017[11]
	gastrointestinal or genitourinary bleeding within the last 2 weeks; patients who have undergone recent surgery (including biopsy) within the last two weeks; patients on warfarin (not applicable if INR known to be <1.5); patients who have received UFH, LMWH or bivalirudin immediately before randomisation; thrombolytic therapy within the last 48 hours
Recruitment/selection of patients	The protocol reports that the decision to randomise patients must be made by a qualified physician or paramedic who is present at the time
Age, gender and ethnicity	Age - Median (IQR): Bivalirudin group: 61 (52-71); Heparin group: 62 (52-72). Gender (M:F): 1675/523. Ethnicity: Not reported
Further population details	1. Renal function: Creatinine clearance ≤60 (Baseline creatinine clearance ≤60 mL/min and >60 mL/min).
Extra comments	Not all participants underwent primary PCI as the principal management strategy (42 underwent CABG and 215 received medical management)
Indirectness of population	No indirectness
Interventions	(n=1089) Intervention 1: Bivalirudin . The protocol reports that bivalirudin is given immediately on enrolment as bolus of 0.75mg/kg followed immediately by an infusion of 1.75mg/kg/h. This infusion should be run continuously until completion of PCI at which time the infusion should be reduced to a dose of 0.25mg/kg/h for at least 4 hours. An optional higher-dose infusion of 1.75mg/kg/h is also permitted for up to 4 hours. Patients who do not undergo PCI and are to be medically managed with continuing anticoagulation should continue the bivalirudin infusion of 0.25mg/kg/h for up to 72 hours. Initial anticoagulation with bivalirudin occurred in 1074/1089 (98.6%). The protocol reports that patients randomised to bivalirudin may only have 'bail out' GPI (abciximab bolus + 12 hour infusion or eptifibatide double bolus + 12-18 hours infusion or tirofiban bolus followed by an 18 to 24 hour infusion) administered during primary PCI for the following two reasons only: the presence of a 'giant' thrombus adjacent to the stent or in the coronary vessel (length >2x that of the diameter of the coronary vessel) after PCI in the absence of a mechanical obstruction; sustained no reflow (TIMI 0-1 flow in the absence of a mechanical obstruction, refractory to intracoronary nitrates, adenosine or a calcium channel blocker delivered intracoronary to the distal coronary bed via an infusion catheter). However, there was a protocol deviation as routine use of GPI occurred in 42/1088 patients in the bivalirudin group. Bail out GPI occurred in 83/1046 (7.9%). . Duration 1-year follow-up. Concurrent medication/care: All patients received aspirin and platelet adenosine diphosphate P2Y12 receptor inhibitor as early as possible after the first medical contact. Decisions regarding access site, performance of thrombus aspiration, and stent type were left to physician preference. As indicated, any of the above drug doses are to be adjusted for renal impairment according to their respective Summary of Product Characteristics.. Indirectness: No indirectness Further details: 1. Drug dose: Not stated / Unclear 2. Number of stents: Not stated / Unclear 3. Type of antiplatelet: Clopidogrel (P2Y12 inhibitor loading and maintenace doses for clopidogrel, prasugrel, ticagrelor). 4. Use of GpIIb/IIIa : Not stated / Unclear

Study	EUROMAX trial: Fabris 2017[11]
	(n=1109) Intervention 2: Heparin - UFH. The protocol reports that the control group includes guideline-driven standard of care not including bivalirudin: UFH (100 IU/kg with no GPI and 60 IU/kg with a GPI); +/- routine or bail out eptifibatide (two 180 µg/kg boluses with a 10 minute interval followed by an infusion of 2.0 µg/kg/min for 72-96 hours) or tirofiban (25 µg/kg followed by an infusion of 0.15 µg/kg/min for 18 to 24 hours) or abciximab (bolus of 0.25 mg/kg followed by an infusion of 0.125 µg/kg/min for 12-24 hours (maximum dose, 10 µg/min). Initial anticoagulation with UFH occurred in 997/1190 (89.9%). Routine GPI occurred in 649/1109 (58.5%)' bail out GPI occurred in 117/460 (25.4%) . Duration 1-year follow-up. Concurrent medication/care: All patients received aspirin and platelet adenosine diphosphate P2Y12 receptor inhibitor as early as possible after the first medical contact. Decisions regarding access site, performance of thrombus aspiration, and stent type were left to physician preference. As indicated, any of the above drug doses are to be adjusted for renal impairment according to their respective Summary of Product Characteristics.. Indirectness: No indirectness Further details: 1. Drug dose: Not stated / Unclear 2. Number of stents: Not stated / Unclear 3. Type of antiplatelet: Clopidogrel (P2Y12 inhibitor loading and maintenace doses for clopidogrel, prasugrel, ticagrelor). 4. Use of GpIIb/IIIa : Not stated / Unclear Comments: UFH or LMWH with optional use of GPIs
Funding	Study funded by industry (This study was supported by The Medicines Company)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BIVALIRUDIN versus UFH OR LMWH + GPI

Protocol outcome 1: Mortality at 1 year at at 1 year
- Actual outcome: All cause mortality at 1 year; Group 1: 59/1089, Group 2: 59/1109
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Subgroups - Low, Comments - Subgroups for renal function and P2Y12 inhibitor use: the study reported 12 prespecified subgroups but these could not be located on review of the supplementary protocol
; Indirectness of outcome: No indirectness ; Baseline details: The heparin group had a higher proportion of participants with diabetes and previous myocardial infarction (P < 0.05 for between-group comparison); Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: Cardiac mortality at 1 year; Group 1: 44/1089, Group 2: 48/1109
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments -
; Indirectness of outcome: No indirectness ; Baseline details: The heparin group had a higher proportion of participants with diabetes and previous myocardial infarction (P < 0.05 for between-group comparison); Blinding details: All deaths were adjudicated as cardiac or non-cardiac by an independent, blinded clinical events committee; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: Non-cardiac mortality at 1 year; Group 1: 15/1089, Group 2: 11/1109

Study	EUROMAX trial: Fabris 2017[11]
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: The heparin group had a higher proportion of participants with diabetes and previous myocardial infarction (P < 0.05 for between-group comparison); Blinding details: All deaths were adjudicated as cardiac or non-cardiac by an independent, blinded clinical events committee; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: All cause mortality at from 30 days to 1 year; Group 1: 27/1089, Group 2: 25/1109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: The heparin group had a higher proportion of participants with diabetes and previous myocardial infarction (P < 0.05 for between-group comparison); Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Cardiac mortality at from 30 days to 1 year; Group 1: 17/1089, Group 2: 15/1109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: The heparin group had a higher proportion of participants with diabetes and previous myocardial infarction (P < 0.05 for between-group comparison); Blinding details: All deaths were adjudicated as cardiac or non-cardiac by an independent, blinded clinical events committee; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Non-cardiac mortality at from 30 days to 1 year; Group 1: 10/1089, Group 2: 10/1109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: The heparin group had a higher proportion of participants with diabetes and previous myocardial infarction (P < 0.05 for between-group comparison); Blinding details: All deaths were adjudicated as cardiac or non-cardiac by an independent, blinded clinical events committee; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life ; Myocardial infarction at up to 30 days ; Cardiac mortality at up to 30 days ; Complications related to bleeding ; Non-haemorrhagic stroke ; Need for revascularisation at at 1 year; Early and late stent thrombosis ; Re-infarction at at 1 year; Length of hospital stay ; All cause mortality at up to 30 days

Study	EUROMAX trial: Steg 2013[49]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2198)
Countries and setting	Conducted in Multiple countries
Line of therapy	Unclear

Study	EUROMAX trial: Steg 2013[49]
Duration of study	Intervention + follow up: 30 days follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Presumed diagnosis of a ST-elevation acute coronary syndrome with onset of symptoms of >20 minutes and <12 hours with 1 or more of the following: ST segment elevation of ≥1mm in ≥2 contiguous leads; presumably new left bundle branch block; an inferolateral myocardial infarction with ST-segment depression of ≥1mm in ≥2 of leads V1-3 with a positive terminal T wave
Stratum	Overall: People with ST-segment elevation myocardial infarction (STEMI)
Subgroup analysis within study	Not applicable
Inclusion criteria	From supplementary material: provide written informed consent before initiation of any study-related procedures. Patients enrolled in the ambulance may initially sign an abridged version; be aged ≥18 years at the time of enrollment; have a presumed diagnosis of a ST-elevation acute coronary syndrome with onset of symptoms of >20 minutes and <12 hours with 1 or more of the following: ST segment elevation of ≥1mm in ≥2 contiguous leads; presumably new left bundle branch block; an inferolateral myocardial infarction with ST-segment depression of ≥1mm in ≥2 of leads V1-3 with a positive terminal T wave; all patients must be scheduled for angiography with/without PCI (if indicated) <2 hours after first medical contact
Exclusion criteria	From supplementary material: any bleeding diathesis or severe haematological disease or history of intracerebral mass, aneurysm, arteriovenous malformation, haemorrhagic stroke, intracranial haemorrhage or gastrointestinal or genitourinary bleeding within the last 2 weeks; patients who have undergone recent surgery (including biopsy) within the last 2 weeks; patients on warfarin (not applicable if international normalised ratio known to be <1.5; patients who have received unfractionated heparin, low-molecular-weight heparin or bivalirudin immediately before randomisation; thrombolytic therapy within the last 48 hours; absolute contraindications or allergy that cannot be premedicated to iodinated contrast or to any of the study medications including aspirin or clopidogrel; contraindications to angiography, including but not limited to severe peripheral vascular disease; if it is known, pregnant or nursing mothers. Women of child-bearing age will be asked if they are pregnant or think that they may be pregnant; if it is known, a creatinine clearance <30 mL/min or dialysis dependent; previous enrollment in this study; treatment with other investigational drugs or devices within the 30 days preceding enrolment or planned use of other investigational drugs or devices in this trial; patients may not be enrolled if the duration of randomised investigational medicinal product antithrombin infusion is likely to be <30 minutes from the time of onset to the commencement of angiography; patients may not be enrolled with a primary PCI-capable hospital (unless at the time of randomisation the catheter laboratory is not available and the patient requires transfer to another primary PCI-capable hospital; estimated body weight of >120kg
Recruitment/selection of patients	Study-drug administration was initiated in the ambulance or in a non-PCI hospital. Patients were transported urgently to the primary PCI hospital, where treatment was continued and outcomes data collected

Study	EUROMAX trial: Steg 2013[49]
Age, gender and ethnicity	Age - Median (IQR): Bivalirudin group: 61 (52-71); Heparin group: 62 (52-72). Gender (M:F): 1675/523. Ethnicity: Not reported
Further population details	1. Renal function: Creatinine clearance ≤60 (Baseline creatine clearance ≤60 and >60 (units not reported)).
Indirectness of population	No indirectness
Interventions	(n=1089) Intervention 1: Bivalirudin . Bivalirudin was to be administered as a bolus of 0.75mg/kg, followed by an infusion of 1.75mg/kg/h. The protocol specified that the infusion should be continued for at least 4 h after PCI at a dose of 0.25mg/kg/h; however, continuation of the full dose (1.75mg/kg/h) used during PCI was also permitted. Both the decision for the use and the selection of GPI agent were left up to the investigator's discretion and preference. The use of GPI was classified as routine when treatment commenced before or during angiography but not after the start of PCI. Bailout use of GPI was permitted after the commencement of PCI in bivalirudin-treated patients, but was limited according to the protocol only for the presence of giant thrombus or no-reflow during or after the index procedure. As a protocol deviation, 42/1088 (3.9%) of the bivalirudin group received routine GPI; 83/1046 (7.9%) received bail out GPI . Duration 30 days. Concurrent medication/care: All patients received aspirin and an approved P2Y12 inhibitor as early as possible after the first medical contact. Decisions regarding access site, performance of thrombus aspiration, and stent type were left to physician preference . Indirectness: No indirectness Further details: 1. Drug dose: Not applicable 2. Number of stents: Not applicable 3. Type of antiplatelet: Clopidogrel (Type of P2Y12 inhibitor loading and maintenance doses for clopidogrel, prasugrel, ticagrelor). 4. Use of GpIIb/IIIa : Not applicable (n=1109) Intervention 2: Heparin - Heparin (UFH and LMWH) alone. Patients who were assigned to the heparin group were to receive either UFH or LMWH. UFH was to be administered at a dose of 100 IU/kg without a GPI or 60 IU/kg with a GPI; LMWH was to be given as a bolus of 0.5mg/kg. Both the decision for the use and the selection of GPI agent were left up to the investigator's discretion and preference. The use of GPI was classified as routine when treatment commenced before or during angiography but not after the start of PCI. Bailout use of GPI was permitted after the commencement of PCI in heparin-treated patients, but was limited according to the protocol only for the presence of giant thrombus or no-reflow during or after the index procedure. In the heparin group, 117/460 (25.4%) received bail out GpIIb/IIIa inhibitor and 649/1109 (58.5%) received routine use GpIIb/IIa inhibitor . Duration 30 days. Concurrent medication/care: All patients received aspirin and an approved P2Y12 inhibitor as early as possible after the first medical contact. Decisions regarding access site, performance of thrombus aspiration, and stent type were left to physician preference. . Indirectness: No indirectness Further details: 1. Drug dose: Not stated / Unclear 2. Number of stents: Not stated / Unclear 3. Type of antiplatelet: Clopidogrel (Type of P2Y12 inhibitor loading and maintenance doses for clopidogrel, prasugrel, ticagrelor). 4. Use of GpIIb/IIIa : Not stated / Unclear

Study	EUROMAX trial: Steg 2013[49]
Funding	Study funded by industry (Supported by The Medicines Company)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BIVALIRUDIN versus HEPARIN (UFH AND LMWH)

Protocol outcome 1: All cause mortality at up to 30 days
- Actual outcome: All cause mortality at 30 days; Group 1: 32/1089, Group 2: 34/1109
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: 'generally well matched between the two groups, although there were higher rates of diabetes and previous myocardial infarction in the control group'; Blinding details: Open label study. An independent clinical-events committee whose members were unaware of study-group assignments adjudicated deaths, bleeding episodes, reinfarction, ischaemia-driven revascularisation, stent thrombosis, and stroke; Group 1 Number missing: 15, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 23, Reason: Withdrew consent or lost to follow-up

Protocol outcome 2: Myocardial infarction at up to 30 days
- Actual outcome: New myocardial infarction: reinfarction at 30 days; Group 1: 19/1089, Group 2: 10/1109
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: 'generally well matched between the two groups, although there were higher rates of diabetes and previous myocardial infarction in the control group'; Blinding details: Open label study. An independent clinical-events committee whose members were unaware of study-group assignments adjudicated deaths, bleeding episodes, reinfarction, ischaemia-driven revascularisation, stent thrombosis, and stroke; Group 1 Number missing: 15, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 23, Reason: Withdrew consent or lost to follow-up

Protocol outcome 3: Cardiac mortality at up to 30 days
- Actual outcome: Cardiac mortality at 30 days; Group 1: 27/1089, Group 2: 33/1109
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: 'generally well matched between the two groups, although there were higher rates of diabetes and previous myocardial infarction in the control group'; Blinding details: Open label study. An independent clinical-events committee whose members were unaware of study-group assignments adjudicated deaths, bleeding episodes, reinfarction, ischaemia-driven revascularisation, stent thrombosis, and stroke; Group 1 Number missing: 15, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 23, Reason: Withdrew consent or lost to follow-up
- Actual outcome: Non-cardiac mortality at 30 days; Group 1: 5/1089, Group 2: 1/1109
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: 'generally well matched between the two groups, although there were higher rates of diabetes and previous myocardial infarction in the control group'; Blinding details: Open label study. An independent clinical-events committee whose members were unaware of study-group assignments adjudicated deaths, bleeding episodes, reinfarction, ischaemia-driven revascularisation, stent thrombosis, and stroke; Group 1 Number missing: 15, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 23, Reason: Withdrew

Study	EUROMAX trial: Steg 2013[49]
consent or lost to follow-up Protocol outcome 4: Complications related to bleeding - Actual outcome: Complications related to bleeding: non-CABG bleeding, major at 30 days; Group 1: 28/1089, Group 2: 67/1109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Subgroups - Low, Comments - Subgroups reported in results section of main paper to be prespecified; Indirectness of outcome: No indirectness ; Baseline details: 'generally well matched between the two groups, although there were higher rates of diabetes and previous myocardial infarction in the control group'; Blinding details: Open label study. An independent clinical-events committee whose members were unaware of study-group assignments adjudicated deaths, bleeding episodes, reinfarction, ischaemia-driven revascularisation, stent thrombosis, and stroke; Group 1 Number missing: 15, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 23, Reason: Withdrew consent or lost to follow-up - Actual outcome: Complications related to bleeding: non-CABG bleeding, major or minor at 30 days; Group 1: 85/1089, Group 2: 146/1109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: 'generally well matched between the two groups, although there were higher rates of diabetes and previous myocardial infarction in the control group'; Blinding details: Open label study. An independent clinical-events committee whose members were unaware of study-group assignments adjudicated deaths, bleeding episodes, reinfarction, ischaemia-driven revascularisation, stent thrombosis, and stroke; Group 1 Number missing: 15, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 23, Reason: Withdrew consent or lost to follow-up - Actual outcome: Complications related to bleeding: blood transfusion at 30 days; Group 1: 23/1089, Group 2: 43/1109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: 'generally well matched between the two groups, although there were higher rates of diabetes and previous myocardial infarction in the control group'; Blinding details: Open label study. An independent clinical-events committee whose members were unaware of study-group assignments adjudicated deaths, bleeding episodes, reinfarction, ischaemia-driven revascularisation, stent thrombosis, and stroke; Group 1 Number missing: 15, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 23, Reason: Withdrew consent or lost to follow-up - Actual outcome: Complications related to bleedings: acquired thrombocytopenia at 30 days; Group 1: 7/1089, Group 2: 14/1109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: 'generally well matched between the two groups, although there were higher rates of diabetes and previous myocardial infarction in the control group'; Blinding details: Open label study. An independent clinical-events committee whose members were unaware of study-group assignments adjudicated deaths, bleeding episodes, reinfarction, ischaemia-driven revascularisation, stent thrombosis, and stroke; Group 1 Number missing: , Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: , Reason: Withdrew consent or lost to follow-up Protocol outcome 5: Non-haemorrhagic stroke - Actual outcome: Stroke: any (type not specified) at 30 days; Group 1: 6/1089, Group 2: 11/1109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: 'generally well matched between the two groups, although there were higher rates of diabetes and previous myocardial infarction in the control group'; Blinding details: Open label study. An independent clinical-events committee	

Study	EUROMAX trial: Steg 2013[49]
whose members were unaware of study-group assignments adjudicated deaths, bleeding episodes, reinfarction, ischaemia-driven revascularisation, stent thrombosis, and stroke; Group 1 Number missing: , Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: , Reason: Withdrew consent or lost to follow-up - Actual outcome: Stroke: ischaemic at 30 days; Group 1: 6/1089, Group 2: 9/1109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: 'generally well matched between the two groups, although there were higher rates of diabetes and previous myocardial infarction in the control group'; Blinding details: Open label study. An independent clinical-events committee whose members were unaware of study-group assignments adjudicated deaths, bleeding episodes, reinfarction, ischaemia-driven revascularisation, stent thrombosis, and stroke; Group 1 Number missing: , Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: , Reason: Withdrew consent or lost to follow-up - Actual outcome: Stroke: haemorrhagic at 30 days; Group 1: 0/1089, Group 2: 2/1109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: 'generally well matched between the two groups, although there were higher rates of diabetes and previous myocardial infarction in the control group'; Blinding details: Open label study. An independent clinical-events committee whose members were unaware of study-group assignments adjudicated deaths, bleeding episodes, reinfarction, ischaemia-driven revascularisation, stent thrombosis, and stroke; Group 1 Number missing: , Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: , Reason: Withdrew consent or lost to follow-up Protocol outcome 6: Need for revascularisation at at 1 year - Actual outcome: Repeat revascularisation: defined as ischaemia-driven revascularisation at 30 days; Group 1: 24/1089, Group 2: 17/1109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: 'generally well matched between the two groups, although there were higher rates of diabetes and previous myocardial infarction in the control group'; Blinding details: Open label study. An independent clinical-events committee whose members were unaware of study-group assignments adjudicated deaths, bleeding episodes, reinfarction, ischaemia-driven revascularisation, stent thrombosis, and stroke; Group 1 Number missing: 15, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 23, Reason: Withdrew consent or lost to follow-up Protocol outcome 7: Early and late stent thrombosis - Actual outcome: Stent thrombosis: definite at 30 days; Group 1: 17/1089, Group 2: 6/1109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: 'generally well matched between the two groups, although there were higher rates of diabetes and previous myocardial infarction in the control group'; Blinding details: Open label study. An independent clinical-events committee whose members were unaware of study-group assignments adjudicated deaths, bleeding episodes, reinfarction, ischaemia-driven revascularisation, stent thrombosis, and stroke; Group 1 Number missing: , Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: , Reason: Withdrew consent or lost to follow-up - Actual outcome: Stent thrombosis: definite at ≤24 hours; Group 1: 12/1089, Group 2: 2/1109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Study	EUROMAX trial: Steg 2013[49]
Comments - ; Indirectness of outcome: No indirectness ; Baseline details: 'generally well matched between the two groups, although there were higher rates of diabetes and previous myocardial infarction in the control group'; Blinding details: Open label study. An independent clinical-events committee whose members were unaware of study-group assignments adjudicated deaths, bleeding episodes, reinfarction, ischaemia-driven revascularisation, stent thrombosis, and stroke; Group 1 Number missing: 15, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 23, Reason: Withdrew consent or lost to follow-up - Actual outcome: Stent thrombosis: definite at >24 hours to 30 days; Group 1: 5/1089, Group 2: 4/1109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: 'generally well matched between the two groups, although there were higher rates of diabetes and previous myocardial infarction in the control group'; Blinding details: Open label study. An independent clinical-events committee whose members were unaware of study-group assignments adjudicated deaths, bleeding episodes, reinfarction, ischaemia-driven revascularisation, stent thrombosis, and stroke; Group 1 Number missing: 15, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 23, Reason: Withdrew consent or lost to follow-up - Actual outcome: Stent thrombosis: probable at 30 days; Group 1: 0/1089, Group 2: 0/1109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: 'generally well matched between the two groups, although there were higher rates of diabetes and previous myocardial infarction in the control group'; Blinding details: Open label study. An independent clinical-events committee whose members were unaware of study-group assignments adjudicated deaths, bleeding episodes, reinfarction, ischaemia-driven revascularisation, stent thrombosis, and stroke; Group 1 Number missing: 15, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 23, Reason: Withdrew consent or lost to follow-up	
Protocol outcomes not reported by the study	Quality of life ; Re-infarction at at 1 year; Length of hospital stay ; Mortality at 1 year at at 1 year

Study	He 2016[18]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=260)
Countries and setting	Conducted in China; Setting: Hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 30 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Acute ST-segment elevation myocardial infarction diagnosed according to the standard of American College of Cardiology/American Heart Association/European Society

Study	He 2016[18]
	of Cardiology: chest pain or discomfort for at least 30 min, 12-lead ECG-adjacent two or more than two leads had ST-segment elevation of more than 0.1mV, or the new left bundle branch blocking
Stratum	Overall: People with ST-segment elevation myocardial infarction (STEMI)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with acute ST-segment elevation myocardial infarction >18 years old, including the patients accompanied by chest pain, persistent ST-segment elevation or new left bundle branch blocking in 12 hours and 12-24 hours of onset
Exclusion criteria	Before random grouping, receive thrombolytic therapy or receive any anticoagulant therapy within 48 hours; active bleeding or a recent history of bleeding or known bleeding tendencies; there is a history of surgery within the past month: aortic dissection is not excluded; at admission high blood pressure is serious (>180/110 mmHg) and not controlled; transaminases three times higher than the upper limit of normal or creatinine clearance <30 ml/min; there is a history of acquired thrombocytopenia caused by heparin; allergic to any study drugs and devices; pregnant or lactating persons; the patient does not or cannot agree to sign a written informed consent
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Bivalirudin group: 56.8 (10.1); Heparin group: 54.4 (11.8). Gender (M:F): 127/133. Ethnicity: Not reported
Further population details	1. Renal function: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=129) Intervention 1: Bivalirudin . Bivalirudin (Salubris Pharmaceutical Co, Ltd.): the first dose-intravenous bolus 0.75 mg/kg, then 1.75 mg/(kg-h) continuous intravenous infusion until PCI surgery was completed; this dose was maintained at least 30 min after surgery, but no more than 4 hours. After the prescribed medication, the doctor may propose intravenous infusion of bivalirudin [0.2 mg/(kg-h)] according to the disease condition, no more than 20 h. If no re-flow or other thrombotic complications occurred during surgery, tirofiban can be applied in temporary. Tirofiban (GPI) use in 6.2% (8/129). Duration 30 days. Concurrent medication/care: All patients received dual antiplatelet therapy; if no long-term use of aspirin or clopidogrel, before surgery aspirin (300mg) and clopidogrel (300mg) of loading dose were given. Surgical puncture site, stent type and thrombectomy devices were decided by surgeons. Indirectness: No indirectness Further details: 1. Drug dose: Not stated / Unclear 2. Number of stents: Not stated / Unclear 3. Type of antiplatelet: Not stated / Unclear 4. Use of GpIIb/IIIa : Not stated / Unclear (n=131) Intervention 2: Heparin - UFH + GpIIb/IIIa inhibitor. First dose-intravenous bolus of unfractionated heparin 100 U/kg and tirofiban 10 ug/kg; then intravenous tirofiban 0.15 ug/(kg.min) for 18-36 hours. Routine

Study	He 2016[18]
	GPI use in 100% (131/131). Duration 30 days. Concurrent medication/care: All patients received dual antiplatelet therapy; if no long-term use of aspirin or clopidogrel, before surgery aspirin (300mg) and clopidogrel (300mg) of loading dose were given. Surgical puncture site, stent type and thrombectomy devices were decided by surgeons. Indirectness: No indirectness Further details: 1. Drug dose: Not stated / Unclear 2. Number of stents: Not stated / Unclear 3. Type of antiplatelet: Not stated / Unclear 4. Use of GpIIb/IIIa : Not stated / Unclear
Funding	Other (This study was funded by the National Natural Science Foundation of China)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BIVALIRUDIN versus UFH + GPIIB/IIIA INHIBITOR

Protocol outcome 1: All cause mortality at up to 30 days
- Actual outcome: All cause mortality at 30 days; Group 1: 2/129, Group 2: 4/130
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline information, treatment and surgical characteristics were matched between the two groups'; Blinding details: Open label study; Group 1 Number missing: 129; Group 2 Number missing: 130, Reason: 1 loss to follow-up

Protocol outcome 2: Myocardial infarction at up to 30 days
- Actual outcome: Cardiac mortality at 30 days; Group 1: 2/129, Group 2: 3/130
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline information, treatment and surgical characteristics were matched between the two groups'; Blinding details: Open label study. All NACE and stent thrombosis events were blindly reviewed by an independent clinical event review committee; Group 1 Number missing: 129; Group 2 Number missing: 130, Reason: 1 loss to follow-up
- Actual outcome: New myocardial infarction (reinfarction) at 30 days; Group 1: 2/129, Group 2: 4/130
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline information, treatment and surgical characteristics were matched between the two groups'; Blinding details: Open label study. All NACE and stent thrombosis events were blindly reviewed by an independent clinical event review committee; Group 1 Number missing: 129; Group 2 Number missing: 130, Reason: 1 loss to follow-up

Protocol outcome 3: Complications related to bleeding
- Actual outcome: Complications related to bleeding (all bleeding) at 30 days; Group 1: 7/129, Group 2: 20/130
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline information, treatment and surgical characteristics were matched between the two groups'; Blinding details: Open label study. All NACE and stent thrombosis events were blindly reviewed by an independent clinical event review committee; Group 1 Number missing: 129; Group 2 Number missing: 130, Reason: 1 loss to follow-up
- Actual outcome: Complications related to bleeding (BRAC 2-5 level) at 30 days; Group 1: 1/129, Group 2: 7/130

Study	He 2016[18]
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline information, treatment and surgical characteristics were matched between the two groups'; Blinding details: Open label study. All NACE and stent thrombosis events were blindly reviewed by an independent clinical event review committee; Group 1 Number missing: 129; Group 2 Number missing: 130, Reason: 1 loss to follow-up - Actual outcome: Complications related to bleeding (BRAC 3-5 level) at 30 days; Group 1: 0/129, Group 2: 1/130 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline information, treatment and surgical characteristics were matched between the two groups'; Blinding details: Open label study. All NACE and stent thrombosis events were blindly reviewed by an independent clinical event review committee; Group 1 Number missing: 129; Group 2 Number missing: 130, Reason: 1 loss to follow-up - Actual outcome: Complications related to bleeding (acquired thrombocytopenia) at 30 days; Group 1: 0/129, Group 2: 1/130 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline information, treatment and surgical characteristics were matched between the two groups'; Blinding details: Open label study. All NACE and stent thrombosis events were blindly reviewed by an independent clinical event review committee; Group 1 Number missing: 129; Group 2 Number missing: 130, Reason: 1 loss to follow-up Protocol outcome 4: Non-haemorrhagic stroke - Actual outcome: Stroke (any, type not specified) at 30 days; Group 1: 0/129, Group 2: 1/130 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline information, treatment and surgical characteristics were matched between the two groups'; Blinding details: Open label study. All NACE and stent thrombosis events were blindly reviewed by an independent clinical event review committee; Group 1 Number missing: 129; Group 2 Number missing: 130, Reason: 1 loss to follow-up Protocol outcome 5: Need for revascularisation at at 1 year - Actual outcome: Repeat revascularisation (ischaemic target vessel revascularisation) at 30 days; Group 1: 3/129, Group 2: 3/130 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline information, treatment and surgical characteristics were matched between the two groups'; Blinding details: Open label study. All NACE and stent thrombosis events were blindly reviewed by an independent clinical event review committee; Group 1 Number missing: 129; Group 2 Number missing: 130, Reason: 1 loss to follow-up Protocol outcome 6: Early and late stent thrombosis - Actual outcome: Stent thrombosis (acute) at <24 hours; Group 1: 0/129, Group 2: 1/130 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline information, treatment and surgical characteristics were matched between the two groups'; Blinding details: Open label study. All NACE and stent thrombosis events were blindly reviewed by an independent clinical event review committee; Group 1 Number missing: 129; Group 2 Number missing: 130, Reason: 1 loss to follow-up - Actual outcome: Stent thrombosis (subacute) at 1-30 days; Group 1: 1/129, Group 2: 4/130 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low;	

Study	He 2016[18]
Indirectness of outcome: No indirectness ; Baseline details: 'Baseline information, treatment and surgical characteristics were matched between the two groups'; Blinding details: Open label study. All NACE and stent thrombosis events were blindly reviewed by an independent clinical event review committee; Group 1 Number missing: 129; Group 2 Number missing: 130, Reason: 1 loss to follow-up - Actual outcome: Stent thrombosis (definite) at 30 days; Group 1: 2/129, Group 2: 3/130 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline information, treatment and surgical characteristics were matched between the two groups'; Blinding details: Open label study. All NACE and stent thrombosis events were blindly reviewed by an independent clinical event review committee; Group 1 Number missing: 129; Group 2 Number missing: 130, Reason: 1 loss to follow-up - Actual outcome: Stent thrombosis (possible) at 30 days; Group 1: 0/129, Group 2: 1/130 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline information, treatment and surgical characteristics were matched between the two groups'; Blinding details: Open label study. All NACE and stent thrombosis events were blindly reviewed by an independent clinical event review committee; Group 1 Number missing: 129; Group 2 Number missing: 130, Reason: 1 loss to follow-up	
Protocol outcomes not reported by the study	Quality of life ; Mortality at 1 year at at 1 year; Re-infarction at at 1 year; Length of hospital stay ; Cardiac mortality at up to 30 days

Study	HEAT-PPCI trial: Shahzad 2014[47]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1829)
Countries and setting	Conducted in United Kingdom; Setting: Hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 28 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People presenting to the PPCI service and scheduled for emergency angiography for suspected STEMI
Stratum	Overall: People presenting to the PPCI service and scheduled for emergency angiography for suspected STEMI
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults (≥18 years)

Study	HEAT-PPCI trial: Shahzad 2014[47]
Exclusion criteria	Known intolerance, hypersensitivity, or contraindication to any trial drug; active bleeding at presentation; artificial ventilation, reduced conscious level or other factors precluding the administration of oral antiplatelet therapy; their physician refused to administer antiplatelet loading (uncertain diagnosis or risk of bleeding); or if they had previously been enrolled in this trial
Recruitment/selection of patients	All patients who presented to the PPCI service at the Liverpool Heart and Chest Hospital (Liverpool, UK) during the recruitment period were screened;
Age, gender and ethnicity	Age - Median (IQR): Bivalirudin group: 62.9 (53.7-74.0); Heparin group: 63.6 (54.0-73.8). Gender (M:F): 1327/502. Ethnicity: White/NonWhite ratio: 1736/93
Further population details	1. Renal function: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=915) Intervention 1: Bivalirudin . Bivalirudin given as a bolus of 0.75mg/kg followed by infusion of 1.75mg/kg/h for the duration of the procedure. A rebolus of 0.3mg/kg was administered if activated clotting time values 5-15 min after the bolus dose or at the end of the procedure were less than 225 seconds. Selective/bail out use of GPI (n=122/905; 13%; abciximab as per the European Society of Cardiology guidelines). The recommended dose was 0.25mg/kg intravenous bolus, followed by a continuous intravenous infusion of 0.125µg/kg/min (to a maximum of 10µg/min for 12h. Duration 28 days. Concurrent medication/care: All patients received dual antiplatelet therapy before PPCI as per routine practice at the host institution and its referring emergency departments. Indirectness: No indirectness Further details: 1. Drug dose: Not stated / Unclear 2. Number of stents: Not stated / Unclear 3. Type of antiplatelet: Not stated / Unclear (Type of P2Y12 inhibitor used: clopidogrel; prasugrel; ticagrelor for primary composite outcome only (major adverse cardiac event)). 4. Use of GpIIb/IIIa : Not stated / Unclear Comments: 907 patients (99%) received treatment as allocated (1 received heparin only and 7 did not receive any trial medication) (n=914) Intervention 2: Heparin - UFH. Unfractionated heparin given as a bolus dose of 70 U/kg body weight before the procedure. Additional doses were administered if activated clotting time values 5-15 min after the bolus dose or at the end of the procedure were less than 200 seconds. Selective/bail out use of GPI (n=140/906; 15%; abciximab as per the European Society of Cardiology guidelines. The recommended dose was 0.25mg/kg intravenous bolus, followed by a continuous intravenous infusion of 0.125µg/kg/min (to a maximum of 10µg/kg/min for 12h)

Study	HEAT-PPCI trial: Shahzad 2014[47]
	Duration 28 days. Concurrent medication/care: All patients received dual antiplatelet therapy before PPCI as per routine practice at the host institution and its referring emergency departments. Indirectness: No indirectness Further details: 1. Drug dose: Not stated / Unclear 2. Number of stents: Not stated / Unclear 3. Type of antiplatelet: Not stated / Unclear (Type of P2Y12 inhibitor used: clopidogrel; prasugrel; ticagrelor for primary composite outcome only (major adverse cardiac event)). 4. Use of GpIIb/IIIa : Not stated / Unclear Comments: 900 patients (98%) received treatment allocated (14 did not receive any trial medication)
Funding	Other (Liverpool Heart and Chest Hospital, UK National Institute of Health Research, The Medicines Company, AstraZeneca, The Bentley Drivers Club (UK))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BIVALIRUDIN versus UFH

Protocol outcome 1: All cause mortality at up to 30 days
- Actual outcome: All cause mortality at 28 days; Group 1: 46/905, Group 2: 39/907
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The baseline characteristics of patients were well matched between the two groups included in the analyses apart from increased rates of patient-reported previous myocardial infarction and PCI in the bivalirudin group'; Blinding details: Open-label study. All primary efficacy and safety outcome measures and stent thrombosis events were assessed by an independent Clinical Events Committee. The members of this group were masked to treatment allocation; Group 1 Number missing: 10, Reason: 10 surviving patients had no consent available; Group 2 Number missing: 9, Reason: 7 surviving patients had no consent available; 2 patients were lost to follow-up at 28 days

Protocol outcome 2: Myocardial infarction at up to 30 days
- Actual outcome: New myocardial infarction: new myocardial infarction or reinfarction at 28 days; Group 1: 24/905, Group 2: 8/907
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The baseline characteristics of patients were well matched between the two groups included in the analyses apart from increased rates of patient-reported previous myocardial infarction and PCI in the bivalirudin group'; Blinding details: Open-label study. All primary efficacy and safety outcome measures and stent thrombosis events were assessed by an independent Clinical Events Committee. The members of this group were masked to treatment allocation; Group 1 Number missing: 10, Reason: 10 surviving patients had no consent available; Group 2 Number missing: 9, Reason: 7 surviving patients had no consent available; 2 patients were lost to follow-up at 28 days

Protocol outcome 3: Complications related to bleeding
- Actual outcome: Complications related to bleeding: major bleed (classified as type 3-5 according to the BARC definition) at 28 days; Group 1: 32/905, Group 2: 28/907
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The baseline characteristics of patients were well matched between the two groups included

Study	HEAT-PPCI trial: Shahzad 2014[47]
in the analyses apart from increased rates of patient-reported previous myocardial infarction and PCI in the bivalirudin group'; Blinding details: Open-label study. All primary efficacy and safety outcome measures and stent thrombosis events were assessed by an independent Clinical Events Committee. The members of this group were masked to treatment allocation; Group 1 Number missing: 10, Reason: 10 surviving patients had no consent available; Group 2 Number missing: 9, Reason: 7 surviving patients had no consent available; 2 patients were lost to follow-up at 28 days - Actual outcome: Complications related to bleeding: minor bleed (classified as type 2 according to the BARC definition) at 28 days; Group 1: 83/905, Group 2: 98/907 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The baseline characteristics of patients were well matched between the two groups included in the analyses apart from increased rates of patient-reported previous myocardial infarction and PCI in the bivalirudin group'; Blinding details: Open-label study. All primary efficacy and safety outcome measures and stent thrombosis events were assessed by an independent Clinical Events Committee. The members of this group were masked to treatment allocation; Group 1 Number missing: 10, Reason: 10 surviving patients had no consent available; Group 2 Number missing: 9, Reason: 7 surviving patients had no consent available; 2 patients were lost to follow-up at 28 days Protocol outcome 4: Need for revascularisation at at 1 year - Actual outcome: Repeat revascularisation: additional unplanned target lesion revascularisation at 28 days; Group 1: 24/905, Group 2: 6/907 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The baseline characteristics of patients were well matched between the two groups included in the analyses apart from increased rates of patient-reported previous myocardial infarction and PCI in the bivalirudin group'; Blinding details: Open-label study. All primary efficacy and safety outcome measures and stent thrombosis events were assessed by an independent Clinical Events Committee. The members of this group were masked to treatment allocation; Group 1 Number missing: 10, Reason: 10 surviving patients had no consent available; Group 2 Number missing: 9, Reason: 7 surviving patients had no consent available; 2 patients were lost to follow-up at 28 days	
Protocol outcomes not reported by the study	Quality of life ; Non-haemorrhagic stroke ; Early and late stent thrombosis ; Mortality at 1 year at at 1 year; Re-infarction at at 1 year; Length of hospital stay ; Cardiac mortality at up to 30 days

Study	HORIZONS-AMI trial: Mehran 2009[29]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=3602)
Countries and setting	Conducted in Multiple countries; Setting: Hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 1 year follow-up

Study	HORIZONS-AMI trial: Mehran 2009[29]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Presenting within 12h after the onset of symptoms with STEMI of 1mm or more in two or more contiguous leads, new left bundle branch block, or true posterior myocardial infarction
Stratum	Overall: People with ST-segment elevation myocardial infarction (STEMI)
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18 years or older and presenting within 12h after the onset of symptoms with STEMI of 1mm or more in two or more contiguous leads, new left bundle branch block, or true posterior myocardial infarction
Exclusion criteria	Contraindications to any of the study drugs; previous administration of fibrinolytic therapy, bivalirudin, GPI, low-molecular-weight heparin, or fondaparinux for the present admission (previous unfractionated heparin was allowed); current use of coumadin; history of bleeding diathesis, conditions predisposing to haemorrhagic risk or refusal to receive blood transfusions; stroke or transient ischaemic attack within 6 months or any permanent neurological deficit; recent or known platelet count less than 100,000 cells per μL or haemoglobin concentration less than 100g/L; planned elective surgical procedure that would necessitate thienopyridine interruption within 6 months or enrolment; coronary stent implantation within 30 days; and non-cardiac comorbid conditions with life expectancy less than 1 year or that might result in protocol non-compliance
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Median (range): Bivalirudin group: 59.8 (26.0-92.3); Heparin group: 60.7 (21.6-91.6). Gender (M:F): 2760/842. Ethnicity: Not reported
Further population details	1. Renal function: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=1800) Intervention 1: Bivalirudin . Bivalirudin was given as an intravenous bolus of 0.75mg/kg followed by an infusion of 1.75mg/kg/h. Bivalirudin was discontinued, as specified by the protocol, at the completion of angiography or PCI but could be continued at low doses if required at the discretion of the operator. A GPI was to be given only to those patients who had refractory no reflow or giant thrombus after PCI. Abciximab (0.25mg/kg bolus plus 0.125μg/kg/min infusion, maximum 10μg/min) or double bolus eptifibatide (180μg/kg bolus plus 2.0μg/kg/min infusion, with a second bolus given in 10 min) were allowed as the GPI at the discretion of the investigator, adjusted for renal impairment as appropriate according to the US Food and Drug Administration label, and continued for 12h (abciximab) or 12-18h (eptifibatide). 126/1675 patients (7.5%) received a GPI . Duration 1 year. Concurrent medication/care: Aspirin (324g chewed or 500mg intravenous) was given in the emergency room, after which 300-325mg was given orally every day during the hospital stay, and 75-81mg every day thereafter indefinitely. A loading dose of clopidogrel (either 300mg or 600mg at the discretion of the investigator) was given before insertion of the catheter, followed by 75mg orally every day for at least 6 months; dual antiplatelet therapy was recommended for 1 year or longer. A

Study	HORIZONS-AMI trial: Mehran 2009[29]
	dynamic (minimisation) allocation scheme was used to balance randomisation for administration of prerandomisation heparin, administration of clopidogel 300mg or 600mg or ticlopidine 500mg before insertion of the catheter, planned administration of abciximab versus eptifibatide if randomised to control, and US or non-US study site . Indirectness: No indirectness Further details: 1. Drug dose: Not stated / Unclear 2. Number of stents: Not stated / Unclear 3. Type of antiplatelet: Not stated / Unclear 4. Use of GpIIb/IIIa : Not stated / Unclear (n=1802) Intervention 2: Heparin - UFH + GpIIb/IIIa inhibitor. Unfractionated heparin was given as an intravenous bolus of 60 IU/kg, with subsequent boluses titrated by nomogram to a target activated clotting time of 200-250 seconds. Heparin was discontinued, as specified by the protocol, at the completion of angiography or PCI but could be continued at low doses if required at the discretion of the operator. A GPI was given before PCI to all patients in the heparin group. Abciximab (0.25mg/kg bolus plus 0.125µg/kg/min infusion, maximum 10µg/min) or double bolus eptifibatide (180µg/kg bolus plus 2.0µg/kg/min infusion, with a second bolus given in 10 min) were allowed as the GPI at the discretion of the investigator, adjusted for renal impairment as appropriate according to the US Food and Drug Administration label, and continued for 12h (abciximab) or 12-18h (eptifibatide). 1625/1664 (97.7%) received a GPI, including abciximab (864; 52%), eptifibatide (758; 45.6%), and tirofiban (three; 0.2%); data were missing for two patients. Duration 1 year. Concurrent medication/care: Aspirin (324g chewed or 500mg intravenous) was given in the emergency room, after which 300-325mg was given orally every day during the hospital stay, and 75-81mg every day thereafter indefinitely. A loading dose of clopidogrel (either 300mg or 600mg at the discretion of the investigator) was given before insertion of the catheter, followed by 75mg orally every day for at least 6 months; dual antiplatelet therapy was recommended for 1 year or longer. A dynamic (minimisation) allocation scheme was used to balance randomisation for administration of prerandomisation heparin, administration of clopidogel 300mg or 600mg or ticlopidine 500mg before insertion of the catheter, planned administration of abciximab versus eptifibatide if randomised to control, and US or non-US study site . Indirectness: No indirectness Further details: 1. Drug dose: Not stated / Unclear 2. Number of stents: Not stated / Unclear 3. Type of antiplatelet: Not stated / Unclear 4. Use of GpIIb/IIIa : Not stated / Unclear
Funding	Other (Cardiovascular Research Foundation, with unrestricted grant support from Boston Scientific Corporation and The Medicines Company)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BIVALIRUDIN versus UFH + GPIIB/IIIA INHIBITOR Protocol outcome 1: Complications related to bleeding - Actual outcome: Complications related to bleeding: major bleeding, all (protocol-defined) at 1 year; Group 1: 17/1800, Group 2: 14/1802	

Study	HORIZONS-AMI trial: Mehran 2009[29]
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - Patients with missing data were censored at the time of withdrawal from the study or last follow-up; Indirectness of outcome: No indirectness ; Baseline details: 'The proportion of patients with hypertension was higher in the heparin group than in the bivalirudin group'; Blinding details: Reported to be an open label study but the following groups were masked to antithrombotic treatment: programmers, data analysis staff, statisticians, all core laboratories (angiographic, intravascular ultrasound, and electrocardiographic), and an independent clinical events committee ; Group 1 Number missing: 104, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year; Group 2 Number missing: 100, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year - Actual outcome: Complications related to bleeding: blood transfusion at 1 year; Group 1: 10/1800, Group 2: 7/1802 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - Patients with missing data were censored at the time of withdrawal from the study or last follow-up; Indirectness of outcome: No indirectness ; Baseline details: 'The proportion of patients with hypertension was higher in the heparin group than in the bivalirudin group'; Blinding details: Reported to be an open label study but the following groups were masked to antithrombotic treatment: programmers, data analysis staff, statisticians, all core laboratories (angiographic, intravascular ultrasound, and electrocardiographic), and an independent clinical events committee ; Group 1 Number missing: 104, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year; Group 2 Number missing: 100, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year - Actual outcome: Complications related to bleeding: decrease in haemoglobin concentration of 40g/L or more without an overt source of bleeding at 1 year; Group 1: 50/1800, Group 2: 85/1802 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - Patients with missing data were censored at the time of withdrawal from the study or last follow-up; Indirectness of outcome: No indirectness ; Baseline details: 'The proportion of patients with hypertension was higher in the heparin group than in the bivalirudin group'; Blinding details: Reported to be an open label study but the following groups were masked to antithrombotic treatment: programmers, data analysis staff, statisticians, all core laboratories (angiographic, intravascular ultrasound, and electrocardiographic), and an independent clinical events committee ; Group 1 Number missing: 104, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year; Group 2 Number missing: 100, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year - Actual outcome: Complications related to bleeding: decrease in haemoglobin concentration of 30g/L or more with an overt source of bleeding at 1 year; Group 1: 31/1800, Group 2: 45/1802 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - Patients with missing data were censored at the time of withdrawal from the study or last follow-up; Indirectness of outcome: No indirectness ; Baseline details: 'The proportion of patients with hypertension was higher in the heparin group than in the bivalirudin group'; Blinding details: Reported to be an open label study but the following groups were masked to antithrombotic treatment: programmers, data analysis staff, statisticians, all core laboratories (angiographic, intravascular ultrasound, and electrocardiographic), and an independent clinical events committee ; Group 1 Number missing: 104, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year; Group 2 Number missing: 100, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year - Actual outcome: Complications related to bleeding: major bleeding, non-CABG (protocol-defined) at 1 year; Group 1: 13/1800, Group 2: 10/1802 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - Patients with missing data were censored at the time of withdrawal from the study or last follow-up; Indirectness of outcome: No indirectness ; Baseline details: 'The proportion of patients with hypertension was higher in the heparin group than in the bivalirudin group'; Blinding details: Reported to be an

Study	HORIZONS-AMI trial: Mehran 2009[29]
open label study but the following groups were masked to antithrombotic treatment: programmers, data analysis staff, statisticians, all core laboratories (angiographic, intravascular ultrasound, and electrocardiographic), and an independent clinical events committee ; Group 1 Number missing: 104, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year; Group 2 Number missing: 100, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year - Actual outcome: Complications related to bleeding: haematomas 5cm or larger at 1 year; Group 1: 22/1800, Group 2: 47/1802 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - Patients with missing data were censored at the time of withdrawal from the study or last follow-up; Indirectness of outcome: No indirectness ; Baseline details: 'The proportion of patients with hypertension was higher in the heparin group than in the bivalirudin group'; Blinding details: Reported to be an open label study but the following groups were masked to antithrombotic treatment: programmers, data analysis staff, statisticians, all core laboratories (angiographic, intravascular ultrasound, and electrocardiographic), and an independent clinical events committee ; Group 1 Number missing: 104, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year; Group 2 Number missing: 100, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year Protocol outcome 2: Non-haemorrhagic stroke - Actual outcome: Stroke (type not specified) at 1 year; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - Patients with missing data were censored at the time of withdrawal from the study or last follow-up; Indirectness of outcome: No indirectness ; Baseline details: 'The proportion of patients with hypertension was higher in the heparin group than in the bivalirudin group'; Blinding details: Reported to be an open label study but the following groups were masked to antithrombotic treatment: programmers, data analysis staff, statisticians, all core laboratories (angiographic, intravascular ultrasound, and electrocardiographic), and an independent clinical events committee ; Group 1 Number missing: 104, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year; Group 2 Number missing: 100, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year Protocol outcome 3: Need for revascularisation at at 1 year - Actual outcome: Repeat revascularisation:target lesion revascularisation for ischaemia at 1 year; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - Patients with missing data were censored at the time of withdrawal from the study or last follow-up; Indirectness of outcome: No indirectness ; Baseline details: 'The proportion of patients with hypertension was higher in the heparin group than in the bivalirudin group'; Blinding details: Reported to be an open label study but the following groups were masked to antithrombotic treatment: programmers, data analysis staff, statisticians, all core laboratories (angiographic, intravascular ultrasound, and electrocardiographic), and an independent clinical events committee ; Group 1 Number missing: 104, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year; Group 2 Number missing: 100, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year Protocol outcome 4: Early and late stent thrombosis - Actual outcome: Stent thrombosis: definite or probable at 1 year; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - Patients with missing data were censored at the time of withdrawal from the study or last follow-up; Indirectness of outcome: No indirectness ; Baseline	

Study	HORIZONS-AMI trial: Mehran 2009[29]
details: 'The proportion of patients with hypertension was higher in the heparin group than in the bivalirudin group'; Blinding details: Reported to be an open label study but the following groups were masked to antithrombotic treatment: programmers, data analysis staff, statisticians, all core laboratories (angiographic, intravascular ultrasound, and electrocardiographic), and an independent clinical events committee ; Group 1 Number missing: 104, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year; Group 2 Number missing: 100, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year - Actual outcome: Stent thrombosis: definite at 1 year; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - Patients with missing data were censored at the time of withdrawal from the study or last follow-up; Indirectness of outcome: No indirectness ; Baseline details: 'The proportion of patients with hypertension was higher in the heparin group than in the bivalirudin group'; Blinding details: Reported to be an open label study but the following groups were masked to antithrombotic treatment: programmers, data analysis staff, statisticians, all core laboratories (angiographic, intravascular ultrasound, and electrocardiographic), and an independent clinical events committee ; Group 1 Number missing: 104, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year; Group 2 Number missing: 100, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year Protocol outcome 5: Mortality at 1 year at at 1 year - Actual outcome: All cause mortality at 1 year; Group 1: 24/1800, Group 2: 30/1802 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - Patients with missing data were censored at the time of withdrawal from the study or last follow-up; Indirectness of outcome: No indirectness ; Baseline details: 'The proportion of patients with hypertension was higher in the heparin group than in the bivalirudin group'; Blinding details: Reported to be an open label study but the following groups were masked to antithrombotic treatment: programmers, data analysis staff, statisticians, all core laboratories (angiographic, intravascular ultrasound, and electrocardiographic), and an independent clinical events committee ; Group 1 Number missing: 104, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year; Group 2 Number missing: 100, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year - Actual outcome: Cardiac mortality at 1 year; Group 1: 6/1800, Group 2: 15/1802 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - Patients with missing data were censored at the time of withdrawal from the study or last follow-up; Indirectness of outcome: No indirectness ; Baseline details: 'The proportion of patients with hypertension was higher in the heparin group than in the bivalirudin group'; Blinding details: Reported to be an open label study but the following groups were masked to antithrombotic treatment: programmers, data analysis staff, statisticians, all core laboratories (angiographic, intravascular ultrasound, and electrocardiographic), and an independent clinical events committee ; Group 1 Number missing: 104, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year; Group 2 Number missing: 100, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year - Actual outcome: Non-cardiac mortality at 1 year; Group 1: 18/1800, Group 2: 15/1802 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - Patients with missing data were censored at the time of withdrawal from the study or last follow-up; Indirectness of outcome: No indirectness ; Baseline details: 'The proportion of patients with hypertension was higher in the heparin group than in the bivalirudin group'; Blinding details: Reported to be an open label study but the following groups were masked to antithrombotic treatment: programmers, data analysis staff, statisticians, all core laboratories (angiographic, intravascular ultrasound, and electrocardiographic), and an independent clinical events committee ; Group 1 Number missing: 104,

Study	HORIZONS-AMI trial: Mehran 2009[29]
Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year; Group 2 Number missing: 100, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year Protocol outcome 6: Re-infarction at at 1 year - Actual outcome: New myocardial infarction: reinfarction at 1 year; Group 1: 29/1800, Group 2: 46/1802 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - Patients with missing data were censored at the time of withdrawal from the study or last follow-up; Indirectness of outcome: No indirectness ; Baseline details: 'The proportion of patients with hypertension was higher in the heparin group than in the bivalirudin group'; Blinding details: Reported to be an open label study but the following groups were masked to antithrombotic treatment: programmers, data analysis staff, statisticians, all core laboratories (angiographic, intravascular ultrasound, and electrocardiographic), and an independent clinical events committee ; Group 1 Number missing: 104, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year; Group 2 Number missing: 100, Reason: Participant drop out (withdrawal or loss to follow-up) at 1 year	
Protocol outcomes not reported by the study	Quality of life ; Myocardial infarction at up to 30 days ; Cardiac mortality at up to 30 days ; Length of hospital stay ; All cause mortality at up to 30 days

Study	HORIZONS-AMI trial: Stone 2008[60]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=3602)
Countries and setting	Conducted in Multiple countries; Setting: Emergency room; 123 centres in 11 countries
Line of therapy	Unclear
Duration of study	Intervention + follow up: 30-days follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients who presented within 12 hours after the onset of symptoms and who had ST-segment elevation of 1mm or more in two or more contiguous leads, new left bundle-branch block, or true posterior myocardial infarction
Stratum	Overall: People with ST-segment elevation
Subgroup analysis within study	Not applicable
Inclusion criteria	Consecutive patients 18 years of age or older who presented within 12 hours after the onset of symptoms and who had ST-segment elevation of 1mm or more in two or more contiguous leads, new left bundle-branch block, or true posterior myocardial infarction

Study	HORIZONS-AMI trial: Stone 2008[60]
Exclusion criteria	The principal exclusion criteria were contraindications to the study medications; prior administration of thrombolytic agents, bivalirudin, glycoprotein IIb/IIIa inhibitors, low-molecular-weight heparin, or fondaparinux for the present admission (although prior unfractionated heparin was allowed); current use of warfarin; history of bleeding diathesis, coagulopathy, heparin-induced thrombocytopenia, intracerebral mass, aneurysm, arteriovenous malformation, or haemorrhagic stroke, stroke or transient ischaemic attack within the previous 6 months or any permanent neurological deficit; refusal to receive blood transfusions; gastrointestinal or genitourinary bleeding within the previous 2 months; major surgery within the previous 6 weeks; a known platelet count of less than 100,000 cells per cubic millimetre or a haemoglobin level of less than 10g per decilitre, a planned elective surgical procedure that would necessitate an interruption in treatment with thienopyridines during the first 6 months after enrollment; coronary stent implantation within the previous 30 days; and noncardiac coexisting conditions that could limit life expectancy to less than 1 year or that might interfere with compliance with the protocol
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Median (range): Bivalirudin group: 59.8 (26.0-92.3); Heparin + GpIIb/IIIa inhibitor group: 60.7 (21.6-91.6). Gender (M:F): 2760/842. Ethnicity:
Further population details	1. Renal function: Not stated / Unclear
Extra comments	. Intended for PPCI but the principle management strategy included PPCI, deferred PCI, CABG and medical management. Those who underwent PPCI were analysed as a subgroup
Indirectness of population	No indirectness
Interventions	(n=1800) Intervention 1: Bivalirudin . Bivalirudin was administered as an intravenous bolus of 0.75mg/kg, followed by an infusion of 1.75mg/kg/h. If heparin was administered in a patient in the bivalirudin group, bivalirudin was started 30 minutes later but in all cases before PCI. The antithrombin agent was discontinued , as specified by the protocol, at the completion of angiography or PCI but could be continued at low doses if they were clinically indicated. A glycoprotein IIb/IIIa inhibitor was administered only in patients with no reflow or with giant thrombus after PCI. Either abciximab (a bolus of 0.25mg/kg followed by an infusion of 0.125µg/kg/minute; maximum dose, 10µg/kg/minute) or double bolus eptifibatide (a bolus of 180µg/kg followed by an infusion of 2.0µg/kg/minute, with a second bolus given 10 minutes after the first; no maximum dose prespecified), adjusted for renal impairment according to the label, was permitted at the discretion of the investigator and was continued for 12 hours (abciximab) or 12 to 18 hours (eptifibatide). Bail out GPI occurred in 129 patients (7.2%). Duration 30 days. Concurrent medication/care: Aspirin (324mg given orally or 500mg administered intravenously) was given in the emergency room, after which 300 to 325mg was given orally every day during the hospitalisation, and 75 to 81mg every day thereafter indefinitely. A loading dose of clopidogrel (either 300mg or 600mg, at the discretion of the investigator), or ticlopidine (500mg, in the case of allergy to clopidogrel, was administered before catheterisation, followed by 75mg orally every day for at least 6 months (1 year or longer recommended). Indirectness: No indirectness

Study	HORIZONS-AMI trial: Stone 2008[60]
	Further details: 1. Drug dose: Not stated / Unclear 2. Number of stents: Not stated / Unclear 3. Type of antiplatelet: Not stated / Unclear 4. Use of GpIIb/IIIa : Not stated / Unclear (n=1802) Intervention 2: Heparin - UFH + GpIIb/IIIa inhibitor. Heparin (unfractionated) was administered as an intravenous bolus of 60 IU/kg of body weight, with subsequent boluses targeted to an activated clotting time of 200 to 250 seconds. The antithrombin agent was discontinued, as specified by the protocol, at the completion of angiography or PCI but could be continued at low doses if they were clinically indicated. A glycoprotein IIb/IIIa inhibitor was administered before PCI in all patients. Either abciximab (a bolus of 0.25mg/kg followed by an infusion of 0.125µg/kg/minute; maximum dose, 10µg/kg/minute) or double bolus eptifibatide (a bolus of 180µg/kg followed by an infusion of 2.0µg/kg/minute, with a second bolus given 10 minutes after the first; no maximum dose prespecified), adjusted for renal impairment according to the label, was permitted at the discretion of the investigator and was continued for 12 hours (abciximab) or 12 to 18 hours (eptifibatide). . Duration 30 days. Concurrent medication/care: Aspirin (324mg given orally or 500mg administered intravenously) was given in the emergency room, after which 300 to 325mg was given orally every day during the hospitalisation, and 75 to 81mg every day thereafter indefinitely. A loading dose of clopidogrel (either 300mg or 600mg, at the discretion of the investigator), or ticlopidine (500mg, in the case of allergy to clopidogrel, was administered before catheterisation, followed by 75mg orally every day for at least 6 months (1 year or longer recommended). Indirectness: No indirectness Further details: 1. Drug dose: Not stated / Unclear 2. Number of stents: Not stated / Unclear 3. Type of antiplatelet: Not stated / Unclear 4. Use of GpIIb/IIIa : Not stated / Unclear
Funding	Other (The trial was sponsored and managed by the Cardiovascular Research Foundation, a nonprofit foundation affiliated with Columbia University (receiving funding from many commercial entities that make products for use in cardiovascular medicine, in addition to various other sources), with grant support from Boston Scientific and the Medicines Company. Other than supplying financial support and the drugs and devices, the funding companies were not involved with study processes, including site selection and management, data collection, and analysis)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BIVALIRUDIN versus UFH + GPIIB/IIIA INHIBITOR Protocol outcome 1: All cause mortality at up to 30 days - Actual outcome: All cause mortality at 30 days; Group 1: 37/1800, Group 2: 56/1802; Comments: In the subgroup analysis of patients who underwent PPCI, there were 33/1678 deaths in the bivalirudin group and 49/1662 deaths in the UFH + GpIIb/IIIa inhibitor group Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: The baseline features of the groups were reported to be well matched and that there were no	

Study	HORIZONS-AMI trial: Stone 2008[60]
	significant differences between groups, except for hypertension (P=0.04); Blinding details: Open label study. Core laboratories blinded and there was a clinical-event adjudication committee that required original-source documentation for event verification; Group 1 Number missing: 23, Reason: 10 withdrew consent; 13 were lost to follow-up; Group 2 Number missing: 24, Reason: 9 withdrew consent; 15 were lost to follow-up - Actual outcome: Non-cardiac mortality: bleeding-related death at 30 days; Group 1: 5/1800, Group 2: 4/1802; Comments: In the subgroup analysis of patients who underwent PPCI, there were 3/1678 deaths in the bivalirudin group and 2/1662 deaths in the UFH + GpIIb/IIIa inhibitor group Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: The baseline features of the groups were reported to be well matched and that there were no significant differences between groups, except for hypertension (P=0.04); Blinding details: Open label study. Core laboratories blinded and there was a clinical-event adjudication committee that required original-source documentation for event verification; Group 1 Number missing: 23, Reason: 10 withdrew consent; 13 were lost to follow-up; Group 2 Number missing: 24, Reason: 9 withdrew consent; 15 were lost to follow-up Protocol outcome 2: Myocardial infarction at up to 30 days - Actual outcome: New myocardial infarction: re-infarction at 30 days; Group 1: 33/1800, Group 2: 32/1802; Comments: In the subgroup analysis of patients who underwent PPCI, there were 33/1678 events in the bivalirudin group and 30/1662 events in the UFH + GpIIb/IIIa inhibitor group Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: The baseline features of the groups were reported to be well matched and that there were no significant differences between groups, except for hypertension (P=0.04); Blinding details: Open label study. Core laboratories blinded and there was a clinical-event adjudication committee that required original-source documentation for event verification; Group 1 Number missing: 23, Reason: 10 withdrew consent; 13 were lost to follow-up; Group 2 Number missing: 24, Reason: 9 withdrew consent; 15 were lost to follow-up Protocol outcome 3: Cardiac mortality at up to 30 days - Actual outcome: Cardiac mortality at 30 days; Group 1: 32/1800, Group 2: 52/1802; Comments: In the subgroup analysis of patients who underwent PPCI, there were 30/1678 cardiac-related deaths in the bivalirudin group and 47/1662 cardiac-related deaths in the UFH + GpIIb/IIIa inhibitor group Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: The baseline features of the groups were reported to be well matched and that there were no significant differences between groups, except for hypertension (P=0.04); Blinding details: Open label study. Core laboratories blinded and there was a clinical-event adjudication committee that required original-source documentation for event verification; Group 1 Number missing: 23, Reason: 10 withdrew consent; 13 were lost to follow-up; Group 2 Number missing: 24, Reason: 9 withdrew consent; 15 were lost to follow-up Protocol outcome 4: Complications related to bleeding - Actual outcome: Complications related to bleeding: major bleeding (defined as intracranial or intraocular haemorrhage; bleeding at the access site, with a haematoma that was 5cm or larger or that required intervention; a decrease in the haemoglobin level of 4g/decilitre or more without an overt bleeding source or 3g/decilitre or more with an overt bleeding source; re-operation for bleeding; or blood transfusion) non-CABG-related at 30 days; Group 1: 89/1800, Group 2: 149/1802; Comments: In the subgroup analysis of patients who underwent PPCI, there were 85/1678 events in the bivalirudin group and 142/1662 events in the UFH + GpIIb/IIIa inhibitor group Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: The baseline features of the groups were reported to be well matched and that there were no

Study	HORIZONS-AMI trial: Stone 2008[60]
significant differences between groups, except for hypertension (P=0.04); Blinding details: Open label study. Core laboratories blinded and there was a clinical-event adjudication committee that required original-source documentation for event verification; Group 1 Number missing: 23, Reason: 10 withdrew consent; 13 were lost to follow-up; Group 2 Number missing: 24, Reason: 9 withdrew consent; 15 were lost to follow-up - Actual outcome: Complications related to bleeding: blood transfusion at 30 days; Group 1: 37/1800, Group 2: 63/1802 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: The baseline features of the groups were reported to be well matched and that there were no significant differences between groups, except for hypertension (P=0.04); Blinding details: Open label study. Core laboratories blinded and there was a clinical-event adjudication committee that required original-source documentation for event verification; Group 1 Number missing: 23, Reason: 10 withdrew consent; 13 were lost to follow-up; Group 2 Number missing: 24, Reason: 9 withdrew consent; 15 were lost to follow-up - Actual outcome: Complications related to bleeding: moderate thrombocytopenia (<100,000 platelets/mm3) at 30 days; Group 1: 19/1665, Group 2: 48/1653 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: The baseline features of the groups were reported to be well matched and that there were no significant differences between groups, except for hypertension (P=0.04); Blinding details: Open label study. Core laboratories blinded and there was a clinical-event adjudication committee that required original-source documentation for event verification; Group 1 Number missing: 23, Reason: 10 withdrew consent; 13 were lost to follow-up; Group 2 Number missing: 24, Reason: 9 withdrew consent; 15 were lost to follow-up - Actual outcome: Complications related to bleeding: severe thrombocytopenia (<50,000 platelets/mm3) at 30 days; Group 1: 5/1665, Group 2: 15/1653 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: The baseline features of the groups were reported to be well matched and that there were no significant differences between groups, except for hypertension (P=0.04); Blinding details: Open label study. Core laboratories blinded and there was a clinical-event adjudication committee that required original-source documentation for event verification; Group 1 Number missing: 23, Reason: 10 withdrew consent; 13 were lost to follow-up; Group 2 Number missing: 24, Reason: 9 withdrew consent; 15 were lost to follow-up - Actual outcome: Complications related to profound thrombocytopenia (<20,000 platelets/mm3) at 30 days; Group 1: 6/1653, Group 2: 0/1665 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: The baseline features of the groups were reported to be well matched and that there were no significant differences between groups, except for hypertension (P=0.04); Blinding details: Open label study. Core laboratories blinded and there was a clinical-event adjudication committee that required original-source documentation for event verification; Group 1 Number missing: 23, Reason: 10 withdrew consent; 13 were lost to follow-up; Group 2 Number missing: 24, Reason: 9 withdrew consent; 15 were lost to follow-up Protocol outcome 5: Non-haemorrhagic stroke - Actual outcome: Stroke (type not specified) at 30 days; Group 1: 13/1800, Group 2: 11/1802; Comments: In the subgroup analysis of patients who underwent PPCI, there were 8/1678 strokes in the bivalirudin group and 8/1662 strokes in the UFH + GpIIb/IIIa inhibitor group Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: The baseline features of the groups were reported to be well matched and that there were no significant differences between groups, except for hypertension (P=0.04); Blinding details: Open label study. Core laboratories blinded and there was a clinical-event adjudication committee that required original-source documentation for event verification; Group 1 Number missing: 23, Reason: 10 withdrew consent; 13 were lost to follow-up; Group 2 Number missing: 24, Reason: 9 withdrew consent; 15 were lost to follow-up

Study	HORIZONS-AMI trial: Stone 2008[60]
Protocol outcome 6: Need for revascularisation at at 1 year - Actual outcome: Repeat revascularisation: revascularisation of target vessel for ischaemia at 30 days; Group 1: 47/1800, Group 2: 35/1802; Comments: In the subgroup analysis of patients who underwent PPCI, there were 47/1678 events in the bivalirudin group and 35/1662 events in the UFH + GpIIb/IIIa inhibitor group Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: The baseline features of the groups were reported to be well matched and that there were no significant differences between groups, except for hypertension (P=0.04); Blinding details: Open label study. Core laboratories blinded and there was a clinical-event adjudication committee that required original-source documentation for event verification; Group 1 Number missing: 23, Reason: 10 withdrew consent; 13 were lost to follow-up; Group 2 Number missing: 24, Reason: 9 withdrew consent; 15 were lost to follow-up	
Protocol outcomes not reported by the study	Quality of life ; Mortality at 1 year at at 1 year; Re-infarction at at 1 year; Length of hospital stay ; Early and late stent thrombosis

Study (subsidiary papers)	MATRIX trial: Leonardi 2016[22]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=7213 with acute coronary syndrome (4010 with ST segment elevation))
Countries and setting	Conducted in Italy, Netherlands, Spain, Sweden; Setting: 78 centres in Italy, the Netherlands, Spain and Sweden
Line of therapy	Unclear
Duration of study	Intervention + follow up: 30-day follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: persistent ST segment elevation
Stratum	Overall: Mixed population of acute coronary syndromes stratified by type i.e. with versus without ST segment elevation
Subgroup analysis within study	Not applicable:
Inclusion criteria	More than 20 minutes of ischaemic symptoms with ST segment elevation of ≥1mm in two or more contiguous electrocardiogram leads, or with a new left bundle branch block, or in case of ST segment depression of ≥1mm in two or more of leads V1-V3 with a positive terminal T wave if presented within 12 hours of symptom onset, or if there was evidence of continuing ischaemia or previous fibrinolytic treatment between 12 and 24 hours after symptom onset. Note that detailed inclusion criteria are listed in a

Study (subsidiary papers)	MATRIX trial: Leonardi 2016[22]
	supplementary appendix
Exclusion criteria	Key exclusion criteria were treatment with low molecular weight heparins within the past six hours; treatment with glycoprotein IIB/IIIa inhibitor in the previous three days; contraindications to angiography, including but not limited to severe peripheral vascular disease; and presumed life expectancy of less than 30 days. Note that detailed exclusion criteria are listed in a supplementary appendix
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Bivalirudin group with ST segment elevation: 63.9 (12.2); Heparin group with ST segment elevation: 63.9 (12.0). Gender (M:F): 5495/1718 (mixed population); 3093/917 (ST segment elevation population). Ethnicity: Not reported
Further population details	1. Renal function: Not applicable
Extra comments	The study uses the term acute coronary syndrome with ST segment elevation instead of ST elevation myocardial infarction to recognise the possibility of an aborted myocardial infarction in patients presenting with acute coronary syndrome and persistent ST segment elevation. 190 participants did not receive percutaneous coronary intervention and 173 had percutaneous coronary intervention for an indication different from primary percutaneous coronary intervention
Indirectness of population	No indirectness
Interventions	(n=3610) Intervention 1: Bivalirudin . Bivalirudin was given as a bolus of 0.75mg/kg body weight followed immediately by an infusion of 1.75mg/kg body weight hourly until completion of percutaneous coronary intervention. Bivalirudin was then stopped at the end of percutaneous coronary intervention, or prolonged in accordance with the subsequent random assignment. In patients allocated to prolonged treatment, bivalirudin could be administered for up to four hours at the full dose or at a reduced dose of 0.25mg/kg body weight hourly for at least six hours, at the discretion of the treating doctors. Overall, 3442 patients (95.3%) in the bivalirudin group (with and without ST segment elevation) received the allocated treatment. Glycoprotein IIb/IIIa inhibitor was restricted only to patients with thrombotic complications at the time of percutaneous coronary intervention, including no reflow or giant thrombus. Bail out GPI occurred in 121/2012 (6%). Duration 30 days. Concurrent medication/care: Use of other drugs was allowed as per guidelines. Indirectness: No indirectness Further details: 1. Drug dose: Not stated / Unclear 2. Number of stents: Not stated / Unclear 3. Type of antiplatelet: Not applicable 4. Use of GpIIb/IIIa : Not stated / Unclear (n=3603) Intervention 2: Heparin - UFH. Heparin was dosed at 70-100 units/kg body weight in patients not receiving glycoprotein IIb/IIIa inhibitors and at 50-70 units/kg body weight in patients receiving glycoprotein IIb/IIIa inhibitors. Subsequent heparin dosing based on activated clotting time was again left to the discretion of the investigator. Overall, 3474 patients (96.4%) in the bivalirudin group (with and without ST segment

Study (subsidiary papers)	MATRIX trial: Leonardi 2016[22]
	elevation) received the allocated treatment. A glycoprotein IIb/IIIa inhibitor could be administered before percutaneous coronary intervention based on investigator judgement. Selective use of GPI occurred in 613/1998 (30.7%); bail out GPI occurred in 86/1998 (4.3%). Duration 30 days. Concurrent medication/care: Use of other drugs was allowed as per guidelines. Indirectness: No indirectness Further details: 1. Drug dose: Not stated / Unclear 2. Number of stents: Not stated / Unclear 3. Type of antiplatelet: Not applicable 4. Use of GpIIb/IIIa : Not stated / Unclear
Funding	Other (The MATRIX programme was sponsored by the Italian Society of Invasive Cardiology (GISE), a non-profit organisation, and received grant support from The Medicines Company and TERUMO. The Medicines Company provided bivalirudin for the study. The sponsor had no role in study design, data collection, data monitoring, analysis, interpretation, or writing of the report)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BIVALIRUDIN versus UFH

Protocol outcome 1: All cause mortality at up to 30 days
- Actual outcome: All cause mortality at 30 days; Group 1: 42/2012, Group 2: 61/1998
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - The main paper reports that at 30 days, complete follow-up information was available for 7198 (99.8%) patients ; Indirectness of outcome: No indirectness ; Baseline details: similar within qualifying groups with acute coronary syndrome, with burden of risk factors for atherothrombosis and comorbidities higher in patients without ST segment elevation than those with ST segment elevation; Blinding details: Open label study. An independent clinical events committee, blinded to randomised treatment allocation, adjudicated all suspected events according to prespecified definitions; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Myocardial infarction at up to 30 days
- Actual outcome: New myocardial infarction: myocardial infarction at 30 days; Group 1: 73/2012, Group 2: 58/1998
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - The main paper reports that at 30 days, complete follow-up information was available for 7198 (99.8%) patients ; Indirectness of outcome: No indirectness ; Baseline details: similar within qualifying groups with acute coronary syndrome, with burden of risk factors for atherothrombosis and comorbidities higher in patients without ST segment elevation than those with ST segment elevation; Blinding details: Open label study. An independent clinical events committee, blinded to randomised treatment allocation, adjudicated all suspected events according to prespecified definitions; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Complications related to bleeding
- Actual outcome: Complications related to bleeding: BARC type 3 or 5 bleeding (major bleeding unrelated to CABG) at 30 days; Group 1: 33/2012, Group 2: 54/1998
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Study (subsidiary papers)	MATRIX trial: Leonardi 2016[22]

Comments - The main paper reports that at 30 days, complete follow-up information was available for 7198 (99.8%) patients ; Indirectness of outcome: No indirectness ; Baseline details: similar within qualifying groups with acute coronary syndrome, with burden of risk factors for atherothrombosis and comorbidities higher in patients without ST segment elevation than those with ST segment elevation; Blinding details: Open label study. An independent clinical events committee, blinded to randomised treatment allocation, adjudicated all suspected events according to prespecified definitions; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Non-haemorrhagic stroke
- Actual outcome: Stroke: type not specified at 30 days; Group 1: 5/2012, Group 2: 14/1998
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,
Comments - The main paper reports that at 30 days, complete follow-up information was available for 7198 (99.8%) patients ; Indirectness of outcome: No indirectness ; Baseline details: similar within qualifying groups with acute coronary syndrome, with burden of risk factors for atherothrombosis and comorbidities higher in patients without ST segment elevation than those with ST segment elevation; Blinding details: Open label study. An independent clinical events committee, blinded to randomised treatment allocation, adjudicated all suspected events according to prespecified definitions; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Early and late stent thrombosis
- Actual outcome: Stent thrombosis: definite stent thrombosis (acute and subacute) at 30 days; Group 1: 26/2012, Group 2: 14/1998
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,
Comments - The main paper reports that at 30 days, complete follow-up information was available for 7198 (99.8%) patients ; Indirectness of outcome: No indirectness ; Baseline details: similar within qualifying groups with acute coronary syndrome, with burden of risk factors for atherothrombosis and comorbidities higher in patients without ST segment elevation than those with ST segment elevation; Blinding details: Open label study. An independent clinical events committee, blinded to randomised treatment allocation, adjudicated all suspected events according to prespecified definitions; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: Stent thrombosis: definite stent thrombosis (acute) at 30 days; Group 1: 17/2012, Group 2: 9/1998
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,
Comments - The main paper reports that at 30 days, complete follow-up information was available for 7198 (99.8%) patients ; Indirectness of outcome: No indirectness ; Baseline details: similar within qualifying groups with acute coronary syndrome, with burden of risk factors for atherothrombosis and comorbidities higher in patients without ST segment elevation than those with ST segment elevation; Blinding details: Open label study. An independent clinical events committee, blinded to randomised treatment allocation, adjudicated all suspected events according to prespecified definitions; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: Stent thrombosis: definite stent thrombosis (subacute) at 30 days; Group 1: 9/2012, Group 2: 5/1998
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,
Comments - The main paper reports that at 30 days, complete follow-up information was available for 7198 (99.8%) patients ; Indirectness of outcome: No indirectness ; Baseline details: similar within qualifying groups with acute coronary syndrome, with burden of risk factors for atherothrombosis and comorbidities higher in patients without ST segment elevation than those with ST segment elevation; Blinding details: Open label study. An independent clinical events committee, blinded to randomised treatment allocation, adjudicated all suspected events according to prespecified definitions; Group 1 Number missing: ; Group 2 Number missing:

Study (subsidiary papers)	MATRIX trial: Leonardi 2016[22]
- Actual outcome: Stent thrombosis: definite or probable stent thrombosis (acute and subacute) at 30 days; Group 1: 32/2012, Group 2: 20/1998 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - The main paper reports that at 30 days, complete follow-up information was available for 7198 (99.8%) patients ; Indirectness of outcome: No indirectness ; Baseline details: similar within qualifying groups with acute coronary syndrome, with burden of risk factors for atherothrombosis and comorbidities higher in patients without ST segment elevation than those with ST segment elevation; Blinding details: Open label study. An independent clinical events committee, blinded to randomised treatment allocation, adjudicated all suspected events according to prespecified definitions; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Stent thrombosis: definite or probable stent thrombosis (acute) at 30 days; Group 1: 19/2012, Group 2: 10/1998 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - The main paper reports that at 30 days, complete follow-up information was available for 7198 (99.8%) patients ; Indirectness of outcome: No indirectness ; Baseline details: similar within qualifying groups with acute coronary syndrome, with burden of risk factors for atherothrombosis and comorbidities higher in patients without ST segment elevation than those with ST segment elevation; Blinding details: Open label study. An independent clinical events committee, blinded to randomised treatment allocation, adjudicated all suspected events according to prespecified definitions; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Stent thrombosis: definite or probable stent thrombosis (subacute) at 30 days; Group 1: 13/2012, Group 2: 10/1998 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Comments - The main paper reports that at 30 days, complete follow-up information was available for 7198 (99.8%) patients ; Indirectness of outcome: No indirectness ; Baseline details: similar within qualifying groups with acute coronary syndrome, with burden of risk factors for atherothrombosis and comorbidities higher in patients without ST segment elevation than those with ST segment elevation; Blinding details: Open label study. An independent clinical events committee, blinded to randomised treatment allocation, adjudicated all suspected events according to prespecified definitions; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life ; Need for revascularisation at at 1 year; Mortality at 1 year at at 1 year; Re-infarction at at 1 year; Length of hospital stay ; Cardiac mortality at up to 30 days

Study	The BRIGHT trial: Han 2015[17]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2194 (mixed population of STEMI and NSTEMI))
Countries and setting	Conducted in China; Setting: hospital; 82 centres in China
Line of therapy	Unclear
Duration of study	Intervention + follow up: One year follow-up

Study	The BRIGHT trial: Han 2015[17]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ST-segment elevation MI (STEMI) within 12 hours after symptom onset or within 12 to 24 hours with ongoing chest pain, ST-segment elevation or new left bundle-branch block, and non-STEMI (NSTEMI) in whom emergency PCI was required for either ongoing chest pain, heart failure, severe arrhythmias, or haemodynamic instability
Stratum	Overall: Mixed population of STEMI and NSTEMI (without stratification)
Subgroup analysis within study	Not applicable:
Inclusion criteria	Patients aged 18 to 80 years with AMI, including ST-segment elevation MI (STEMI) within 12 hours after symptom onset or within 12 to 24 hours with ongoing chest pain, ST-segment elevation or new left bundle-branch block, and non-STEMI (NSTEMI) in whom emergency PCI was required for either ongoing chest pain, heart failure, severe arrhythmias, or haemodynamic instability
Exclusion criteria	Major exclusion criteria included cardiogenic shock; thrombolytic therapy administered before randomisation or any anticoagulant administered within 48 hours of randomisation; active or recent major bleeding or bleeding predisposition; major surgery within 1 month; clinical syndrome suspicious for aortic dissection, pericarditis, or endocarditis; blood pressure higher than 180/100 mm Hg; known haemoglobin less than 10g/dL, platelet count less than 100 x 10*9/L, aminotransferase level greater than 3 x the upper limit of normal, or creatinine clearance less than 30mL/min; history of heparin-induced thrombocytopenia; allergy to any of the study drugs or devices; pregnancy or lactation; any condition making PCI unsuitable or that might interfere with study adherence; and patient unwilling or unable to provide written informed consent
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Range: 18 to 80 years. Gender (M:F): 1802/392 (STEMI and NSTEMI population); 1605/320 (STEMI subgroup) . Ethnicity: Not reported
Further population details	1. Renal function: Not stated / Unclear
Extra comments	
Indirectness of population	No indirectness
Interventions	(n=735) Intervention 1: Bivalirudin . Bivalirudin ((Salubris Pharmaceutical Co) was given as a bolus of 0.75mg/kg followed by infusion of 1.75mg/kg/h during the PCI procedure and for at least 30 minutes but no more than 4 hours afterwards. Following this mandatory infusion, a reduced-dose infusion (0.2mg/kg/h) for up to 20 hours could be administered at physician discretion. An additional bivalirudin bolus of 0.3mg/kg was given if the activated clotting time 5 minutes after the initial bolus (measured with the Hemotec assay) was less than 225 seconds. Provisional (bail out) tirofiban use was allowed for no reflow or other thrombotic complications. Bail out GPI occurred in 32/735 (4.4%). Duration 1 year . Concurrent medication/care: All patients received an oral loading dose prior to PCI of 300mg aspirin if not taking aspirin long-term (100-300mg otherwise) and 300-600mg clopidogrel if not taking long-term clopidogrel. Prasugrel and ticagrelor were not available for use during the trial. Other cardiovascular medications were given in accordance with

Study	The BRIGHT trial: Han 2015[17]
	current guidelines. Decisions regarding selection of access site, use of aspiration and stent type were at the operator discretion pursuant to local standards of care. Indirectness: No indirectness Further details: 1. Drug dose: Not stated / Unclear 2. Number of stents: Not stated / Unclear 3. Type of antiplatelet: Not stated / Unclear 4. Use of GpIIb/IIIa : Not stated / Unclear Comments: 723 underwent PPCI, 6 underwent CABG surgery and 6 underwent medical treatment following emergency angiography (n=729) Intervention 2: Heparin - Heparin (UFH and LMWH) alone. A heparin bolus dose of 100 U/kg was administered according to current guidelines. Additional heparin was administered if the post-bolus activated clotting time was less than 225 seconds. Provisional (bail out) tirofiban use was allowed for no reflow or other thrombotic complications. Bail out GPI occurred in 41/729 (5.6%). Duration 1 year. Concurrent medication/care: All patients received an oral loading dose prior to PCI of 300mg aspirin if not taking aspirin long-term (100-300mg otherwise) and 300-600mg clopidogrel if not taking long-term clopidogrel. Prasugrel and ticagrelor were not available for use during the trial. Other cardiovascular medications were given in accordance with current guidelines. Decisions regarding selection of access site, use of aspiration and stent type were at the operator discretion pursuant to local standards of care. Indirectness: No indirectness Further details: 1. Drug dose: Not stated / Unclear 2. Number of stents: Not stated / Unclear 3. Type of antiplatelet: Not stated / Unclear 4. Use of GpIIb/IIIa : Not stated / Unclear Comments: 719 underwent PPCI, 6 underwent CABG surgery and 4 underwent medical treatment following emergency angiography (n=730) Intervention 3: Heparin - Heparin (UFH and LMWH) + GpIIb/IIIa inhibitor. Heparin 60 U/kg and tirofiban 10μg/kg boluses were given followed by a 0.15μg/kg/min tirofiban infusion for 18 to 36 hours. Additional heparin was administered if the postbolus activated clotting time was less than 200 seconds . Duration 1 year. Concurrent medication/care: All patients received an oral loading dose prior to PCI of 300mg aspirin if not taking aspirin long-term (100-300mg otherwise) and 300-600mg clopidogrel if not taking long-term clopidogrel. Prasugrel and ticagrelor were not available for use during the trial. Other cardiovascular medications were given in accordance with current guidelines. Decisions regarding selection of access site, use of aspiration and stent type were at the operator discretion pursuant to local standards of care. Indirectness: No indirectness Further details: 1. Drug dose: Not stated / Unclear 2. Number of stents: Not stated / Unclear 3. Type of antiplatelet: Not stated / Unclear 4. Use of GpIIb/IIIa : Not stated / Unclear Comments: 722 underwent PPCI, 4 underwent CABG surgery and 4 underwent medical treatment following emergency angiography
Funding	Other (The BRIGHT trial was sponsored by the General Hospital of Shenyang Military Region, supported by a general research fund from the General Hospital of Shenyang Military Region, as well as profit grants from

Study	The BRIGHT trial: Han 2015[17]
	the Chinese Government National Key Research and Development project for the 12th five-year plan, and a research grant and study drug supply from Salubris Pharmaceutical Co (Shenzen, China))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BIVALIRUDIN versus HEPARIN (TYPE UNSPECIFIED) ALONE

Protocol outcome 1: All cause mortality at up to 30 days
- Actual outcome: STEMI subgroup all cause mortality at 1 year; Group 1: 12/655, Group 2: 16/641
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 5, Reason: Withdrew consent or lost to follow-up
- Actual outcome: STEMI subgroup cardiac mortality at 1 year; Group 1: 10/655, Group 2: 15/641
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 5, Reason: Withdrew consent or lost to follow-up
- Actual outcome: STEMI subgroup all cause mortality at 30 days; Group 1: 9/655, Group 2: 13/641
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 5, Reason: Withdrew consent or lost to follow-up

Protocol outcome 2: Myocardial infarction at up to 30 days
- Actual outcome: STEMI subgroup new myocardial infarction: reinfarction at 1 year; Group 1: 12/655, Group 2: 11/641
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 5, Reason: Withdrew consent or lost to follow-up
- Actual outcome: STEMI subgroup new myocardial infarction: reinfarction at 30 days; Group 1: 7/655, Group 2: 8/641

Study	The BRIGHT trial: Han 2015[17]
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 5, Reason: Withdrew consent or lost to follow-up	
Protocol outcome 3: Cardiac mortality at up to 30 days - Actual outcome: STEMI subgroup cardiac mortality at 30 days; Group 1: 8/655, Group 2: 13/641 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 5, Reason: Withdrew consent or lost to follow-up	
Protocol outcome 4: Complications related to bleeding - Actual outcome: STEMI subgroup complications related to bleeding: BARC 3-5 classification at 30 days; Group 1: 3/655, Group 2: 10/641 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 5, Reason: Withdrew consent or lost to follow-up - Actual outcome: STEMI subgroup complications related to bleeding: BARC 2-5 classification at 1 year; Group 1: 10/655, Group 2: 25/641 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 5, Reason: Withdrew consent or lost to follow-up - Actual outcome: STEMI subgroup complications related to bleeding: BARC 3-5 classification at 1 year; Group 1: 3/655, Group 2: 10/641 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number	

Study	The BRIGHT trial: Han 2015[17]
missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 5, Reason: Withdrew consent or lost to follow-up - Actual outcome: STEMI subgroup complications related to bleeding: BARC 2-5 classification at 30 days; Group 1: 8/655, Group 2: 23/641 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 5, Reason: Withdrew consent or lost to follow-up - Actual outcome: STEMI subgroup complications related to bleeding: acquired thrombocytopenia at 30 days; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 5, Reason: Withdrew consent or lost to follow-up Protocol outcome 5: Non-haemorrhagic stroke - Actual outcome: STEMI subgroup stroke: type unspecified at 30 days; Group 1: 5/655, Group 2: 6/641 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 5, Reason: Withdrew consent or lost to follow-up - Actual outcome: STEMI subgroup stroke: type unspecified at 1 year; Group 1: 6/655, Group 2: 10/641 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 5, Reason: Withdrew consent or lost to follow-up Protocol outcome 6: Need for revascularisation at at 1 year - Actual outcome: STEMI subgroup repeat revascularisation: ischaemic target vessel revascularisation at 30 days; Group 1: 10/655, Group 2: 12/641 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All	

Study	The BRIGHT trial: Han 2015[17]
	baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 5, Reason: Withdrew consent or lost to follow-up - Actual outcome: STEMI subgroup repeat revascularisation: ischaemic target vessel revascularisation at 1 year; Group 1: 13/655, Group 2: 13/641 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 5, Reason: Withdrew consent or lost to follow-up - Actual outcome: STEMI subgroup complications related to bleeding: all bleeding at 1 year; Group 1: 42/655, Group 2: 67/641 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 5, Reason: Withdrew consent or lost to follow-up Protocol outcome 7: Early and late stent thrombosis - Actual outcome: STEMI subgroup stent thrombosis: acute stent thrombosis at <24 hours; Group 1: 2/655, Group 2: 2/641 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 5, Reason: Withdrew consent or lost to follow-up - Actual outcome: STEMI subgroup stent thrombosis: subacute stent thrombosis at 1-30 days; Group 1: 2/655, Group 2: 4/641 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 5, Reason: Withdrew consent or lost to follow-up - Actual outcome: STEMI subgroup stent thrombosis: definite stent thrombosis at 30 days; Group 1: 3/655, Group 2: 5/641 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All

Study	The BRIGHT trial: Han 2015[17]
baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 5, Reason: Withdrew consent or lost to follow-up - Actual outcome: STEMI subgroup stent thrombosis: definite stent thrombosis at 1 year; Group 1: 6/655, Group 2: 10/641 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 5, Reason: Withdrew consent or lost to follow-up - Actual outcome: STEMI subgroup stent thrombosis: probable stent thrombosis at 30 days; Group 1: 1/655, Group 2: 1/641 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 5, Reason: Withdrew consent or lost to follow-up - Actual outcome: STEMI subgroup stent thrombosis: probable stent thrombosis at 1 year; Group 1: 1/655, Group 2: 1/641 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 5, Reason: Withdrew consent or lost to follow-up RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BIVALIRUDIN versus HEPARIN (TYPE UNSPECIFIED) + GPIIB/IIIA INHIBITOR Protocol outcome 1: All cause mortality at up to 30 days - Actual outcome: STEMI subgroup all cause mortality at 30 days; Group 1: 9/655, Group 2: 14/629 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 4, Reason: Withdrew consent or lost to follow-up - Actual outcome: STEMI subgroup all cause mortality at 1 year; Group 1: 12/655, Group 2: 17/629

Study	The BRIGHT trial: Han 2015[17]
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 4, Reason: Withdrew consent or lost to follow-up - Actual outcome: STEMI subgroup cardiac mortality at 1 year; Group 1: 10/655, Group 2: 15/629 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 4, Reason: Withdrew consent or lost to follow-up Protocol outcome 2: Myocardial infarction at up to 30 days - Actual outcome: STEMI subgroup new myocardial infarction: reinfarction at 30 days; Group 1: 7/655, Group 2: 5/629 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 4, Reason: Withdrew consent or lost to follow-up - Actual outcome: STEMI subgroup new myocardial infarction: reinfarction at 1 year; Group 1: 12/655, Group 2: 10/629 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 4, Reason: Withdrew consent or lost to follow-up Protocol outcome 3: Cardiac mortality at up to 30 days - Actual outcome: STEMI subgroup cardiac mortality at 30 days; Group 1: 8/655, Group 2: 14/629 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number	

Study	The BRIGHT trial: Han 2015[17]
missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 4, Reason: Withdrew consent or lost to follow-up Protocol outcome 4: Complications related to bleeding - Actual outcome: STEMI subgroup complications related to bleeding: acquired thrombocytopenia at 30 days; Group 1: 1/655, Group 2: 7/629 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 4, Reason: Withdrew consent or lost to follow-up - Actual outcome: STEMI subgroup complications related to bleeding: BARC 3-5 classification at 30 days; Group 1: 3/655, Group 2: 15/641 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 4, Reason: Withdrew consent or lost to follow-up - Actual outcome: STEMI subgroup complications related to bleeding: BARC 2-5 classification at 1 year; Group 1: 10/655, Group 2: 35/629 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 4, Reason: Withdrew consent or lost to follow-up - Actual outcome: STEMI subgroup complications related to bleeding: BARC 3-5 classification at 1 year; Group 1: 3/655, Group 2: 16/629 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 4, Reason: Withdrew consent or lost to follow-up - Actual outcome: STEMI subgroup complications related to bleeding: BARC 2-5 classification at 30 days; Group 1: 8/655, Group 2: 33/629 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number

Study	The BRIGHT trial: Han 2015[17]
missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 4, Reason: Withdrew consent or lost to follow-up Protocol outcome 5: Non-haemorrhagic stroke - Actual outcome: STEMI subgroup stroke: type unspecified at 30 days; Group 1: 5/655, Group 2: 4/629 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 4, Reason: Withdrew consent or lost to follow-up - Actual outcome: STEMI subgroup stroke: type unspecified at 1 year; Group 1: 6/655, Group 2: 6/629 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 4, Reason: Withdrew consent or lost to follow-up Protocol outcome 6: Need for revascularisation at at 1 year - Actual outcome: STEMI subgroup repeat revascularisation: ischaemic target vessel revascularisation at 30 days; Group 1: 10/655, Group 2: 8/629 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 4, Reason: Withdrew consent or lost to follow-up - Actual outcome: STEMI subgroup repeat revascularisation: ischaemic target vessel revascularisation at 1 year; Group 1: 13/655, Group 2: 11/629 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 4, Reason: Withdrew consent or lost to follow-up - Actual outcome: STEMI subgroup complications relating to bleeding: all bleeding at 1 year; Group 1: 42/655, Group 2: 87/629 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All	

Study	The BRIGHT trial: Han 2015[17]
	baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 4, Reason: Withdrew consent or lost to follow-up Protocol outcome 7: Early and late stent thrombosis - Actual outcome: STEMI subgroup stent thrombosis: acute stent thrombosis at <24 hours; Group 1: 2/655, Group 2: 2/629 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 4, Reason: Withdrew consent or lost to follow-up - Actual outcome: STEMI subgroup stent thrombosis: subacute stent thrombosis at 1-30 days; Group 1: 2/655, Group 2: 3/629 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 4, Reason: Withdrew consent or lost to follow-up - Actual outcome: STEMI subgroup stent thrombosis: definite stent thrombosis at 30 days; Group 1: 3/655, Group 2: 4/629 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 4, Reason: Withdrew consent or lost to follow-up - Actual outcome: STEMI subgroup stent thrombosis: definite stent thrombosis at 1 year; Group 1: 6/655, Group 2: 6/629 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organisation. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomisation assignment; Group 1 Number missing: 8, Reason: Withdrew consent or lost to follow-up; Group 2 Number missing: 4, Reason: Withdrew consent or lost to follow-up - Actual outcome: STEMI subgroup stent thrombosis: probable stent thrombosis at 30 days; Group 1: 1/655, Group 2: 1/629 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline details for mixed population (STEMI and NSTEMI) reported to be well matched between groups, as were treatments and procedures. There was no stratification by STEMI versus NSTEMI ; Blinding details: Open label trial. All

Study	The BRIGHT trial: Han 2015[17]
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Protocol outcomes not reported by the study	Quality of life ; Re-infarction at at 1 year; Length of hospital stay ; Mortality at 1 year at at 1 year

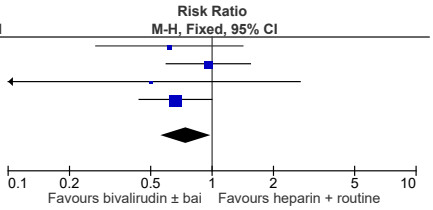
Appendix E: Forest plots

E.1 Bivalirudin ± bailout glycoprotein inhibitor versus heparin + routine glycoprotein inhibitor

Figure 1: All cause mortality (at 30 days)

Study or Subgroup	Bivalirudin ± bailout GPI Events	Total	Heparin + routine GPI Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BRIGHT (Han 2015)	9	655	14	629	13.2%	0.62 [0.27, 1.42]
EUROMAX (Steg 2013)	32	1089	34	1109	31.2%	0.96 [0.60, 1.54]
He 2016	2	129	4	130	3.7%	0.50 [0.09, 2.70]
HORIZONS-AMI (Stone 2008)	37	1800	56	1802	51.9%	0.66 [0.44, 1.00]
Total (95% CI)		**3673**		**3670**	**100.0%**	**0.74 [0.56, 0.99]**
Total events	80		108			

Heterogeneity: Chi² = 1.81, df = 3 (P = 0.61); I² = 0%
Test for overall effect: Z = 2.05 (P = 0.04)

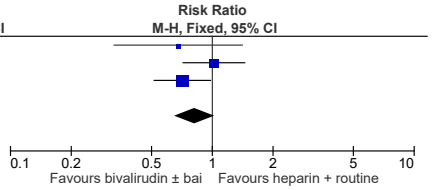


Bailout GPI use: 4.4-7.9%. Routine GPI use: 100% (Han 2015); 58.5% (Steg 2013); 100% (He 2016); 97.7% of those undergoing PPCI (Stone 2008). Concurrent antiplatelet therapy: aspirin, clopidogrel (Han 2015); aspirin, P2Y12 inhibitor (Steg 2013); aspirin, clopidogrel (He 2016); aspirin, clopidogrel or ticlopidine (Stone 2008). Radial access: 78.5% (Han 2015); 47% (Steg 2013); 84% (He 2016); % not reported (Stone 2008)*

Figure 2: All cause mortality (at 1 year)

Study or Subgroup	Bivalirudin ± bailout GPI Events	Total	Heparin + routine GPI Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BRIGHT (Han 2015)	12	655	17	629	10.7%	0.68 [0.33, 1.41]
EUROMAX (Fabris 2017)	59	1089	59	1109	36.1%	1.02 [0.72, 1.45]
HORIZONS-AMI (Mehran 2009)	61	1800	86	1802	53.1%	0.71 [0.51, 0.98]
Total (95% CI)		**3544**		**3540**	**100.0%**	**0.82 [0.65, 1.02]**
Total events	132		162			

Heterogeneity: Chi² = 2.49, df = 2 (P = 0.29); I² = 20%
Test for overall effect: Z = 1.75 (P = 0.08)

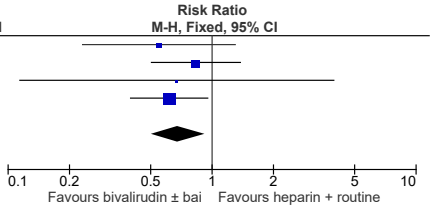


Bailout GPI use: 4.4-7.9%. Routine GPI use: 100% (Han 2015); 58.5% (Fabris 2017); 97.7% of those undergoing PPCI (Mehran 2009). Concurrent antiplatelet therapy: aspirin, clopidogrel (Han 2015); aspirin, P2Y12 inhibitor (Fabris 2017); aspirin, clopidogrel or ticlopidine (Mehran 2009). Radial access: 78.5% (Han 2015); 47% (Fabris 2017); % not reported (Mehran 2009)*

Figure 3: Cardiac mortality (at 30 days)

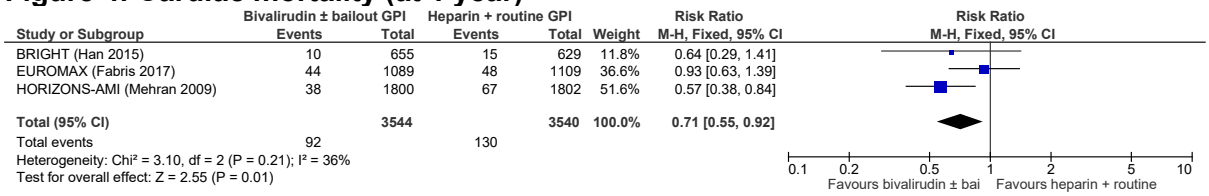
Study or Subgroup	Bivalirudin ± bailout GPI Events	Total	Heparin + routine GPI Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BRIGHT (Han 2015)	8	655	14	629	14.0%	0.55 [0.23, 1.30]
EUROMAX (Steg 2013)	27	1089	33	1109	32.1%	0.83 [0.50, 1.38]
He 2016	2	129	3	130	2.9%	0.67 [0.11, 3.95]
HORIZONS-AMI (Stone 2008)	32	1800	52	1802	51.0%	0.62 [0.40, 0.95]
Total (95% CI)		**3673**		**3670**	**100.0%**	**0.68 [0.50, 0.92]**
Total events	69		102			

Heterogeneity: Chi² = 1.07, df = 3 (P = 0.79); I² = 0%
Test for overall effect: Z = 2.52 (P = 0.01)



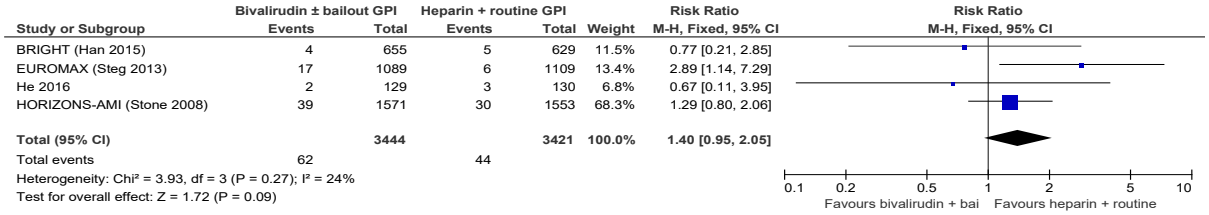
Bailout GPI use: 4.4-7.9%. Routine GPI use: 100% (Han 2015); 58.5% (Steg 2013); 100% (He 2016); 97.7% of those undergoing PPCI (Stone 2008). Concurrent antiplatelet therapy: aspirin, clopidogrel (Han 2015); aspirin, P2Y12 inhibitor (Steg 2013); aspirin, clopidogrel (He 2016); aspirin, clopidogrel or ticlopidine (Stone 2008). Radial access: 78.5% (Han 2015); 47% (Steg 2013); 84% (He 2016); % not reported (Stone 2008)*

Figure 4: Cardiac mortality (at 1 year)



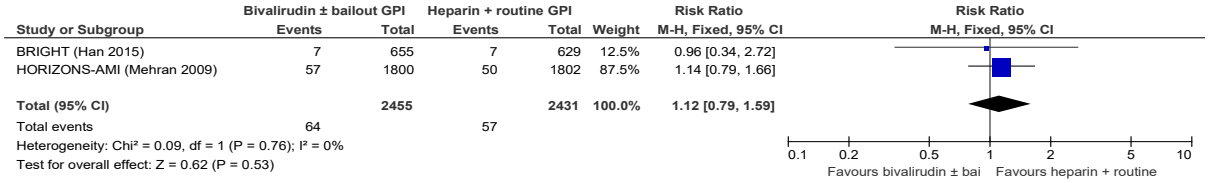
Bailout GPI use: 4.4-7.9%. Routine GPI use: 100% (Han 2015); 58.5% (Fabris 2017); 97.7% of those undergoing PPCI (Mehran 2009). Concurrent antiplatelet therapy: aspirin, clopidogrel (Han 2015); aspirin, P2Y12 inhibitor (Fabris 2017); aspirin, clopidogrel or ticlopidine (Mehran 2009). Radial access: 78.5% (Han 2015); 47% (Fabris 2017); % not reported (Mehran 2009)*

Figure 5: Stent thrombosis (definite and probable at up to 30 days)



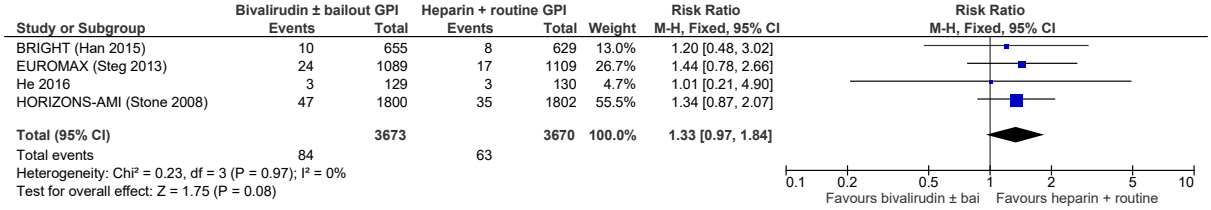
Bailout GPI use: 4.4-7.2%. Routine GPI use: 100% (Han 2015; He 2016); 58.5% (Steg 2013); 97.7% of those undergoing PPCI (Stone 2008). Concurrent antiplatelet therapy: aspirin, clopidogrel (Han 2015; He 2016); aspirin, P2Y12 inhibitor (Steg 2013); clopidogrel or ticlopidine (Stone 2008). Radial access: 78.5% (Han 2015); 47% (Steg 2013); 84% (He 2016); % not reported (Stone 2008)

Figure 6: Stent thrombosis (definite and probable at 1 year)



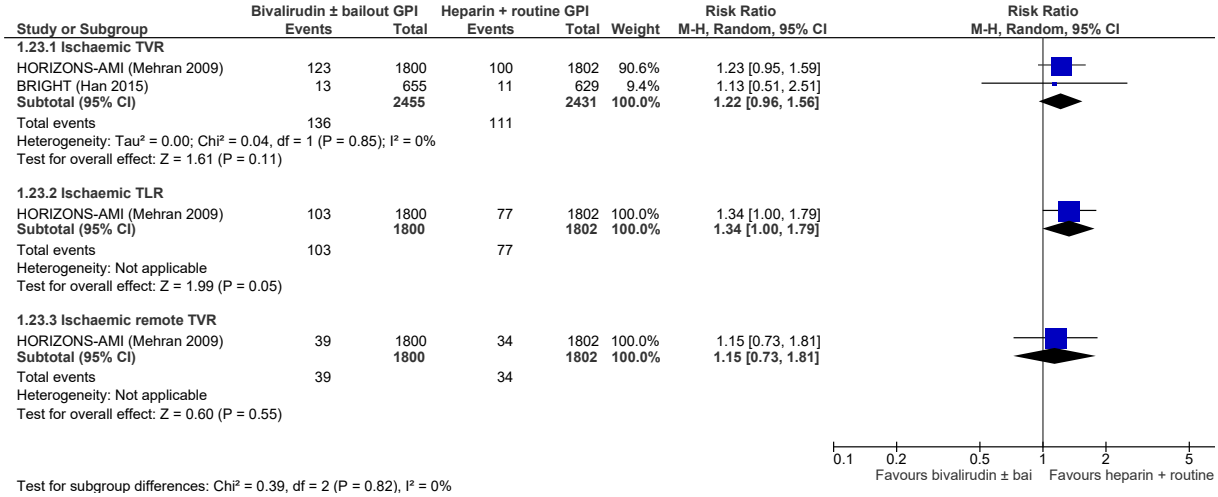
Bailout GPI use: 4.4-7.2%. Routine GPI use: 100% (Han 2015; He 2016); 58.5% (Steg 2013); 97.7% of those undergoing PPCI (Stone 2008). Concurrent antiplatelet therapy: aspirin, clopidogrel (Han 2015; He 2016); aspirin, P2Y12 inhibitor (Steg 2013); clopidogrel or ticlopidine (Stone 2008). Radial access: 78.5% (Han 2015); 47% (Steg 2013); 84% (He 2016); % not reported (Stone 2008)

Figure 7: Repeat revascularisation (ischaemia-driven revascularisation at 30 days)



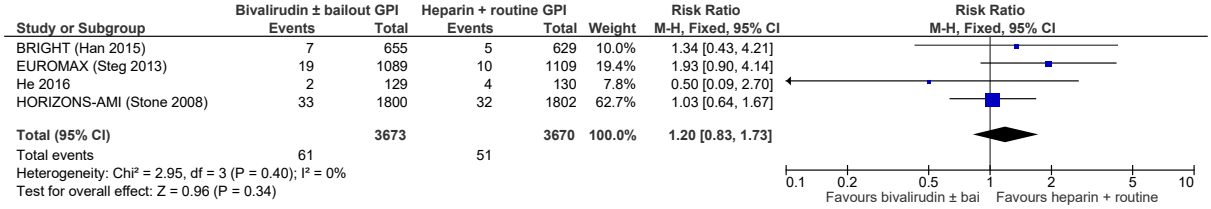
Bailout GPI use: 4.4-7.9%. Routine GPI use: 100% (Han 2015); 58.5% (Steg 2013); 100% (He 2016); 97.7% of those undergoing PPCI (Stone 2008). Concurrent antiplatelet therapy: aspirin, clopidogrel (Han 2015); aspirin, P2Y12 inhibitor (Steg 2013); aspirin, clopidogrel (He 2016); aspirin, clopidogrel or ticlopidine (Stone 2008). Radial access: 78.5% (Han 2015); 47% (Steg 2013); 84% (He 2016); % not reported (Stone 2008)*

Figure 8: Repeat revascularisation (at 1 year)



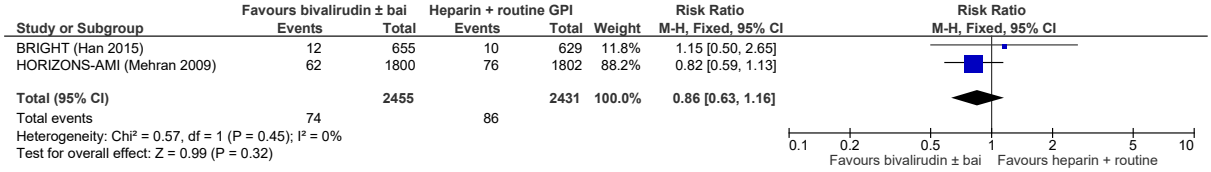
Bailout GPI use: 4.4-7.5%. Routine GPI use: 100% (Han, 2015); 97.7% of those undergoing PPCI (Mehran 2009). Concurrent antiplatelet therapy: aspirin, clopidogrel (Han 2015); aspirin, clopidogrel or ticlopidine (Mehran 2009). Radial access: 78.5% (Han 2015); % not reported (Mehran 2009)

Figure 9: New myocardial infarction (reinfarction at 30 days)



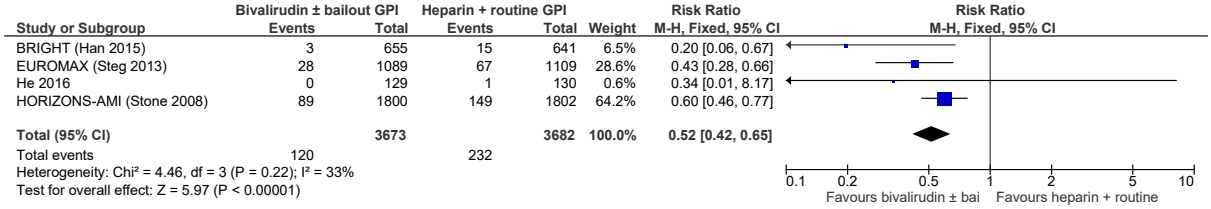
Bailout GPI use: 4.4-7.9%. Routine GPI use: 100% (Han 2015); 58.5% (Steg 2013); 100% (He 2016); 97.7% of those undergoing PPCI (Stone 2008). Concurrent antiplatelet therapy: aspirin, clopidogrel (Han 2015); aspirin, P2Y12 inhibitor (Steg 2013); aspirin, clopidogrel (He 2016); aspirin, clopidogrel or ticlopidine (Stone 2008). Radial access: 78.5% (Han 2015); 47% (Steg 2013); 84% (He 2016); % not reported (Stone 2008)*

Figure 10: New myocardial infarction (reinfarction at 1 year)



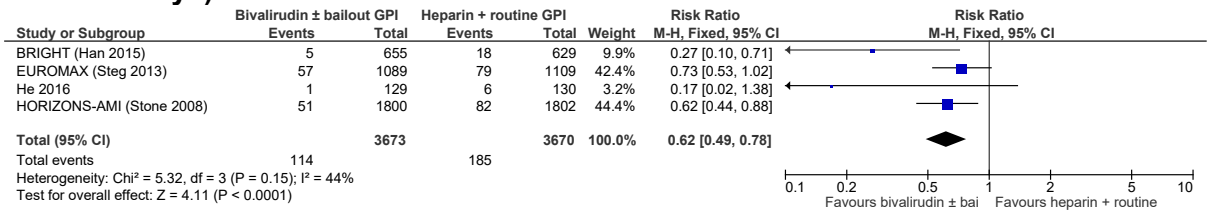
Bailout GPI use: 4.4-7.5%. Routine GPI use: 100% (Han 2015); 97.7% of those undergoing PPCI (Mehran 2009). Concurrent antiplatelet therapy: aspirin, clopidogrel (Han 2015); aspirin, clopidogrel or ticlopidine (Mehran 2009). Radial access: 78.5% (Han 2015); % not reported (Mehran 2009)

Figure 11: Complications related to bleeding (major including BARC 3-5 at 30 days)



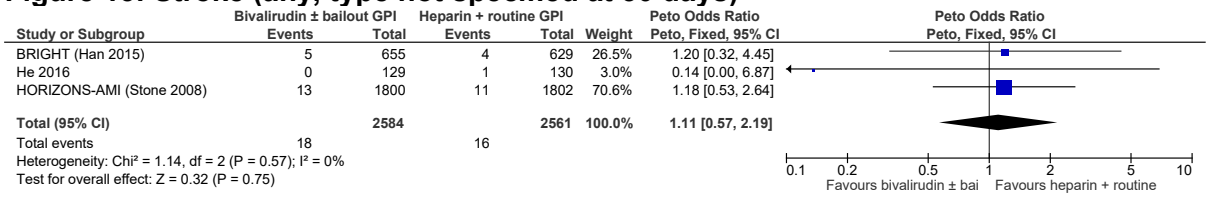
Bailout GPI use: 4.4-7.9%. Routine GPI use: 100% (Han 2015); 58.5% (Steg 2013); 100% (He 2016); 97.7% of those undergoing PPCI (Stone 2008). Concurrent antiplatelet therapy: aspirin, clopidogrel (Han 2015); aspirin, P2Y12 inhibitor (Steg 2013); aspirin, clopidogrel (He 2016); aspirin, clopidogrel or ticlopidine (Stone 2008). Radial access: 78.5% (Han 2015); 47% (Steg 2013); 84% (He 2016); % not reported (Stone 2008). Bleeding scores: BARC 3-5 (Han 2015 and He 2016); major (Steg 2013 and Stone 2008)*

Figure 12: Complications related to bleeding (minor including TIMI and BARC 2 at 30 days)



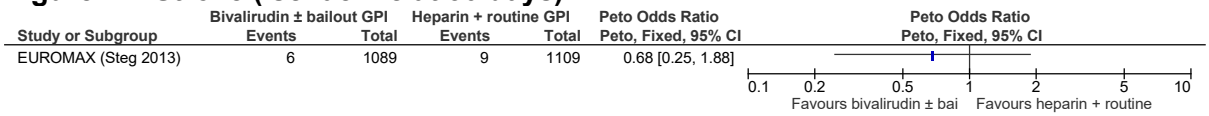
Bailout GPI use: 4.4-7.9%. Routine GPI use: 100% (Han 2016; He 2016); 97.7% of those undergoing PPCI (Stone 2008); 58.5%. (Steg 2013). Concurrent antiplatelet therapy: aspirin, clopidogrel (Han 2015; He 2016); aspirin, P2Y12 inhibitor (Steg 2013). Radial access: 78.5% (Han 2015); 47% (Steg 2013); 84% (He 2016); % not reported (Stone 2008). Bleeding scores: BARC 2 (Han 2015 and He 2016); minor (Steg 2013); minor, TIMI (Stone 2008)*

Figure 13: Stroke (any, type not specified at 30 days)



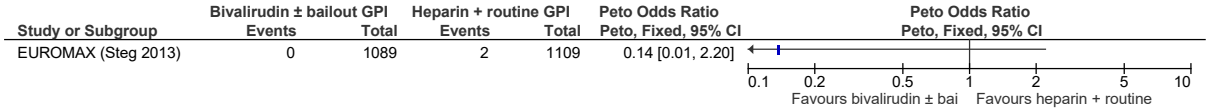
Bailout GPI use: 4.4-7.2%. Routine GPI use: 100% (Han 2015; He 2016); 97.7% of those undergoing PPCI (Stone 2008). Concurrent antiplatelet therapy: aspirin, clopidogrel (Han 2015; He 2016); aspirin, clopidogrel or ticlopidine (Stone 2008). Radial access: 78.5% (Han 2015); 84% (He 2016); % not reported (Stone 2008)

Figure 14: Stroke (ischaemic at 30 days)



Bailout GPI use: 7.9%. Routine GPI use: 58.5%. Concurrent antiplatelet therapy: aspirin, P2Y12 inhibitor. Radial access: 47%*

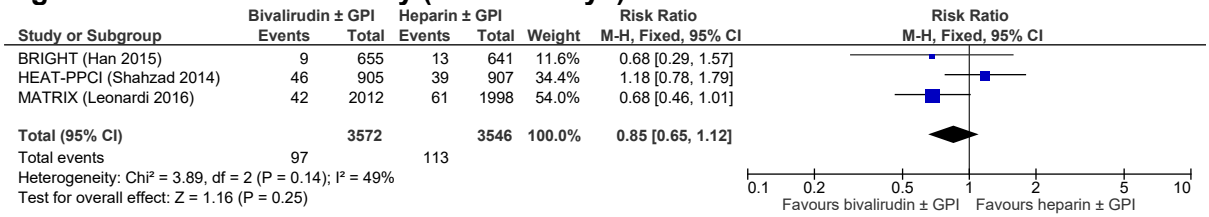
Figure 15: Stroke (haemorrhagic at 30 days)



Bailout GPI use: 7.9%. Routine GPI use: 58.5%. Concurrent antiplatelet therapy: aspirin, P2Y12 inhibitor. Radial access: 47%*

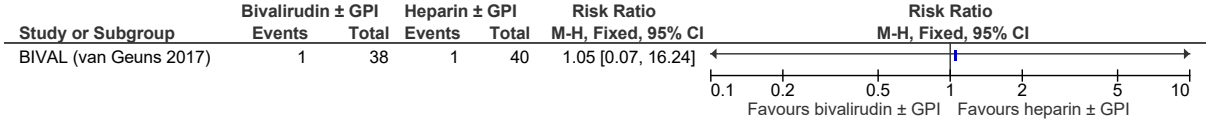
E.2 Bivalirudin ± bailout/selective glycoprotein inhibitor versus heparin ± bailout/selective glycoprotein inhibitor

Figure 16: All cause mortality (at 28-30 days)



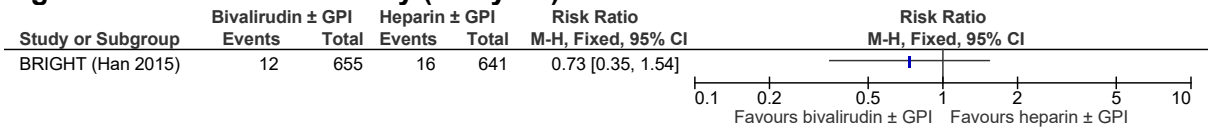
GPI use 4.3-35%. Concurrent antiplatelet therapy: aspirin, clopidogrel (Han 2015); dual antiplatelet therapy (Shahzad 2014); P2Y12 inhibitor (clopidogrel, ticagrelor or prasugrel) (Leonardi 2016). Radial access: 78.5% (Han 2015); 81% (Shahzad 2014); 50% (Leonardi 2016)

Figure 17: All cause mortality (at unclear timepoint)



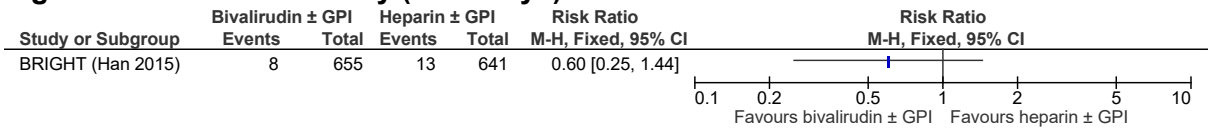
GPI use 8-11%. Concurrent antiplatelet therapy: aspirin, P2Y12 inhibitor. Radial access: 94% (van Geuns 2017)

Figure 18: All cause mortality (at 1 year)



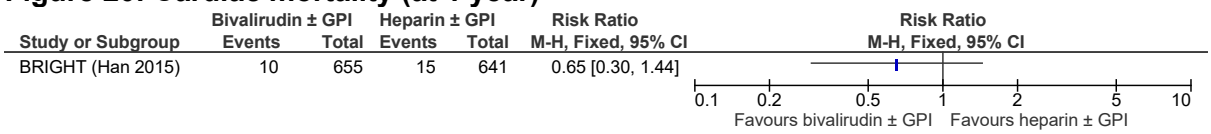
GPI use: 4.4-5.6%. Concurrent antiplatelet therapy: aspirin, clopidogrel. Radial access: 78.5%

Figure 19: Cardiac mortality (at 30 days)



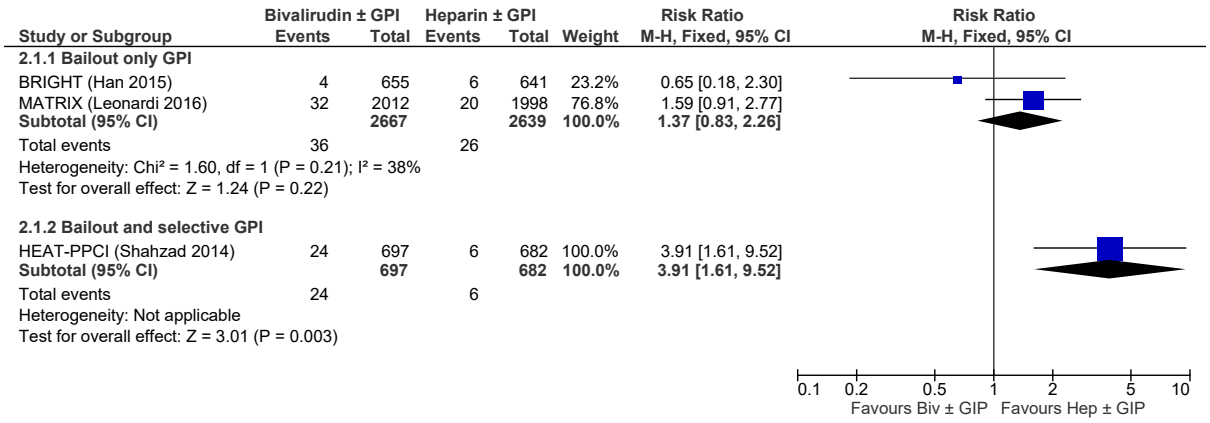
GPI use 4.4-5.6%. Concurrent antiplatelet therapy: aspirin, clopidogrel. Radial access: 78.5%

Figure 20: Cardiac mortality (at 1 year)



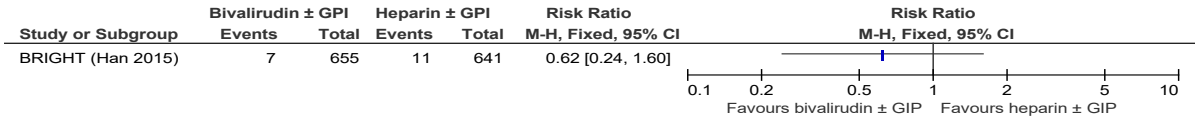
GPI use 4.4-5.6%. Concurrent antiplatelet therapy: aspirin, clopidogrel. Radial access: 78.5%

Figure 21: Stent thrombosis (definite and probable at up to 30 days)



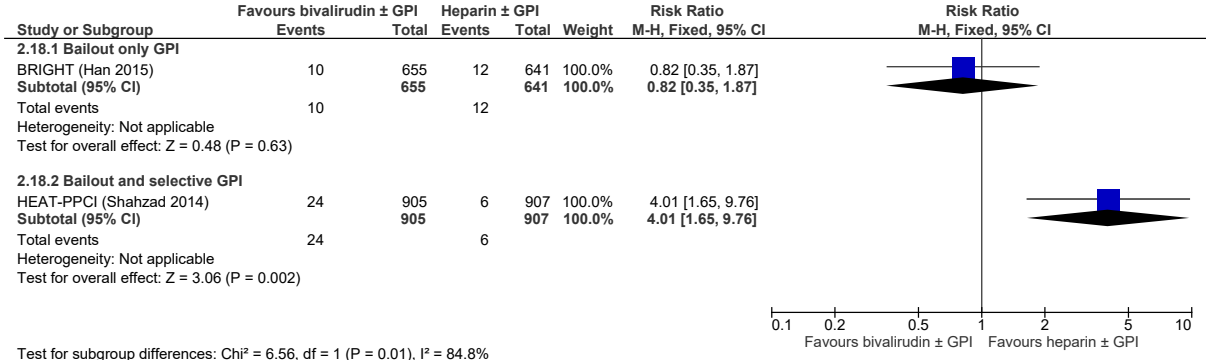
GPI use: 4.4-5.6% (Han 2015); 4.3-35% (Leonardi 2016);13-15% (Shahzad 2014). Concurrent antiplatelet therapy: aspirin, clopidogrel (Han 2015); P2Y12 inhibitor (Leonardi 2016); dual antiplatelet therapy (Shahzad 2014). Radial access: 78.5% (Han 2015); 50% (Leonardi 2016); 81% (Shahzad 2014)

Figure 22: Stent thrombosis (definite or probable at 1 year)



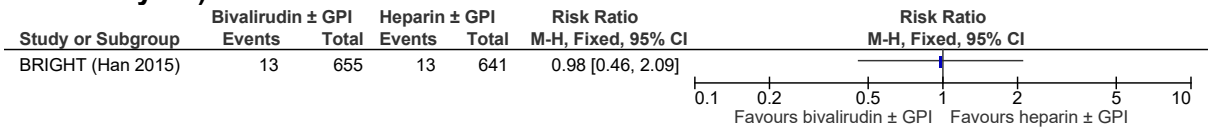
GPI use: 4.4-5.6%. Concurrent antiplatelet therapy: aspirin, clopidogrel. Radial access: 78.5%

Figure 23: Repeat revascularisation (ischaemic target vessel/unplanned target lesion revascularisation at 28-30 days)



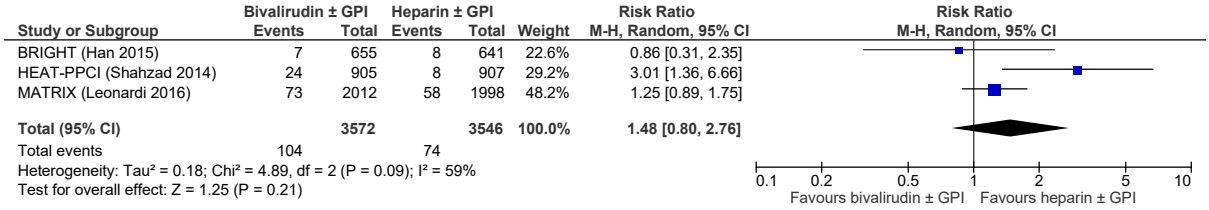
GPI use: 4.4-5.6% (Han 2015); 13-15% (Shahzad 2014). Concurrent antiplatelet therapy: aspirin, clopidogrel (Han 2015); dual antiplatelet therapy (Shahzad 2014). Radial access: 78.5%

Figure 24: Repeat revascularisation (ischaemic target vessel revascularisation at 1 year)



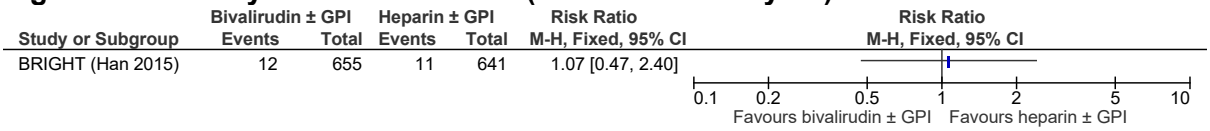
GPI use: 4.4-5.6%. Concurrent antiplatelet therapy: aspirin, clopidogrel. Radial access: 78.5%

Figure 25: New myocardial infarction (myocardial infarction/reinfarction at 28-30 days)



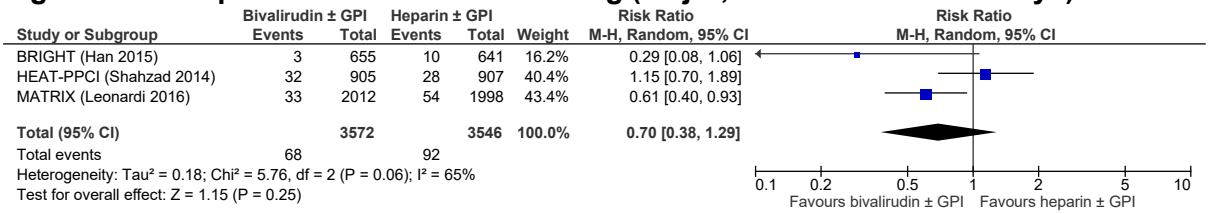
GPI use: 4.3-35%. Concurrent antiplatelet therapy: aspirin, clopidogrel (Han 2015); dual antiplatelet therapy (Shahzad 2014); P2Y12 inhibitor (clopidogrel, ticagrelor or prasugrel) (Leonardi 2016). Radial access: 78.5% (Han 2015); 81% (Shahzad 2014); 50% (Leonardi 2016)

Figure 26: New myocardial infarction (reinfarction at 1 year)



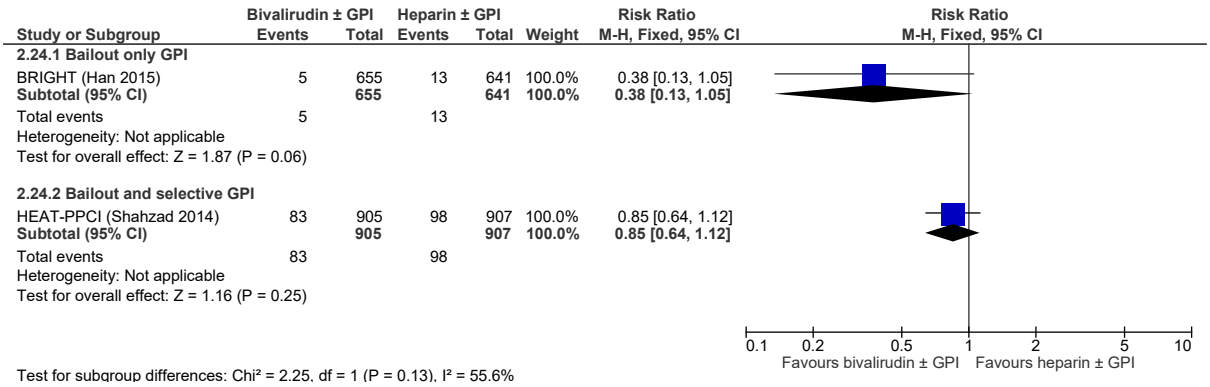
GPI use: 4.4-5.6%; Concurrent antiplatelet therapy: aspirin, clopidogrel. Radial access: 78.5%

Figure 27: Complications related to bleeding (major, BARC 3-5 at 28-30 days)



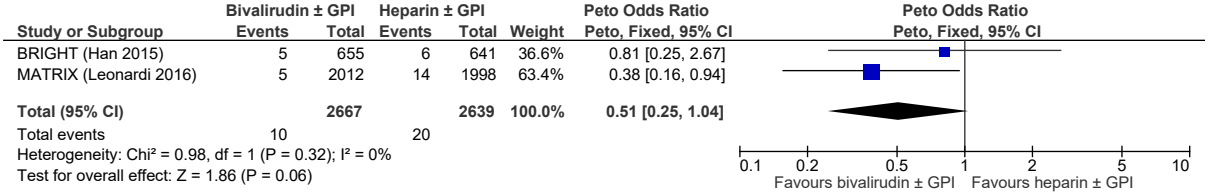
GPI use: 4.3-35% (Han 2015; Leonardi 2016); 13-15% (Shahzad 2014). Concurrent antiplatelet therapy: aspirin, clopidogrel (Han 2015); P2Y12 inhibitor (clopidogrel, ticagrelor or prasugrel) (Leonardi 2016); dual antiplatelet therapy (Shahzad 2014). Radial access: 78.5% (Han 2015); 81% (Shahzad 2014); 50% (Leonardi 2016). Bleeding scores: BARC 3-5 (Han 2015 and Shahzad 2014); BARC 3 or 5 (Leonardi 2016)

Figure 28: Complications related to bleeding (minor, BARC 2 at 28-30 days)



GPI use: 4.4-5.6% (Han 2016); 13-15% (Shahzad 2014). Concurrent antiplatelet therapy: aspirin, clopidogrel (Han 2015); dual antiplatelet therapy (Shahzad 2014). Radial access: 78.5% (Han 2015); 81% (Shahzad 2014). Bleeding scores: BARC 2 (Han 2015 and Shahzad 2014)

Figure 29: Stroke (any, type not specified at 30 days)



GPI use: 4.3-35%. Concurrent antiplatelet therapy: aspirin, clopidogrel (Han 2015); P2Y12 inhibitor (clopidogrel, ticagrelor or prasugrel) (Leonardi 2016). Radial access: 78.5% (Han 2015); 50% (Leonardi 2016)

Appendix F: GRADE tables

Table 12: Clinical evidence profile: Bivalirudin ± bailout glycoprotein inhibitor versus heparin + routine glycoprotein inhibitor

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bivalirudin ± bailout GPI versus heparin + routine GPI		Relative (95% CI)	Absolute		
All cause mortality (follow-up 30 days)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	80/3673 (2.2%)	3.1%	RR 0.74 (0.56 to 0.99)	8 fewer per 1000 (from 0 fewer to 14 fewer)	⊕⊕⊕O MODERATE	CRITICAL
All cause mortality (follow-up 1 year)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	132/3544 (3.7%)	4.8%	RR 0.82 (0.65 to 1.02)	9 fewer per 1000 (from 17 fewer to 1 more)	⊕⊕⊕O MODERATE	IMPORTANT
Cardiac mortality (follow-up 30 days)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	69/3673 (1.9%)	2.6%	RR 0.68 (0.5 to 0.92)	8 fewer per 1000 (from 2	⊕⊕⊕O MODERATE	CRITICAL

										fewer to 13 fewer)		
Cardiac mortality (follow-up 1 year)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	92/3544 (2.6%)	3.7%	RR 0.71 (0.55 to 0.92)	11 fewer per 1000 (from 3 fewer to 17 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
Definite and probable stent thrombosis (follow-up 30 days)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	62/3444 (1.8%)	1.4%	RR 1.4 (0.95 to 2.05)	6 more per 1000 (from 1 fewer to 15 more)	⊕⊕⊕O MODERATE	IMPORTANT
Definite and probable stent thrombosis (follow-up 1 year)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	64/2455 (2.6%)	1.9%	RR 1.12 (0.79 to 1.59)	2 more per 1000 (from 4 fewer to 11 more)	⊕⊕OO LOW	IMPORTANT
Repeat revascularisation (ischaemia-driven revascularisation; follow-up 30 days)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	84/3673 (2.3%)	1.7%	RR 1.33 (0.97 to 1.84)	6 more per 1000 (from 1 fewer to 14 more)	⊕⊕⊕O MODERATE	IMPORTANT
Repeat revascularisation (ischaemic TVR; follow-up 1 years)												

2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	136/2455 (5.5%)	3.7%	RR 1.22 (0.96 to 1.56)	8 more per 1000 (from 1 fewer to 21 more)	⊕⊕⊕O MODERATE	IMPORTANT
Repeat revascularisation (ischaemic TLR; follow-up 1 year)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	103/1800 (5.7%)	4.3%	RR 1.34 (1 to 1.79)	15 more per 1000 (from 0 more to 34 more)	⊕⊕⊕O MODERATE	IMPORTANT
Repeat revascularisation (ischaemic remote TVR; follow-up 1 year)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	39/1800 (2.2%)	1.9%	RR 1.15 (0.73 to 1.81)	3 more per 1000 (from 5 fewer to 15 more)	⊕⊕OO LOW	IMPORTANT
New myocardial infarction (reinfarction; follow-up 30 days)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	61/3673 (1.7%)	1.30%	RR 1.2 (0.83 to 1.73)	3 more per 1000 (from 2 fewer to 9 more)	⊕⊕⊕O MODERATE	CRITICAL
New myocardial infarction (reinfarction; follow-up 1 year)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	74/2455 (3%)	2.9%	RR 0.86 (0.63 to 1.16)	4 fewer per 1000 (from 11 fewer to 5 more)	⊕⊕⊕O MODERATE	IMPORTANT
Complications related to bleeding (major including BARC 3-5; follow-up 30 days)												

4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	120/3673 (3.3%)	4.2%	RR 0.52 (0.42 to 0.65)	20 fewer per 1000 (from 15 fewer to 24 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Complications related to bleeding (minor including TIMI and BARC 2; follow-up 30 days)												
4	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	114/3673 (3.1%)	4.6%	RR 0.62 (0.49 to 0.78)	17 fewer per 1000 (from 10 fewer to 23 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Stroke (any, type not specified; follow-up 30 days)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	18/2584 (0.7%)	0.6%	Peto OR 1.11 (0.57 to 2.19)	1 more per 1000 (from 3 fewer to 7 more)	⊕⊕OO LOW	IMPORTANT
Stroke (ischaemic; follow-up 30 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	6/1089 (0.55%)	0.8%	Peto OR 0.68 (0.25 to 1.88)	3 fewer per 1000 (from 6 fewer to 7 more)	⊕OOO VERY LOW	IMPORTANT
Stroke (haemorrhagic; follow-up 30 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	0/1089 (0%)	0.2%	Peto OR 0.14 (0.01 to 2.2)	2 fewer per 1000 (from 2 fewer to 2 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 13: Clinical evidence summary: Bivalirudin ± bailout/selective glycoprotein inhibitor versus heparin ± bailout/selective glycoprotein inhibitor

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bivalirudin ± bailout/selective GPI versus heparin ± bailout/selective GPI	Control	Relative (95% CI)	Absolute		
All cause mortality (follow-up 28-30 days)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	97/3572 (2.7%)	3.1%	RR 0.85 (0.65 to 1.12)	5 fewer per 1000 (from 11 fewer to 4 more)	⊕OOO VERY LOW	CRITICAL
All cause mortality (follow-up unclear timepoint)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/38 (2.6%)	2.5%	RR 1.05 (0.07 to 16.24)	1 more per 1000 (from 23 fewer to 381 more)	⊕OOO VERY LOW	CRITICAL
All cause mortality (follow-up 1 year)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12/655 (1.8%)	2.5%	RR 0.73 (0.35 to 1.54)	7 fewer per 1000 (from 16	⊕OOO VERY LOW	IMPORTANT

										fewer to 13 more)		
Cardiac mortality (follow-up 30 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/655 (1.2%)	2%	RR 0.6 (0.25 to 1.44)	8 fewer per 1000 (from 15 fewer to 9 more)	⊕OOO VERY LOW	CRITICAL
Cardiac mortality (follow-up 1 year)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/655 (1.5%)	2.3%	RR 0.65 (0.3 to 1.44)	8 fewer per 1000 (from 16 fewer to 10 more)	⊕OOO VERY LOW	IMPORTANT
Stent thrombosis (acute; follow-up ≤24 hours)												
Definite and probable stent thrombosis (up to 30 days) - Bailout only GPI (follow-up 30 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	36/2667 (1.3%)	1%	RR 1.37 (0.83 to 2.26)	4 more per 1000 (from 2 fewer to 12 more)	⊕⊕OO LOW	IMPORTANT
Definite and probable stent thrombosis (up to 30 days) - Bailout and selective GPI (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	24/697 (3.4%)	0.9%	RR 3.91 (1.61 to 9.52)	26 more per 1000 (from 5 more to 75 more)	⊕⊕⊕O MODERATE	IMPORTANT
Definite and probable stent thrombosis (up to 1 year) (follow-up 1 year)												

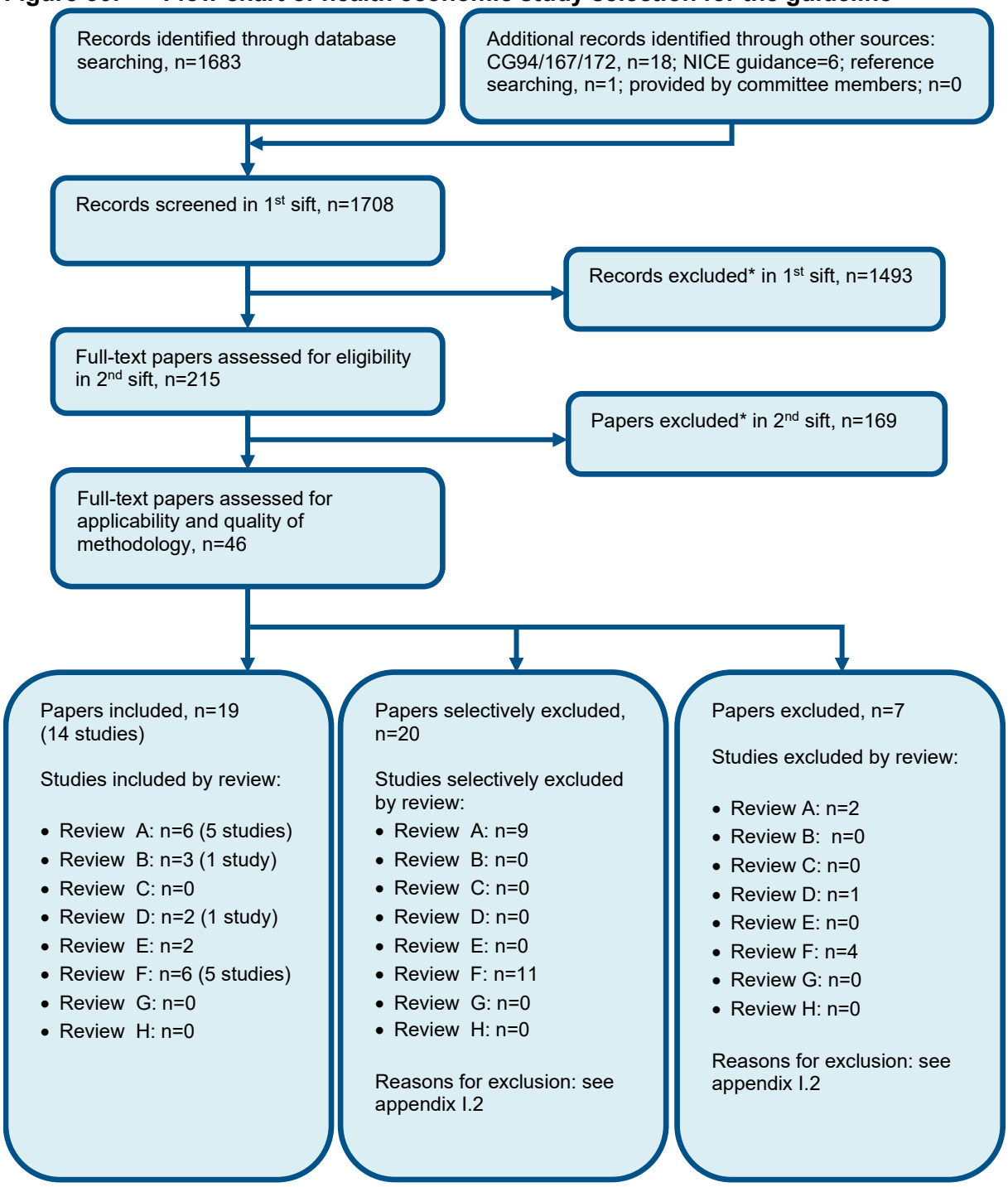
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/655 (1.1%)	1.7%	RR 0.62 (0.24 to 1.6)	6 fewer per 1000 (from 13 fewer to 10 more)	⊕OOO VERY LOW	IMPORTANT
Repeat revascularisation (ischaemic target vessel revascularisation; bailout only GPI;follow-up 30 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/655 (1.5%)	1.9%	RR 0.82 (0.35 to 1.87)	3 fewer per 1000 (from 12 fewer to 17 more)	⊕OOO VERY LOW	IMPORTANT
Repeat revascularisation (unplanned target lesion revascularisation; bailout and selective GPI;follow-up 28 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	24/905 (2.7%)	0.7%	RR 4.01 (1.65 to 9.76)	21 more per 1000 (from 5 more to 61 more)	⊕⊕⊕O MODERATE	IMPORTANT
Repeat revascularisation (ischaemic target vessel revascularisation;follow-up 1 year)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	13/655 (2%)	2%	RR 0.98 (0.46 to 2.09)	0 fewer per 1000 (from 11 fewer to 22 more)	⊕OOO VERY LOW	IMPORTANT
New myocardial infarction (myocardial infarction/reinfarction;follow-up 28-30 days)												
3	randomised trials	very serious[1]	serious[4]	no serious indirectness	very serious[2]	none	104/3572 (2.9%)	1.3%	RR 1.48 (0.8 to 2.76)	6 more per 1000 (from 3 fewer to 23 more)	⊕OOO VERY LOW	CRITICAL
New myocardial infarction (reinfarction;follow-up 1 year)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12/655 (1.8%)	1.7%	RR 1.07 (0.47 to 2.4)	1 more per 1000 (from 9	⊕OOO VERY LOW	IMPORTANT

										fewer to 24 more)		
Complications related to bleeding (major, BARC 3-5;follow-up 28-30 days)												
3	randomised trials	very serious[1]	serious[5]	no serious indirectness	very serious[2]	none	68/3572 (1.9%)	2.7%	RR 0.7 (0.38 to 1.29)	8 fewer per 1000 (from 17 fewer to 8 more)	⊕OOO VERY LOW	CRITICAL
Complications related to bleeding (minor, BARC 2; bailout only GPI;follow-up 30 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5/655 (0.76%)	2%	RR 0.38 (0.13 to 1.05)	12 fewer per 1000 (from 17 fewer to 1 more)	⊕OOO VERY LOW	CRITICAL
Complications related to bleeding (minor, BARC 2; bailout and selective GPI;follow-up 28 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	83/905 (9.2%)	10.8%	RR 0.85 (0.64 to 1.12)	16 fewer per 1000 (from 39 fewer to 13 more)	⊕⊕OO LOW	CRITICAL
Stroke (any, type not specified;follow-up 30 days)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/2667 (0.37%)	0.8%	Peto OR 0.51 (0.25 to 1.04)	4 fewer per 1000 (from 6 fewer to 0 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Risk difference calculated in Review Manager
[4] Downgraded by 1 or 2 increments because heterogeneity, I2= 59%, p= 0.09, unexplained by subgroup analysis
[5] Downgraded by 1 or 2 increments because heterogeneity, I2= 65%, p= 0.06, unexplained by subgroup analysis

Appendix G: Health economic evidence selection

Figure 30: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Review A = dual-antiplatelet therapy; Review B = early invasive investigation for UA/NSTEMI; Review C = antithrombins in UA/NSTEMI; Review D = bivalirudin in STEMI; Review E = multi-vessel PCI; Review F = drug-eluting stents; Review G = combination of antiplatelets and anticoagulants; Review H = beta-blocker therapy.

Appendix H: Health economic evidence tables

Study	Schwenkglenks 2012[33, 46]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Initial decision tree that capture differences in events between treatment strategies (1 year period in base case analysis); possible events included major and minor bleeding, ischaemic stroke, repeat MI, repeat revascularisation or death. Following this a Markov model with two states (dead and alive) is used to model long-term survival. Treatment effects and resource use based on individual-level data collected within HORIZONS-AMI RCT[60],[29] adjusted to reflect UK practices if required.	**Population:** Acute STEMI patients: angiography undertaken in all and the majority received PPCI (others received CABG or medical management) **Cohort settings:** Start age: 60.9 years Male: 76.6% Derived from HORIZONS-AMI data. **Intervention 1:** Heparin + GPI GPI use in RCT 95.3% **Intervention 2:** Bivalirudin (use allowed in people that experienced no reflow or giant thrombus after PCI) Bivalirudin use in RCT 96.9%	**Total costs (mean per patient):** *Main analysis (using 1 year trial data)* Intervention 1: £13,110 Intervention 2: £12,843 Incremental (2−1): -£267 (95% CI: NR; p=NR) Cost breakdown (Heparin+GPI/Bivalirudin): Bivalirudin: £0/£370 GPI: £573/£42 Ward cost (initial hospitalisation): £2,259/£2,064 Procedures and clinical events during year 1: £2,509/£2,484 CV outpatient treatment and drugs in year 1: £864/£876 Long-term CV treatment after year 1: £6,906/£7,006 *Alternative analysis (using 3 year trial data)* Intervention 1: £13,730 Intervention 2: £13,480 Incremental (2−1): -£250 (95% CI: NR; p=NR)	**QALYs (mean per patient):** *Main analysis (using 1 year trial data)* Intervention 1: 6.17 Intervention 2: 6.26 Incremental (2−1): 0.09 (95% CI: NR; p=NR) *Alternative analysis (using 3 year trial data)* Intervention 1: 6.32 Intervention 2: 6.43 Incremental (2−1): 0.11 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** *Main analysis (using 1 year trial data)* Intervention 2 dominant 95% CI: NR Probability Intervention 2 cost effective (£20K/30K threshold): 99.2%/NR (and cost saving 95.0%) *Alternative analysis (using 3 year trial data)* Intervention 2 dominant 95% CI: NR Probability Intervention 2 cost effective (£20K/30K threshold): NR/NR (noted as similar to the main analysis) **Analysis of uncertainty:** A wide range of sensitivity analyses around baseline risks, relative risks, costs, utilities and other inputs were undertaken. The dominance of bivalirudin was maintained in most sensitivity analyses. In a scenario combing several unfavourable assumptions (100% eptifitatide use, 100% radial

Perspective: UK NHS **Time horizon:** lifetime **Treatment effect duration:**[a] 1 year (base case); 3 years (alternative) **Discounting:** Costs: 3.5%; Outcomes: 3.5%	GPI use in RCT 7.6% All patients also received aspirin + clopidogrel prior to angiography.	**Currency & cost year:** 2009/10 UK pounds **Cost components incorporated:** Bivalirudin, GPIs, initial hospital length of stay, procedures (angiography, PCI, CABG), event costs (reinfarction, stroke, major and minor bleeds), long term annual CVD treatment costs for survivors. The cost of heparin treatment was considered insignificant and was omitted from the model.		access use with a correspondingly reduced survival advantage for bivalirudin, no difference in initial hospital length of stay) the ICER was £5,428 per QALY gained.
Data sources				
Health outcomes: Baseline event rates for the heparin+GPI arm and relative treatment effects with bivalirudin were derived from analysis of individual-level data from the HORIZONS-AMI RCT. Radial arterial access in the trial was lower than in the UK (5.9% in trial vs 42.5% from UK audit data) and so data was adjusted to account for this by assuming a radial route in 42.5% of patient and assuming there would be no access site bleeding in these patients (non-access site bleeding remained the same) – this reduced bleeding. The reduced risk for non-CABG major bleeding was assumed to lead to a proportional reduction in the length of stay difference between treatment strategies. Survival beyond the initial period (modelled by the decision tree; 1 year in the base case and 3 years in an alternative analysis) was based on data from the Nottingham Heart Attack Register and life tables for England and Wales. **Quality-of-life weights:** EQ-5D (administered in MI survivors), UK population tariff. Quality of life was independent of intervention used. **Cost sources:** UK national sources or published studies.				
Comments				
Source of funding: The Medicines Company. **Limitations:** Comparator is heparin + GPI (95% use) - heparin alone or heparin plus lower GPI use not included. International resource use from 2005-2007 and UK 2009/10 unit costs may not reflect the current UK context. Note that in this analysis differences in radial access in the UK at the time compared to in the study were attempted to be accounted for through modelling. Length of stay data from the study was also adjusted to account for lower UK length of stay. Differences in the type of GPI used in the UK compared to the trial were also accounted for in cost calculations. Analysis based on a single study (HORIZONS-AMI) and so does not reflect full body of available evidence for this area (4 RCTs included in clinical review comparing bivalirudin with bailout GPIs and heparin with routine GPIs– overall mortality and MI effect size estimates from the meta-analysis in the clinical review for this guideline were slightly less favourable than in the HORIZONS-AMI RCT individually; revascularisation effect sizes were very similar; bleeding effect sizes were generally similar or slightly more favourable). Study funded by The Medicines Company. **Other:**				
Overall applicability:[c] Partially applicable **Overall quality:**[d] Potentially serious limitations				

Abbreviations: 95% CI = 95% confidence interval; CUA = cost–utility analysis; CVD = cardiovascular disease; EQ-5D = Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); GPI = glycoprotein inhibitor; ICER = incremental cost-effectiveness ratio; MI = myocardial infarction; NR = not reported; PCI = percutaneous coronary intervention; QALYs = quality-adjusted life years; RCT = randomised clinical trial

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable / Partially applicable / Not applicable
(c) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 14: Studies excluded from the clinical review

Study	Exclusion reason
Bangalore 2014[1]	Systematic reivew (references checked)
Barria Perez 2016[2]	Systematic review (references checked)
Bittl 2015[3]	Systematic review (references checked)
Capodanno 2016[4]	Systematic review (references checked)
Chacko 2006[5]	Incorrect study population (urgent or elective PCI)
De servi 2013[7]	Incorrect study design
Erlinge 2016[9]	Study design and rationale only
Erlinge 2017[10]	Relevant outcomes reported for mixed STEMI and NSTEMI population only
Feldman 2014[12]	Incorrect study population (NSTEMI or angina)
Ferdous 2017[13]	Incorrect study design
Garg 2018[14]	Citation only; meta-analysis
Gargiulo 2018[15]	Outcomes reported for mixed population (acute coronary syndromes with/without ST elevation)
Grajek 2018[16]	Systematic review (references checked)
Ibebuogu 2015[19]	Systematic review (references checked)
Kastrati 2008[21]	Incorrect study population (stable or unstable angina)
Liang 2016[23]	Outcomes reported for mixed population (STEMI and NSTEMI) only
Lincoff 2002[27]	Incorrect intervention (elective coronary balloon angioplasty or stenting)
Lincoff 2003[24]	Incorrect intervention (urgent or elective PCI)
Lincoff 2004[25]	Incorrect intervention (urgent or elective PCI)
Lincoff 2004[26]	Incorrect intervention (urgent or elective PCI)
Mehran 2009[30]	Citation only; meta-analysis (in chronic kidney disease with stable or unstable angina undergoing PPCI)
Moliterno 2011[31]	Outcomes for mixed population (NSTEMI and STEMI) only
Navarese 2015[34]	Network meta-analysis (in stable coronary artery disease and acute coronary syndromes; references checked)
Navarese 2015[35]	Systematic review (references checked)
Ndrepepa 2012[36]	Incorrect study population (NSTEMI)
Ng 2016[37]	Pooled analysis (in STEMI and NSTEMI population)
Nikolsky 2010[38]	Citation only; incorrect comparison
Nuhrenberg 2018[39]	Meta-analysis (references checked)
Olmedo 2017[40]	Systematic review (references checked)
Patti 2012[41]	Incorrect study population (coronary artery disease undergoing PCI excluding PPCI for acute myocardial infarction)
Ray 2009[42]	Relevant outcomes not reported; mixed population (STEMI and NSTEMI)
Schulz 2014[43]	Incorrect comparison (bivalirudin + prasugrel versus heparin + clopidogrel)

Study	Exclusion reason
Schulz 2014[44]	Incorrect comparison (bivalirudin + prasugrel versus heparin + clopidogrel)
Schulze 2015[45]	Citation only; network meta-analysis
Steg 2013[48]	Study design and rationale only
Stone 2004[51]	Study design and rationale only (in moderate to high risk acute coronary syndromes excluding acute STEMI requiring immediate thrombolytic or interventional reperfusion therapy)
Stone 2006[53]	Incorrect study population (moderate to high risk acute coronary syndromes excluding acute STEMI)
Stone 2007[56]	Incorrect study population (acute coronary syndromes excluding acute STEMI)
Stone 2007[57]	Incorrect study population (acute coronary syndromes excluding acute STEMI)
Stone 2009[55]	Abstract only; meta-analysis in ischaemic heart disease
Stone 2010[58]	Abstract only (in acute myocardial infarction population)
Stone 2011[59]	Outcomes reported at 3 years
Stone 2012[50]	Abstract only
Stone 2012[61]	Abstract only
Stone 2014[52]	Outcomes reported at 3 years
Stone 2014[62]	Outcomes reported incompletely at 3 years for STEMI with stent population
Stone 2015[54]	Pooled analysis
Valgimigli 2015[63]	No additionally relevant outcomes
Waksman 2013[65]	Incorrect study population (NSTEMI)
Wang 2015[66]	Abstract only
Witzenbichler 2009[68]	Citation only (in diabetes mellitus and acute myocardial infarction)
Witzenbichler 2011[67]	Citation only (in diabetes mellitus and acute myocardial infarction)
Xu 2017[69]	Incorrect intervention (urgent or elective PCI)
Yu 2012[70]	Abstract only
Yu 2015[71]	Subgroup analysis not addressing review question
Zeymer 2014[72]	No additionally relevant outcomes

I.2 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2003 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 15: Studies excluded from the health economic review

Reference	Reason for exclusion
Deharo 2018[8]	Excluded as rated very serious limitations due to the study not meeting the clinical review inclusion criteria. Also partially applicable, reasons include: UK NHS perspective, time horizon is too short and the analysis did not use QALYs as the health outcome.