Online Supplement

Supplementary lable A. Details of MeSH Search Terms							
Treatment	MeSH terms						
Unfractionated Heparin	Heparin, Randomized controlled trial or Controlled clinical trial						
Low-molecular- weight Heparin	Low-molecular-weight heparin, Enoxaparin, Dalteparin, Nadroparin, Randomized controlled trial or Controlled clinical trial						
Bivalirudin	Bivalirudin, Randomized controlled trial or Controlled clinical trial						
Fondaparinux	Fondaparinux, Randomized controlled trial or Controlled clinical trial						
Glycoprotein IIb/IIIa inhibitors	Abciximab, Tirofiban, Eptifibatide, Randomized controlled trial or Controlled clinical trial						

Supplementary table A. Details of MeSH Search Terms

Supplementary table B. Anticoagulant and their mechanism of action							
Study groups	Mechanism of action						
Bivalirudin	A direct thrombin inhibitor						
Fondaparinux	A synthetic pentasaccharide factor Xa inhibitor						
GPI	Inhibits the <u>GpIIb/IIIa</u> receptor on the surface of the <u>platelets</u> and thus prevents <u>platelet</u> aggregation and <u>thrombus</u> formation						
LMWH and UFH	Binds to and activates antithrombin III which inactivates thrombin and factor Xa and thus acts as an indirect thrombin inhibitor						

GPI=Glycoprotein IIb/IIIa inhibitors; LMWH=Low molecular weight heparin; UFH=Unfractionated heparin

Trial	Year	Study	Treatment	Comparison	Sample Size
ACE ^{1,2}	2003	UFH + GPI vs UFH	Abciximab 0.25 mg/kg IV bolus, then 0.125 mcg/kg/min for 12 hours + UFH 70 IU/kg IV bolus, with additional boluses during PCI to achieve ACT of 200-300 s	UFH 70U/kg IV bolus, with additional boluses during PCI to achieve ACT of at least 300 secs, then UFH infusion for 48 hours	400
ADMIRAL ^{3,4}	2001	UFH + GPI vs UFH	Abciximab 0.25 mg/kg IV bolus, then 0.125 mcg/kg/min for 12 hours + UFH 70 IU/kg IV bolus, with additional boluses during PCI to achieve ACT of 200 s then 7 IU/kg/h infusion for 24 hours	UFH 70 IU/kg IV bolus, with additional boluses during PCI to achieve ACT of 200 s then 7 IU/kg/h infusion for 24 hours	300
ASSIST⁵	2009	UFH + GPI vs UFH	Eptifibatide 180 mcg/kg IV bolus x2, then 2 mcg/kg/min infusion for 16 hours + UFH 60 IU/kg IV bolus (max 4000 IU), with additional boluses during PCI to achieve ACT 200 s	UFH 60 IU/kg IV bolus (max 4000 IU), with additional boluses during PCI to achieve ACT > 250 s	400
ATOLL ⁶	2011	LMWH vs UFH	Enoxaparin 0.5 mg/kg IV bolus	If patient received GPI: UFH 50 - 70 IU/kg IV bolus; If patient did not receive GPI: UFH 70 - 100 IU/kg IV bolus administered, with additional boluses during PCI to achieve ACT 200-300 s or 300- 350s respectively.	910

Supplementary table C. Baseline characteristics of the included trials

Trial	Year	Study	Treatment	Comparison	Sample Size
BRAVE-3 ^{7,8}	2009	UFH + GPI vs UFH	Abciximab 0.25 mg/kg IV bolus, then 0.125 mcg/kg/min for 12 hours + UFH 60 IU/kg IV bolus (max 5000 IU)	UFH 60 IU/kg initial IV bolus (max 5000U) with additional 70 IU/kg IV bolus	800
BRAVE-4 ^{9,10}	2014	Bivalirudin + Prasugrel vs UFH + Clopidogrel	Bivalirudin 0.75 mg/kg IV bolus, then 1.75 mg/kg/h infusion through PCI + Prasugrel 60 mg LD, then 10 mg/d for at least 30 days	UFH 70-100 IU/kg IV bolus + Clopidogrel 600 mg LD then ≥75 mg/d for at least 30 days	548
BRIGHT ¹¹	2014	Bivalirudin vs UFH	Bivalirudin 0.75 mg/kg IV bolus, then 1.75 mg/kg/h infusion through PCI	UFH 100 IU/kg IV bolus pre-PCI	1452
BRIGHT ¹¹	2014	UFH + GPI vs UFH	Tirofiban 10 mcg/kg IV bolus, then 0.15 mcg/kg/min infusion through PCI + UFH 60 IU/kg IV bolus pre-PCI	UFH 100 IU/kg IV bolus pre-PCI	1450
CADILLAC (STEMI subgroup) ^{12,13}	2002	UFH + GPI vs UFH	Abciximab 0.25 mg/kg IV bolus, then 0.125 mcg/kg/min for 12 hours + UFH 5000 IU IV bolus, with additional boluses to achieve ACT 200-300 s	UFH 5000 IU IV bolus, with additional boluses to achieve ACT of at least 350 s	1725
DEBATER ¹⁴	2012	UFH + GPI vs UFH	Abciximab 0.25 mg/kg IV bolus, then 0.125 mcg/kg/min for 12 hours + UFH 5000 IU IV bolus in the ambulance, additional 5000 IU before PCI	UFH 5000 IU IV bolus in the ambulance, additional 5000 IU before PCI	873

Trial	Year	Study	Treatment	Comparison	Sample Size
EUROMAX ¹⁵	2013	Bivalirudin vs UFH/LMWH	Bivalirudin 0.75 mg/kg IV bolus, then 1.75 mg/kg/h infusion through PCI; 0.25 mg/kg/h (or optional 1.75 mg/kg/h) infusion post-PCI for at least 4 hours	UFH 60 IU/kg IV bolus if received GPI (UFH 100 IU/kg if not received GPI) or Enoxaparin 0.5 mg/kg IV bolus	2198
Fu XH et al ¹⁶	2008	UFH + GPI vs UFH	Tirofiban 10 mcg/kg IV bolus, then 0.15 mcg/kg/min infusion for 24 hours + UFH 70 IU/kg IV bolus with additional boluses during PCI to achieve ACT 250 s	UFH 70 IU/kg IV bolus with additional boluses during PCI to achieve ACT 250 s	150
HEAT-PPCI ¹⁷	2014	Bivalirudin vs UFH	Bivalirudin 0.75 mg/kg IV bolus, then 1.75 mg/kg/h infusion through PCI	UFH 70 IU/kg IV bolus pre-PCI	1829
HORIZONS - AMI ^{18,19}	2008	Bivalirudin vs UFH + GPI	Bivalirudin 0.75 mg/kg IV bolus, then 1.75 mg/kg/h infusion through PCI	UFH 60 IU/kg IV bolus, with additional boluses to achieve ACT of 200-250 s + GPI (Abciximab 0.25 mcg/kg IV bolus, then 0.125 mcg/kg/min for 12 hours; or Eptifibatide 180 mcg/kg IV bolus x2, then 2 mcg/kg/min infusion for 12-18 hours)	3602
ISAR-2 ^{20,21}	2000	UFH + GPI vs UFH	Abciximab 0.25 mg/kg IV bolus, then 10 mcg/min infusion for 12 hours + UFH 5000 IU IV bolus and addition 2500 U IV bolus at the time of PCI	UFH 5000 IU IV bolus and addition 10000 IU IV bolus at the time of PCI, then 1000 IU/h infusion for 12 hours	401

Trial	Year	Study	Treatment	Comparison	Sample Size
ITTI ²²	2012	UFH + GPI vs UFH	Tirofiban 10 mcg/kg IV bolus, then 0.15 mcg/kg/min infusion for 24 hours + UFH 100 IU/kg IV bolus with additional boluses during PCI to achieve ACT of 250–300 s	UFH 100 IU/kg IV bolus with additional boluses during PCI to achieve ACT of >300 s	100
Li WM et al ²³	2011	LMWH + GPI vs UFH + GPI	Dalteparin 100 IU/kg IV bolus + Tirofiban 10 mcg/kg IV bolus, then 0.15 mcg/kg/min infusion for 36 hours	UFH 5000 IU IV bolus with additional boluses according to ACT values + Tirofiban 10 mcg/kg IV bolus, then 0.15 mcg/kg/min infusion for 36 hours	120
Neumann FJ et al ²⁴	1998	UFH + GPI vs UFH	Abciximab 0.25 mg/kg IV bolus, then 10 mcg/min infusion for 12 hours + UFH 5000 IU IV bolus pre-PCI and additional 25000 IU during PCI	UFH 5000 IU IV bolus pre-PCI and additional 10000 IU during PCI, then 1000 IU/h infusion for 12 hours	200
OASIS-6 (Primary PCI cohort) ²⁵	2006	LMWH vs UFH	Fondaparinux 2.5 mg IV bolus if received GPI (5 mg IV bolus if not received GPI), then 2.5 mg SQ daily for 8 days	UFH 65 IU/kg IV bolus if received GPI (100 IU/kg bolus if not received GPI), then 12 IU/kg/h infusion for 45 hours	3789
On-TIME 2 ^{26,27}	2010	UFH + GPI vs UFH	Tirofiban 25 mcg/kg IV bolus, then 0.15 mcg/kg/min infusion + UFH 5000 IU IV bolus with additional 2500 IU boluses during PCI to achieve ACT of at least 200 s	UFH 5000 IU IV bolus with additional 2500 IU boluses during PCI to achieve ACT of at least 200 s	1398

Trial	Year	Study	Treatment	Comparison	Sample Size
Shen J et al ²⁸	2007	UFH + GPI vs UFH	Tirofiban 10 mcg/kg IV bolus, then 0.15 mcg/kg/min infusion for 36 hours + UFH 100 IU/kg IV bolus with additional boluses during PCI to achieve ACT of 150-350 s	UFH 100 IU/kg IV bolus with additional boluses during PCI to achieve ACT of 150-350 s	160
Shen J et al ²⁹	2008	UFH + GPI vs UFH	Tirofiban 10 mcg/kg IV bolus, then 0.15 mcg/kg/min infusion for 36 hours + UFH 100 IU/kg IV bolus with additional boluses during PCI to achieve ACT of 200-350 s	UFH 100 IU/kg IV bolus with additional boluses during PCI to achieve ACT of 200-350 s	172
Zorman S et al ³⁰	2002	UFH + GPI vs UFH	Abciximab 0.25 mg/kg IV bolus, then 0.125 mcg/kg/min for 12 hours + UFH 70 IU/kg IV bolus in ER	UFH 70 IU/kg IV bolus in ER	163

ACE= Abciximab and Carbostent Evaluation; ACT=Activated clotting time; ADMIRAL= Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up; ASSIST=A Safety and Efficacy Study of Integrilin-Facilitated PCI Versus Primary PCI in ST-Elevation Myocardial Infarction; ATOLL=Acute Myocardial Infarction Treated with Primary Angioplasty and Intravenous Enoxaparin or Unfractionated Heparin to Lower Ischemic and Bleeding Events at Short- and Long-term Follow-up; BRAVE=Bavarian Reperfusion Alternatives Evaluation; BRIGHT=Bivalirudin versus Heparin Monotherapy and Glycoprotein IIb/IIIa Plus Heparin for Patients with AMI Undergoing Coronary Stenting; CADILLAC=Controlled Abciximab And Device Investigation To Lower Late Angioplasty Complications; DEBATER=Comparison of Drug Eluting and Bare Metal Stents With or Without Abciximab in ST Elevation Myocardial Infarction; EUROMAX=European Ambulance Acute Coronary Syndrome Angiography; GPI=Glycoprotein IIb/IIIa inhibitors; HEAT-PPCI=How Effective are Antithrombotic Therapies in PPCI; HORIZONS-AMI=Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction; ISAR=Intracoronary Stenting and Antithrombotic Regimen; ITTI=Initial Thrombosuction and Tirofiban Infusion; LMWH=Low-molecular-weight heparin; OASIS= Organization for the Assessment of Strategies for Ischemic Syndromes; On-TIME=Ongoing Tirofiban In Myocardial infarction Evaluation; RAPPORT=ReoPro and Primary PTCA Organization and Randomized Trial; UFH=Unfractionated heparin

Trial	Access Site	Thienopyridine	Bleeding Definition	MACE Definition	MI Definition	ST Definition	Quality of Trial*
ACE ^{1,2}	NR	Clopidogrel or Ticlopidine	Blood transfusion	Death, MI, TVR and Stroke	Chest pain with ST-segment or T-wave changes and elevation of cardiac enzymes	NR	++-
ADMIRAL ^{3,4}	Femoral	Ticlopidine	ТІМІ	Death, MI, TVR	Clinical symptoms and new electrocardiographic changes with a new elevation of the creatine kinase or creatine kinase MB isoenzyme levels	NR	+±-
ASSIST⁵	Femoral (87%)	Clopidogrel	TIMI	Death, MI, recurrent severe ischemia	Ischemic symptoms at rest, lasting at least 30 minutes and accompanied by any one of the following: (1) new or recurrent ST-segment elevation of equal or >1 mm (0.1 mV) in any contiguous leads, (2) new left bundle branch block, or (3) elevation in serum creatine kinase level more than twice the upper limit of normal and at least more than 50% of the lowest level measured postinfarction	NR	++-
ATOLL ⁶	Radial (67%)	Clopidogrel	ТІМІ	Death, MI, Emergent revascularization	NR	ARC	+++

Supplementary table D. Baseline characteristics of included trials

Trial	Access Site	Thienopyridine	Bleeding Definition	MACE Definition	MI Definition	ST Definition	Quality of Trial*
BRAVE-3 ^{7,8}	NR	Clopidogrel	ΤΙΜΙ	Death, MI, TVR, Stroke	If the biomarkers of the index MI were still increasing or the peak had not been reached, the patients had to have both new ECG changes consistent with MI (new or re-elevation of ST segments >=0.2 mV in >=2 contiguous precordial leads, >=0.1 mV in >=2 adjacent limb ECG leads, or development of new, abnormal Q waves considered distinct from the evolution of the index MI) and recurrent ischemic discomfort lasting >20 minutes at rest or ischemia triggered hemodynamic instability; if the biomarkers of the index MI were falling but still above the upper limit of normal, the patients had to have either an increase in creatine kinase-MB >=50% over the nadir level or new ECG changes consistent with MI (see above); if the biomarkers of the index MI were normalized, the patients had to have a new increase in creatine kinase-MB >=3 times the upper limit of normal	NR	+++
BRAVE-4 ^{9,31}	NR	Clopidogrel or Prasugrel	ТІМІ	Death, MI, TVR, Stent thrombosis, Stroke	TIMI	ARC	+++
BRIGHT ¹¹	Radial (79%)	Clopidogrel	BARC 3 or 5	Death, MI, TVR, Stroke	NR	NR	+±±

Trial	Access Site	Thienopyridine	Bleeding Definition	MACE Definition	MI Definition	ST Definition	Quality of Trial*
CADILLAC (STEMI subgroup) ^{12,13}	NR	Clopidogrel or Ticlopidine	NR	Death, MI, TVR, Stroke	Ischemic symptoms or electrocardiographic changes accompanied by a creatine kinase level that was more than twice the upper limit of the normal range (with an elevated MB isoform level) or more than 50 percent higher than the previous value obtained during hospitalization	NR	+±±
DEBATER ¹⁴	NR	Clopidogrel	NR	Death, MI, Revascularization, Stroke	New episode of chest pain followed by creatine kinase or troponin concentrations exceeding twice the upper limit of normal or new Q waves on the electrocardiogram. Recurrent MI during the first 48 h was diagnosed when there was a decrease from a previous peak value of enzyme level followed by a subsequent rise to a level exceeding twice the upper limit of normal.	ARC	++±
EUROMAX ¹⁵	Femoral (53%)	Clopidogrel, Prasugrel or Ticagrelor	ТІМІ	Death, MI, Revascularization, Stroke		ARC	+++
Fu XH et al ¹⁶	Radial	Clopidogrel	ΤΙΜΙ	Death, MI, Serious heart failure, arrhythmia	NR	NR	±±-

Trial	Access Site	Thienopyridine	Bleeding Definition	MACE Definition	MI Definition	ST Definition	Quality of Trial*
HEAT-PPCI ¹⁷	Radial (81%)	Clopidogrel, Prasugrel or Ticagrelor	BARC 3 or 5	Death, MI, TLR, Stroke	Detection of rise of cardiac enzymes (Troponin or CK-MB) with at least one value above the 99th percentile upper reference limit together with at least one of the following: 1) Symptoms of ischaemia; 2) ECG changes suggestive of new ischaemia (ST-T changes or new onset LBBB); 3) Development of new pathological Q waves, in at least 2 consecutive leads	NR	+±±
HORIZONS - AMI ^{18,19}	Femoral (94%)	Clopidogrel	TIMI	Death, MI, TVR, Stroke		ARC	++-
ISAR-2 ^{20,21}	NR	Ticlopidine	Blood transfusion	Death, MI, TLR	During the initial hospitalization, the diagnosis was based on the presence of chest pain with either new ST-segment changes or an increase in creatine kinase (CK) and its MB isoenzyme of at least 50% over the previous trough level in at least 2 samples exceeding 3 times the upper limit of normal. After discharge, the diagnosis was based on the presence of typical chest pain accompanied by either the appearance of pathological Q-waves on electrocardiogram or an increase of CK/CK-MB >2 times the upper limit of normal.	NR	++-
ITTI ²²	NR	Clopidogrel	TIMI	Death, MI, TLR, Stroke	NR	NR	+±±
Li WM et al ²³	NR	Clopidogrel	TIMI	Death, MI, TVR	NR	NR	+±-

Trial	Access Site	Thienopyridine	Bleeding Definition	MACE Definition	MI Definition	ST Definition	Quality of Trial*
Neumann FJ et al ²⁴	NR	Ticlopidine	NR	Death, MI, TLR	Based on typical chest pain, new ST- segment changes and an increase in creatine kinase of at least 50% over the previous trough level in at least two samples reaching >=240 U/liter	NR	+++
OASIS-6 (Primary PCI cohort) ²⁵	NR	Clopidogrel or Ticlopidine	Modified TIMI	Death or MI	(1) within 24 hours of randomization— recurrent ischemic symptoms with new persistent ST elevation greater than 1 mm in at least 2 contiguous leads or new persistent ST depression greater than 1 mm in at least 2 contiguous leads not due to changes from evolution of the index MI; (2) between 24 hours and 7 days of randomization— ischemic symptoms greater than 20 minutes and either creatine kinase-CK (CK-MB; or total CK if CK-MB not available) greater than twice the upper limit of normal or further elevations more than 50% above previous lowest level in patients with already elevated enzymes or new or recurrent STEMI or depression of more than 1 mm or new significant Q waves in at least 2 contiguous leads, which was separate from the baseline MI; (3) after 7 days of randomization—either typical rise and fall of biochemical markers of myocardial necrosis to greater than twice the upper limit of normal or if markers were already elevated, further elevation of a marker to greater than 50% of the lowest recovery level from the index MI	NR	+±±

Trial	Access Site	Thienopyridine	Bleeding Definition	MACE Definition	MI Definition	ST Definition	Quality of Trial*
On-TIME 2 ^{26,27}	NR	Clopidogrel	TIMI	Death, MI, TVR	with either ischemic symptoms, development of new pathological Q waves, or other ischemic changes on the electrocardiogram or coronary artery intervention. After PCI, a new MI was defined by CK-MB greater than 3 times the upper limit of normal (and this elevation was greater than 50% of the lowest recovery level) Recurrent myocardial infarction was defined as a new increase of creatine kinase MB that was three or more times the upper limit of normal, present in two separate blood samples, and accompanied by chest pain or ECG changes. Early recurrent myocardial infarction was defined as a decrease in creatine kinase MB of at least 50% of the upper limit of normal from a previous peak concentration to a valley, followed by a new increase with a value above the sum of the preceding valley and three	NR	+++
Shen J et al ²⁸	Femoral	Clopidogrel or	TIMI	Death, MI, TVR	NR	NR	++±
Shen J et al ²⁹	Femoral	Clopidogrel	ΤΙΜΙ	Death, MI, TVR	NR	NR	++±
Zorman S et al ³⁰	NR	NR	NR	NR	NR	NR	+±±

See foot note of Table 1 for expansion of trial names; ARC = Academic Research Consortitium; MACE=Major adverse cardiac and/or cerebrovascular events; MI=Myocardial infarction; NR=Not reported; TLR=Target lesion revascularization; TVR=Target vessel revascularization

*Represents risk of bias based on: sequence generation of allocation; allocation concealment and blinding. '+' represents low bias risk, '-' high bias risk and '±' unclear bias risk.

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Supplementary figure 1. Study Selection





Supplementary figure 2a. Rankogram for the outcome of MACCE. Plot presents the ranking probabilities and their uncertainty.

Supplementary figure 2b. Hierarchy of treatments for the outcome of MACCE using surface under cumulative ranking curves (SUCRA). The higher the SUCRA value higher is the treatment rank.





Supplementary figure 3a. Rankogram for the outcome of death. Plot presents the ranking probabilities and their uncertainty.

Supplementary figure 3b. Hierarchy of treatments for the outcome of death using surface under cumulative ranking curves (SUCRA). The higher the SUCRA value higher is the treatment rank.



Supplementary figure 4a. Rankogram for the outcome of myocardial infarction. Plot presents the ranking probabilities and their uncertainty.



Supplementary figure 4b. Hierarchy of treatments for the outcome of myocardial infarction using surface under cumulative ranking curves (SUCRA). The higher the SUCRA value higher is the treatment rank.





Supplementary figure 5a. Rankogram for the outcome of urgent revascularization. Plot presents the ranking probabilities and their uncertainty.

Supplementary figure 5b. Hierarchy of treatments for the outcome of urgent revascularization using surface under cumulative ranking curves (SUCRA). The higher the SUCRA value higher is the treatment rank.







Supplementary figure 6b. Hierarchy of treatments for the outcome of stent thrombosis using surface under cumulative ranking curves (SUCRA). The higher the SUCRA value higher is the treatment rank.





Supplementary figure 7a. Rankogram for the outcome of major bleeding. Plot presents the ranking probabilities and their uncertainty.

Supplementary figure 7b. Hierarchy of treatments for the outcome of major bleeding using surface under cumulative ranking curves (SUCRA). The higher the SUCRA value higher is the treatment rank.



Supplementary figure 8a. Rankogram for the outcome of minor bleeding. Plot presents the ranking probabilities and their uncertainty.



Supplementary figure 8b. Hierarchy of treatments for the outcome of minor bleeding using surface under cumulative ranking curves (SUCRA). The higher the SUCRA value higher is the treatment rank.



Supplementary figure 9a. Comparison adjusted funnel plot for the outcome of MACE. A= UFH+GPI; B=UFH; C=Bivalirudin; D=Fondaparinux; E=LMWH+GPI. The horizontal axis is the study-specific effect sizes centered to the respective comparison-specific pooled effect size while the vertical axis is the inverted standard error of the effect sizes as used in a standard funnel plot.



Supplementary figure 9b. Comparison adjusted funnel plot for the outcome of death. A= UFH+GPI; B=UFH; C=Bivalirudin; D=Fondaparinux; E=LMWH+GPI.







Supplementary figure 9d. Comparison adjusted funnel plot for the outcome of urgent revascularization. A= UFH+GPI; B=UFH; C=Bivalirudin; D=Fondaparinux; E=LMWH+GPI









Supplementary figure 10. Relationship between newer P2Y12 inhibitor use and the relative risk for major bleeding with bivalirudin when compared with UFH with or without GPI.



Supplementary figure 11. Relationship between access site and the relative risk for major bleeding with bivalirudin when compared with UFH with or without GPI.

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Supplementary figure 12. Relationship between newer P2Y12 inhibitor use and the relative risk for MACCE with bivalirudin when compared with UFH with or without GPI.