Supplementary Appendix

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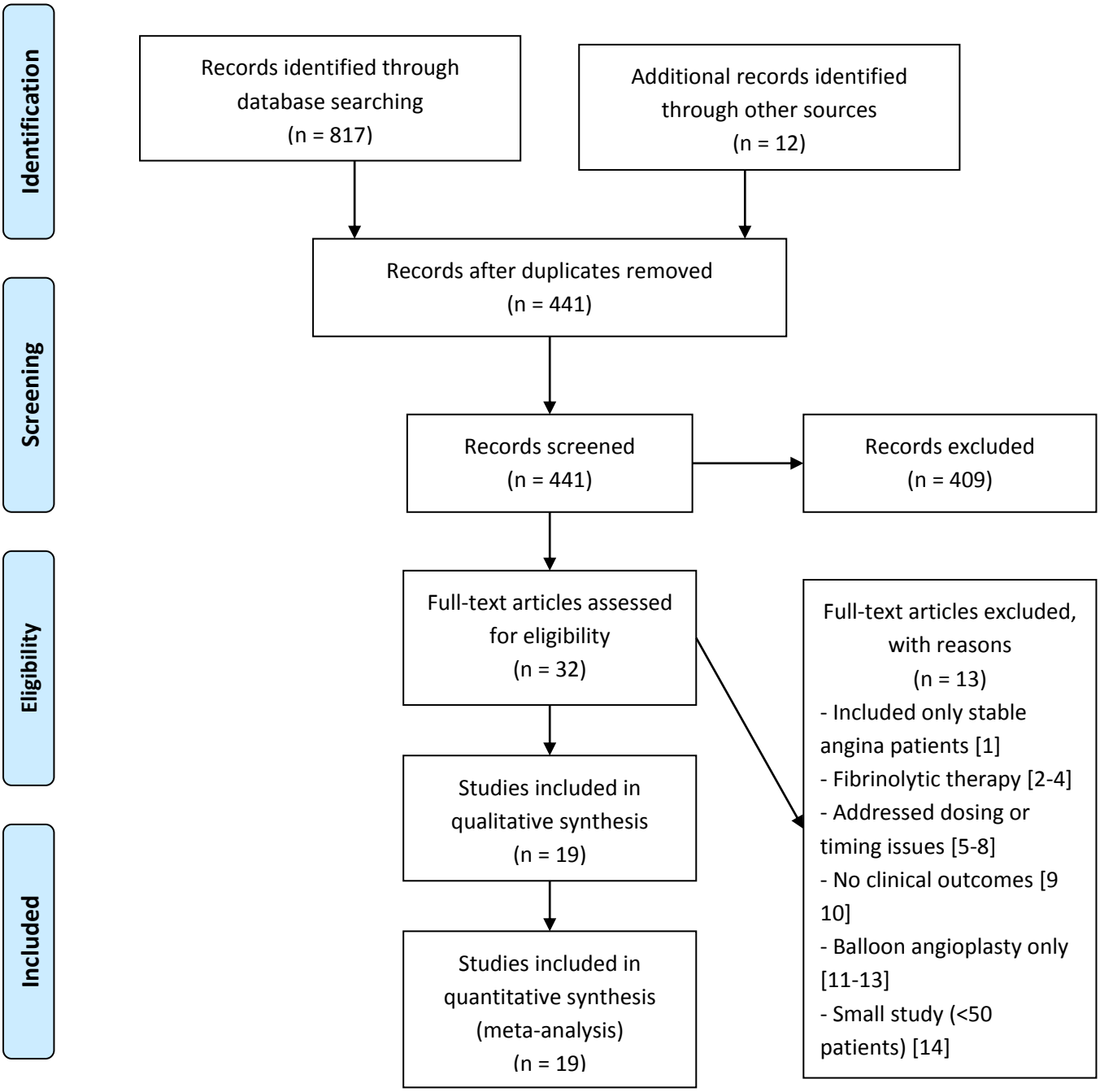
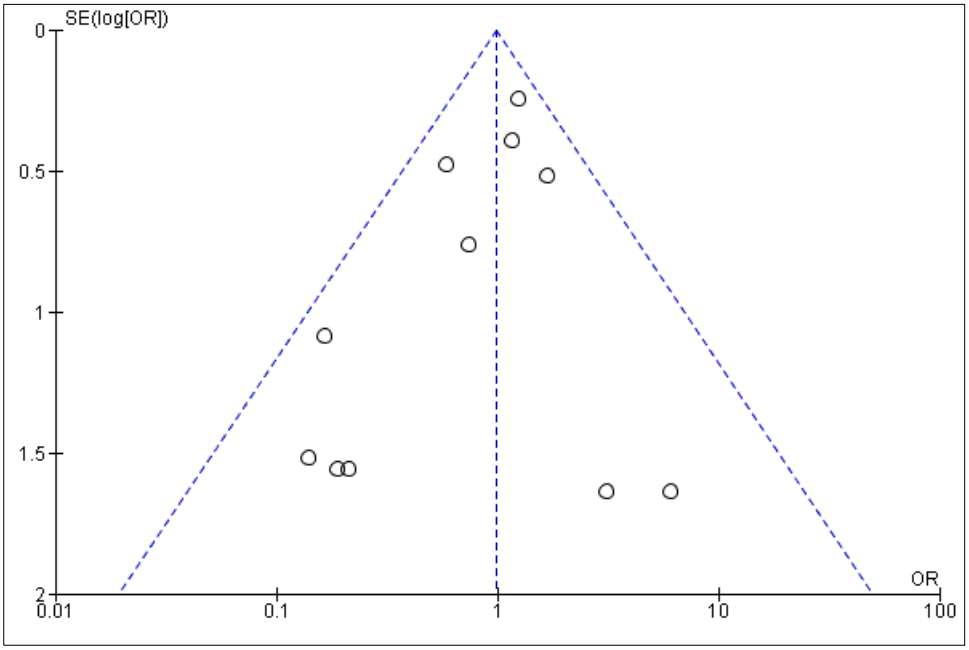
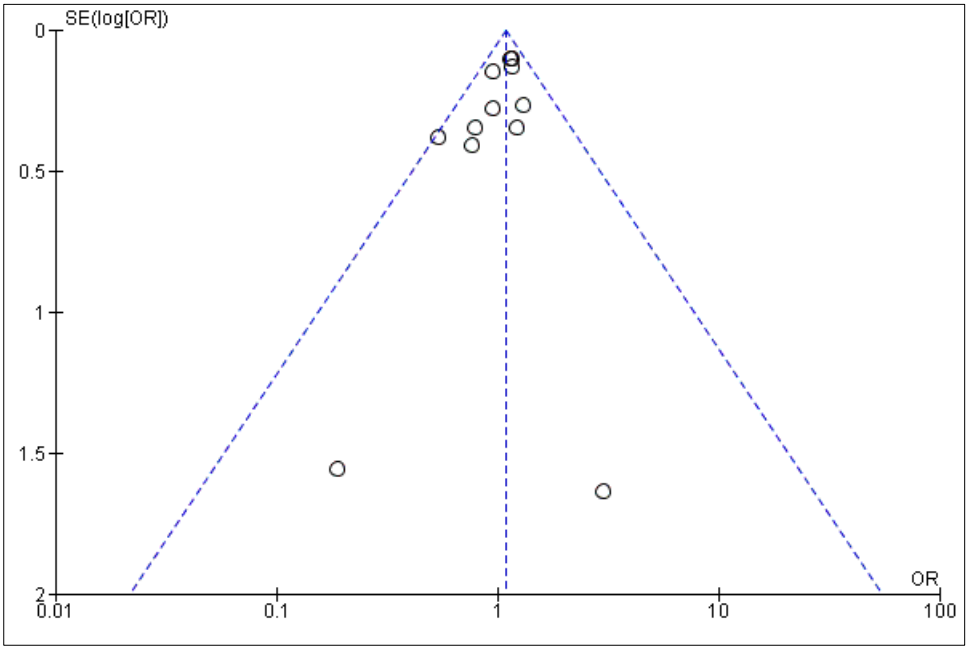
Supplemental Figure 1: PRISMA flow chart



Supplemental Figure 2: Death with bivalirudin versus unfractionated heparin in predominantly NSTE-ACS studies, the funnel plot suggesting that publication bias was minimal



Supplemental Figure 3: Myocardial infarction with bivalirudin versus unfractionated heparin in predominantly NSTE-ACS studies, the funnel plot suggesting that publication bias was minimal



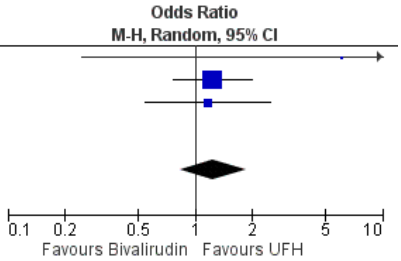
Supplemental Figure 4: Death, myocardial infarction, any stent thrombosis, and major bleeding with bivalirudin versus unfractionated heparin in predominantly NSTEMI studies

(A) Death, (B) Myocardial infarction, (C) Any stent thrombosis, and (D) Major bleeding with GPI predominantly provisional in the bivalirudin arm versus planned use in the heparin arm

(A)

Study or Subgroup	Bivalirudin Events	Bivalirudin Total	Unfractioned Heparin Events	Unfractioned Heparin Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
PROTECT-TIMI 30	1	284	0	573	1.6%	6.07 [0.25, 149.44]	2006
ACUITY-PCI	58	5228	23	2561	70.8%	1.24 [0.76, 2.01]	2007
ISAR-REACT 4	14	860	12	861	27.6%	1.17 [0.54, 2.55]	2011
SWITCH III	0	51	0	49		Not estimable	2013
Total (95% CI)		**6423**		**4044**	**100.0%**	**1.25 [0.83, 1.88]**	
Total events	73		35				

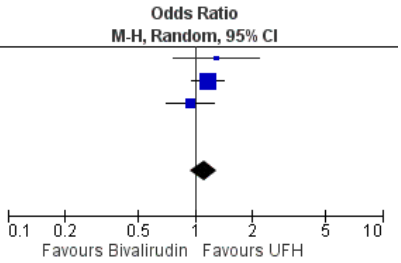
Heterogeneity: Tau² = 0.00; Chi² = 0.96, df = 2 (P = 0.62); I² = 0%
Test for overall effect: Z = 1.07 (P = 0.28)



(B)

Study or Subgroup	Bivalirudin Events	Bivalirudin Total	Unfractioned Heparin Events	Unfractioned Heparin Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
PROTECT-TIMI 30	24	284	38	573	8.9%	1.30 [0.76, 2.21]	2006
ACUITY-PCI	341	5228	144	2561	62.2%	1.17 [0.96, 1.43]	2007
ISAR-REACT 4	98	860	103	861	29.0%	0.95 [0.71, 1.27]	2011
SWITCH III	0	51	0	49		Not estimable	2013
Total (95% CI)		**6423**		**4044**	**100.0%**	**1.11 [0.95, 1.30]**	
Total events	463		285				

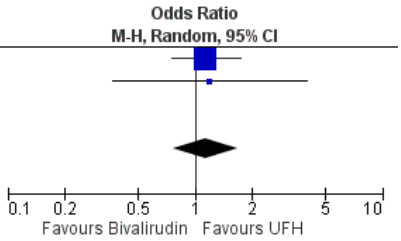
Heterogeneity: Tau² = 0.00; Chi² = 1.74, df = 2 (P = 0.42); I² = 0%
Test for overall effect: Z = 1.31 (P = 0.19)



(C)

Study or Subgroup	Bivalirudin Events	Bivalirudin Total	Unfractioned Heparin Events	Unfractioned Heparin Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
ACUITY-PCI	72	5228	31	2561	88.8%	1.14 [0.75, 1.74]	2007
ISAR-REACT 4	6	822	5	822	11.2%	1.20 [0.37, 3.95]	2011
SWITCH III	0	51	0	49		Not estimable	2013
Total (95% CI)		**6101**		**3432**	**100.0%**	**1.15 [0.77, 1.71]**	
Total events	78		36				

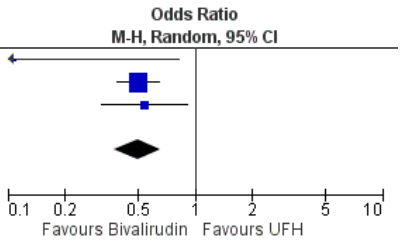
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.67 (P = 0.50)



(D)

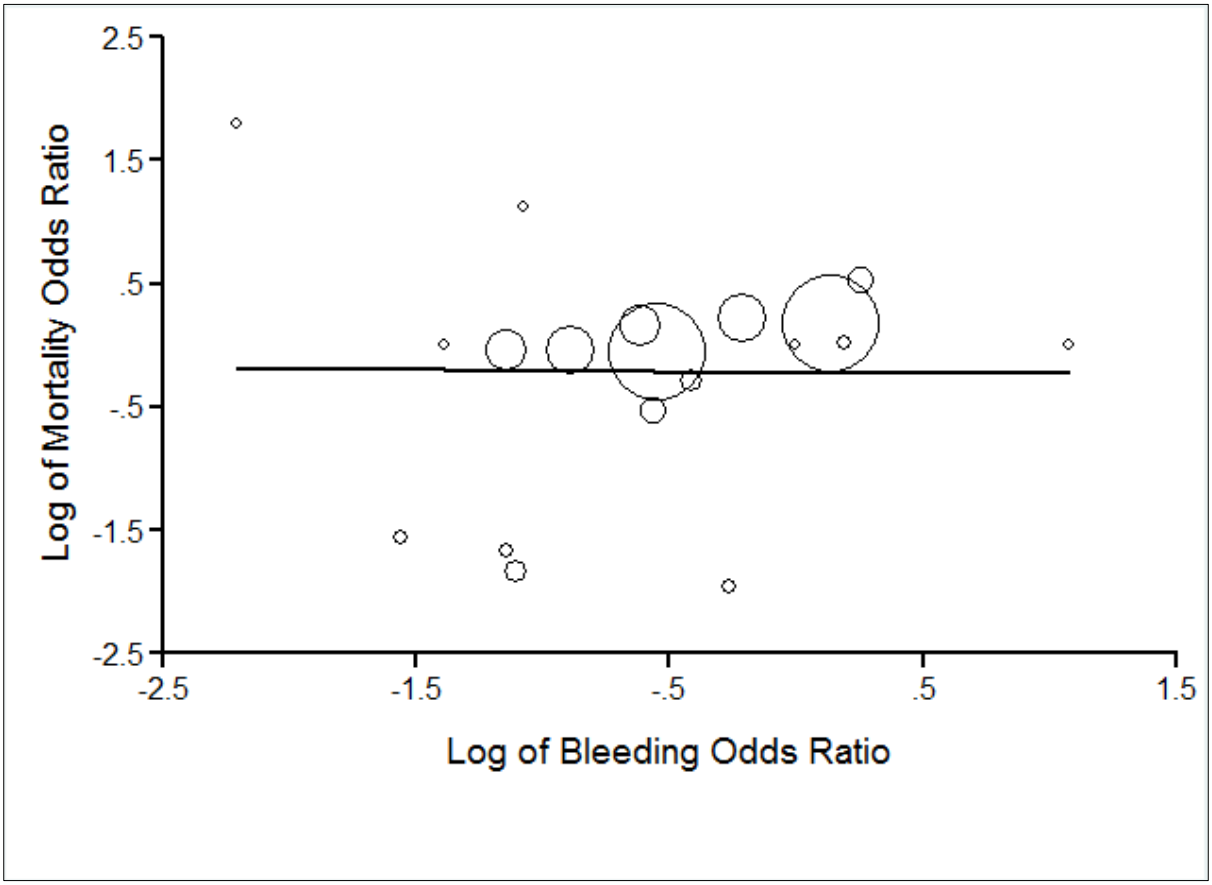
Study or Subgroup	Bivalirudin Events	Bivalirudin Total	Unfractioned Heparin Events	Unfractioned Heparin Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
PROTECT-TIMI 30	1	284	18	573	2.0%	0.11 [0.01, 0.82]	2006
ACUITY-PCI	92	2619	174	2561	72.5%	0.50 [0.39, 0.65]	2007
ISAR-REACT 4	22	860	40	861	25.5%	0.54 [0.32, 0.91]	2011
Total (95% CI)		**3763**		**3995**	**100.0%**	**0.49 [0.37, 0.66]**	
Total events	115		232				

Heterogeneity: Tau² = 0.01; Chi² = 2.30, df = 2 (P = 0.32); I² = 13%
Test for overall effect: Z = 4.78 (P < 0.00001)



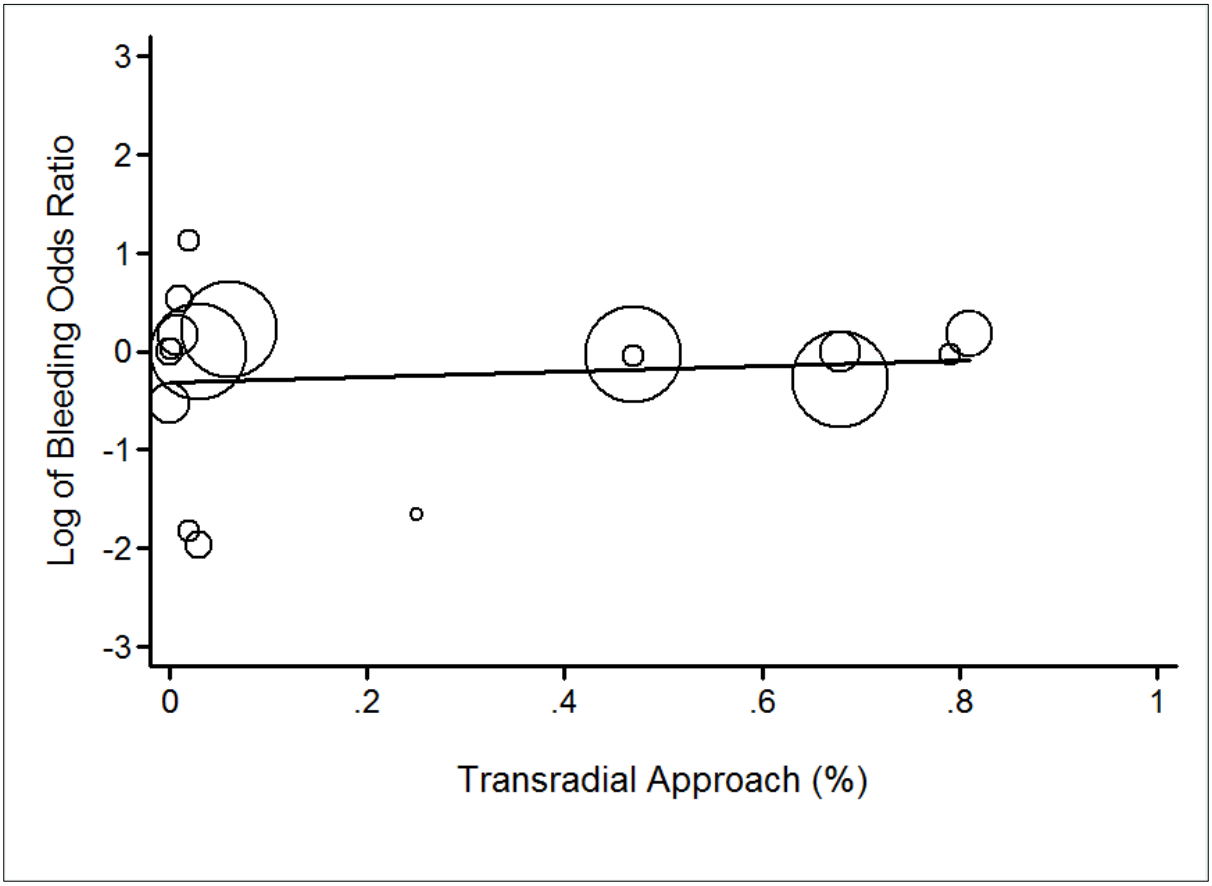
Supplemental Figure 5: Relationship between the effect of bivalirudin on bleeding and mortality

The regression line is almost flat (slope -0.61), P=0.9539.



Supplemental Figure 6: Relationship between the effect of bivalirudin on bleeding and the use of transradial approach

The regression line is almost flat (slope -0.54), P=0.4985.



Supplemental Table 1: Primary Outcomes and Definition of Major Bleeding

Study	Primary Outcomes	Major Bleeding Definition
REPLACE-2	Composite death, MI, urgent repeat revascularization and major bleeding	Non-CABG, intracranial, intraocular, retroperitoneal, 4gm Hgb decline without bleeding, 3gm Hgb decline with bleeding or ≥2U RBC transfusion
REPLACE-1	Composite death, MI and repeat revascularisation at 48 hours	Non-CABG, intracranial, intraocular, retroperitoneal, 3gm Hgb decline or ≥2U transfusion
PROTECT-TIMI 30	Coronary flow reserve or TIMI major bleeding	TIMI major or minor
ACUITY-PCI	Composite death, MI and unplanned revascularization or major bleeding or net clinical outcomes (composite ischaemia or major bleeding)	Non-CABG, intracranial, intraocular, access site haemorrhage requiring intervention, 5 cm hematoma, 4gm Hgb decline without bleeding, 3gm Hgb decline with bleeding or transfusion
ARNO	Major bleeding	Non-CABG, intracranial, intraocular, retroperitoneal, 4gm Hgb decline without bleeding, 3gm Hgb decline with bleeding or ≥2U RBC transfusion
HORIZONS-AMI	Composite death, MI and target vessel revascularization and stroke or major bleeding	Non-CABG, intracranial, intraocular, access site haemorrhage requiring intervention, 5 cm hematoma, 4gm Hgb decline without bleeding, 3gm Hgb decline with bleeding or transfusion
ISAR-REACT 3	Composite death, MI, urgent target vessel revascularization and major bleeding	Non-CABG, intracranial, intraocular, retroperitoneal, 4gm Hgb decline without bleeding, 3gm Hgb decline with bleeding or ≥2U RBC transfusion
NAPLES	Composite death, MI, urgent repeat revascularization and major bleeding	Intracranial, intraocular, retroperitoneal, access site haemorrhage requiring intervention, 4gm Hgb decline without bleeding, 3gm Hgb decline with bleeding or ≥2U transfusion
TENACITY	Composite death, MI and urgent target vessel revascularization	Non-CABG, intracranial, intraocular, retroperitoneal, 4gm Hgb decline without bleeding, 3gm Hgb decline with bleeding or ≥2U RBC transfusion
ISAR-REACT 4	Composite death, MI, urgent target vessel revascularization and major bleeding	Non-CABG, intracranial, intraocular, retroperitoneal, 4gm Hgb decline + overt bleeding or transfusion of at least 2 U
ARMYDA-7 BIVALVE	Composite death, MI, urgent target vessel revascularization and ST or any bleeding	Any bleeding
Deshpande et al.	post procedural time to sheath removal and ambulation of the patient	Non-CABG, intracranial, intraocular, retroperitoneal, 4gm Hgb decline without bleeding, 3gm Hgb decline with bleeding or ≥2U RBC transfusion
EUROMAX	Composite of death or major bleeding	Non-CABG, intracranial, intraocular, access site haemorrhage requiring intervention, retroperitoneal, 4gm Hgb decline without bleeding, 3gm Hgb decline with bleeding or transfusion
SWITCH III	Major bleeding	Fatal bleeding, intracranial, intraocular, retroperitoneal, 3gm Hgb decline with bleeding or ≥2U RBC transfusion
Xiang et al.	Composite death, MI and target vessel revascularization or ACT values or any bleeding	Non-CABG, intracranial, intraocular, retroperitoneal, 4gm Hgb decline without bleeding, 3gm Hgb decline with bleeding or ≥2U RBC transfusion
Heat-PPCI	Composite death, MI, stroke and unplanned target vessel revascularization or major bleeding	BARC 3-5

NAPLES III	Major bleeding	In-hospital intracranial, intraocular, retroperitoneal, access site haemorrhage requiring intervention, 4gm Hgb decline without bleeding, 3gm Hgb decline with bleeding or ≥2U transfusion
BRIGHT	Composite death, MI, urgent target vessel revascularization, stroke and major bleeding	BARC 3 or 5
BRAVE 4	Composite death, MI, unplanned revascularization, ST, stroke and major bleeding	Non-CABG, intracranial, intraocular, access site haemorrhage requiring intervention, 5 cm hematoma, 4gm Hgb decline without bleeding, 3gm Hgb decline with bleeding or transfusion

ACT: activated clotting time, BARC: Bleeding Academic Research Consortium, CABG: coronary artery bypass grafting, Hgb: haemoglobin, MI: myocardial infarction, ST: stent thrombosis

Supplemental Table 2: The methodological quality assessment of included studies

Study	Randomisation Scheme	Blinding	Dropout Rate (%)	Endpoint adjudication	Potential Sources of Bias
REPLACE-2	By central telephone system	Double-blind	<1%	By blinded central committee	None identified
REPLACE-1	By central telephone system	Open-label	Not reported	Central adjudication was not used	Performance bias, attrition bias
PROTECT-TIMI 30	By central permuted block design system	Open-label	<1%	By blinded central committee	Performance bias
ACUITY-PCI	By interactive voice response system	Open-label	<1%	By blinded central committee	Performance bias
ARNO *	Not reported	Open-label	Not reported	By blinded central committee	Selection bias, performance bias, attrition bias
HORIZONS-AMI	By interactive voice response system	Open-label	<1%	By blinded central committee	Performance bias
ISAR-REACT 3	Not reported	Double-blind	<1%	By blinded central committee	Selection bias
NAPLES	By block randomisation system	Open-label	Not reported	By blinded central committee	Performance bias, attrition bias
TENACITY	Not reported	Double-blind	Not reported	By central committee	Selection bias, attrition bias
ISAR-REACT 4	By double-dummy-drug system	Double-blind	<1%	By blinded central committee	None identified
ARMYDA-7 BIVALVE	By random numbers system	Open-label	Not reported	By blinded central committee	Performance bias, attrition bias
Deshpande et al.	Not reported	Open-label	Not reported	Not reported	Selection bias, performance bias, attrition bias
EUROMAX	Not reported	Open-label	1%	By blinded central committee	Selection bias, Performance bias
SWITCH III	By block randomisation system	Open-label	0	Not reported	Performance bias
Xiang et al.	Not reported	Single-blind	4%	Not reported	Selection bias, Performance bias
Heat-PPCI	By computerized randomisation system	Open-label	<1%	By blinded central committee	Performance bias
NAPLES III	Not reported	Double-blind	0	By central committee	Selection bias
BRIGHT	Not reported	Single-blind	<1%	By central committee	Selection bias
BRAVE 4	Not reported	Open-label	<1%	By blinded central committee	Selection bias, performance bias, premature termination of the trial

* The trial had been presented, but not published.

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percutaneous coronary intervention in relation to platelet activation and the inhibition of coagulation. EuroIntervention 2009;**5**(3):330-5