National Institute for Health and Care Excellence

Final

Acute Coronary Syndromes

[B] Evidence review for early invasive versus conservative management

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: In adults with unstable angina or non-ST-segment elevation MI does early routine invasive investigation (i.e. angiography) with intent to assess for (and in those patients deemed suitable, to perform) revascularization improve outcomes in comparison with conservative or selective treatment, with or without later angiography?

1.2 Introduction

In people presenting with unstable angina (UA) or a non-ST-segment elevation myocardial infarction (NSTEMI), urgent angiography can be performed with a view to revascularisation of the obstructed coronary artery. Medical management including anti-thrombotic therapy is instigated immediately on presentation and continued until angiography and any revascularisation procedure has been performed. When the techniques for acute coronary stenting were first developed trials were carried out to determine whether angiography, with a view to performing a revascularisation procedure, should be offered routinely to all patients with UA or NSTEMI, or whether this approach should be employed only in selected cases since in some patients medical treatment alone is successful in stabilising symptoms. The relevant evidence was considered in the development of NICE guideline CG94, the Guideline Committee concluding that in those people with higher risk of adverse cardiovascular outcomes early angiography should be performed, whereas in those at lower baseline risk conservative management is preferable with angiography being offered later if ischaemic problems persist.

An unresolved question at the time CG94 was developed was the optimal timing of routine angiography. This is affected by the need to stabilise acutely unwell patients, the practicalities of transporting them to a unit capable of performing angiography and PCI, and by the capacity of such PCI units. The recommendation in CG94 is that angiography should be performed within 96 hours, based on the evidence from trials and a practical assessment of the situation in the UK at that time. The current review will take into account both new evidence and changes in the availability of urgent angiography and PCI.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Adults (≥ 18 years old) with UA/NSTEMI
Intervention	Routine invasive strategy (and intervention if indicated) Invasive procedures include: • angiography • stents • angioplasty • CABG

Comparison	Conservative approach including: • deferred or selective angiography in patients with ongoing or recurrent symptoms or ischaemia. • medical management (anti-thrombotic and anti-anginal)
Outcomes	**CRITICAL** Outcomes at following time intervals: in hospital, 30 days, 1 year (or closest to 1 year) • Mortality (all-cause and cardiovascular specific) • Non-fatal and all (non-fatal and fatal) myocardial reinfarction • Unplanned revascularisation (where information is available we will record whether index lesion or not) • Major bleeding • Minor bleeding. Intracranial bleeding recorded separately • Quality of life at 1 year including EQ-5D (EuroQol), SF-36 and SF6D **IMPORTANT** • Length of hospital stay • Refractory ischaemia The following outcomes at latest time point available (>1 year): • Stroke • Unplanned rehospitalisation for any reason • Mortality (all-cause and cardiovascular specific) • Non-fatal and all (non-fatal and fatal) myocardial reinfarction • Unplanned revascularisation • Major and minor bleeding. Intracranial bleeding recorded separately
Study design	• Randomised Controlled Trials (RCTs • Systematic Reviews (SR) of RCTs

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[52] 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

A search was conducted for randomised controlled trials comparing routine invasive to conservative or selective invasive strategies for the management of UA/NSTEMI.

A Cochrane systematic review (Fanning 2016) was identified.[18] The review included 8 trials (FRISC II, [33, 38-40, 71, 72] ICTUS, [11, 29, 30] Italian Elderly ACS,[60, 61] LIPSIA-NSTEMI,[69] OASIS 5,[65] RITA-3, [20, 21, 26] TACTIC-TIMI 18[8] and VINO[64]).

The Cochrane review was incorporated in the following ways:

- The search strategy was verified to ensure it would adequately cover our review question. The search was conducted with a date limit of 2008 onwards
- Two additional papers which were 10 year follow up studies of the ICTUS[30] and RITA-3[26] trials were identified and included in this review

Article selection and risk of bias assessment **per study** were directly adopted without further checking.

- GRADE assessments for risk of bias, inconsistency, indirectness and imprecision **per outcome** were redone to ensure consistency with our methodology.
- Data for all outcomes were incorporated into the review.
- Outcomes of interest that were not included in the Cochrane were added. These included all-cause and cardiovascular mortality at latest time point available and stroke.

Evidence from the included studies is summarised in the clinical evidence summary below, **Table 2**).

See also the study selection flow chart in appendix C, study evidence tables including rates of angiography and revascularisation 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 the Cochrane review

Study	Intervention and comparison	Population	Outcomes	Comments
Fanning 2016[18] Systematic review of RCTs (8 studies, see Table 3 below)	Routine invasive strategy: routine angiography with or without revascularisation in all patients. This was performed in all eligible patients unless they had contraindications to angiography. Conservative or 'selective invasive' strategy: angiography with or without revascularisation only in eligible patients with evidence of cardiac ischaemia; e.g. recurrent ischaemia, dynamic ECG changes or a positive stress test.	8915 participants (4545 invasive strategies, 4370 conservative strategies)	**Primary outcomes** 1. All-cause mortality 2. Myocardial infarction (MI) 3. Death (all causes) or non-fatal MI. 4. Refractory angina. **Secondary outcomes** 1. Rehospitalisation for ACS. 2. Complications of angiography or revascularisation (e.g. bleeding, procedure-related MI, stroke).	Death (all causes) or non-fatal MI was not included in our guideline review. One of the main issues with the included trials is that they all used different definitions of MI. Table 3 is a summary of the various definitions.

Table 3: Summary of studies included in the Cochrane review

Study	Intervention and comparison	Population	Outcomes	Comments
FRISC-II Anon 1999[33] Lagerqvist 2002[38] Lagerqvist 2006[39] Lagerqvist 2001[40] Wallentin 2000[71] Wallentin 2016[72] Prospective, randomised, multicentre trial with parallel groups. Invasive and non-invasive treatments compared by factorial design	Conservative arm: aspirin, beta blocker, statin, ACEI, dalteparin or UFH. Invasive arm: as above and routine angiography (average time to angiography: 4 days). 10% glycoprotein 2b/3a receptor antagonist use Each strategy further randomised to placebo or dalteparin in a double-blind fashion	2457 participants with anginal pain within the last 48 hours and ST depression or elevated cardiac markers.	All-cause mortality (6, 12, 24 months, 5 years), MI (6, 12, 24 months, 5 years), refractory angina (6 months), death or non-fatal MI (6, 12, 24 months, 5 years), rehospitalisation (6 weeks, 6, 12 months), procedural MI, bleeding, contrast allergy	Pharma sponsored
ICTUS de Winter 2005[11] Hirsch 2007[29] Hoedemaker 2017[30] Prospective, randomised, multicentre trial.	Conservative arm: aspirin, enoxaparin, statin, clopidogrel. Invasive arm: as above, abciximab and routine angiography (median time to angiography: 23 hours) post randomisation. 94% glycoprotein 2b/3a receptor antagonist use	1200 participants with accelerating angina or angina at rest in the preceding 24 hours and an elevated cardiac troponin T > 0.3 µg/L and either ischaemic ECG changes or a documented history of coronary artery disease (CAD) (previous catheterization, history	All-cause mortality (1, 3 and 4 years), MI (1 and 3 years), rehospitalisation (1 and 3 years), major bleeding during the index admission Additional 10 year follow up study not included in the Cochrane review was also identified.	Clopidogrel was more common at discharge for early invasive (61%) versus selective invasive (49%) strategies.

Study	Intervention and comparison	Population	Outcomes	Comments
		of myocardial infarction (MI) or positive exercise test).		
Italian Elderly ACS Savonitto 2012[60] Savonitto 2008[61] Prospective, randomised, multicentre trial	Conservative arm: initially conservative strategy (angiography and revascularization only for recurrent ischaemia) Invasive arm: early aggressive strategy (coronary angiography and, when indicated, revascularization within 72 hours)	313 participants with symptoms suggestive of acute myocardial ischaemia at rest within 48 hours before randomisation and ischaemic ECG changes (transient or persistent ST segment elevation or depression > 0.5 mm but < 1 mm in the case of ST-elevation or persistent and definite T wave inversion > 1 mm in at least 2 contiguous leads) and/or elevate levels (> upper limit of normal) of creatine kinase-myocardial band (CK-MB) or cTn Median time from symptoms to randomisation 24 hours (IQR: 11-36)	All-cause death (6 months, 1 year), MI (6 months, 1 year), rehospitalisation (6 month, 1 year), major bleeding (6 months, 1 year), days spent in hospital (6 months, 1 year), stroke (6 month, 1 year)	There was no industry sponsorship.
LIPSIA-NSTEMI	Conservative/selective invasive arm: selective	602 participants with NSTEMI (ischaemic	All-cause mortality (6 months, non-fatal	Though results were expressed in terms of the 3

Study	Intervention and comparison	Population	Outcomes	Comments
Thiele 2012[69] Prospective, randomised, multicentre trial comparing immediate versus early versus selective invasive strategies	invasive only if refractory ischaemia Invasive arm: < 2 hours after randomisation; early invasive strategy: 10 to 48 hours after randomisation	symptoms that were increasing or occurred at rest, with the last episode < 24 hours before randomisation plus elevated troponin T level ≥ 0.1 ng/mL) were admitted across 6 tertiary care centres with 24 hour PCI facilities	infarction (6 months), refractory ischaemia (6 months) and rehospitalisation for unstable angina (6 months)	groups of randomisation (immediate versus early versus selective invasive) for the purposes of this review, the immediate and early invasive strategies were grouped and considered “early invasive”, whereas the criteria for the selective invasive was most consistent with a conservative strategy Pharma sponsored
OASIS 5 Swahn 2012[65] Randomised, multicentre, prospectively designed substudy of the OASIS 5 trial (a double- blinded trial in which fondaparinux was compared with	Conservative/selective invasive arm: with coronary angiography only if symptoms or signs of severe ischaemia Invasive arm: routine coronary angiography within 4 days of admission and, if appropriate, revascularisation within 7 days of admission	184 female participants were recruited when the OASIS 5 main trial was stopped. These participants presented to hospital with symptoms of UA or MI without persistent ST elevation and at least 2 of: age ≥ 60 years, troponin T or I or CK-MB above the upper limit of normal or ECG changes compatible	All-cause mortality (30 days, 1 year), MI (30 days, 1 year)	Recruitment ceased early and sample sizes curtailed.

Study	Intervention and comparison	Population	Outcomes	Comments
enoxaparin in participants with UA/NSTEMI)		with ischaemia (ST depression ≥ 1 mm in 2 contiguous leads or T wave inversion > 3 mm or any dynamic ST shift or transient ST elevation)		
RITA-3 Fox 2005[20] Fox 2002[21] Henderson 2015[26] Prospective, randomised mulitcentre trial with parallel groups	Conservative arm: aspirin, beta blocker, enoxaparin Invasive arm: as above and routine angiography (median time to angiography: 2 days). 25% glycoprotein 2b/3a receptor antagonist use	1810 participants with chest pain within the last 72 hours, a documented history of CAD, and one of the following: ischaemic ECG changes or Qwaves suggesting previous MI or proven CAD on angiogram. The trial excluded those with probable evolving MI or those with elevated cardiac biomarkerss (2x) before randomisation.	All-cause mortality (4, 12, 24 months, 5 years), MI (4, 12, 24 months, 5 years), refractory angina (4,12mo), procedural bleeding and MI Additional 10 year follow up study not included in the Cochrane review was also identified.	All participants were accounted for at 2 years, 99.8% at 3 years and 59% at 5 years follow-up. The trial used ITT analysis
TACTICS-TIMI 18 Cannon 2001[8] Prospective, randomised, multicentre trial	Conservative arm: aspirin, beta blocker, UFH, tirofiban, statin Invasive arm: as above and routine angiography (median time to angiography: 22 hours). 94% glycoprotein	2220 participants with angina (accelerating or prolonged) at rest in preceding 24 hours and at least 1 of the following: ischaemic ECG changes, elevated cardiac markers or documented CAD	All-cause mortality (30 days, 6 months), refractory angina (6 months), rehospitalisation (30 days, 6 months)	Sponsored by Merck.

Study	Intervention and comparison	Population	Outcomes	Comments
with parallel groups	2b/3a receptor antagonist use	(previous catheterisation, revascularisation or MI)		
VINO Spacek 2002[64] Prospective, randomised, multicentre trial with parallel groups	Conservative arm: aspirin, beta blocker, UFH Invasive arm: as above and routine angiography (average time to angiography: 6.2 hours). 0% glycoprotein 2b/3a receptor antagonist use	131 participants with ischaemic chest pain lasting more than 20 mins (within the preceding 24 hours) and ECG changes and elevated cardiac markers	All-cause mortality (30 days, 6 months), MI (30 days, 6 months), rehospitalisation (30 days, 6 months)	All participants were accounted for by the end of the trial; the trial used ITT analysis

See appendix D for full evidence tables.

1.5.4 Quality assessment of clinical studies included in the evidence review

Table 4: Clinical evidence summary: routine invasive versus conservative management

Outcomes (follow up)	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with conservative	Risk difference with routine invasive (95% CI)
Index death (all-cause mortality in hospital)	8094 (6 studies)	⨁⨁⊖⊖ LOW[1,3]	RR 1.54 (1.03 to 2.31)	9 per 1000	5 more per 1000 (from 0 more to 12 more)

Outcomes (follow up)	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with conservative	Risk difference with routine invasive (95% CI)
		due to imprecision, risk of bias			
Early death (all-cause mortality 30 days)	4345 (4 studies)	⨁⨁⊖⊖ LOW[1,3] due to imprecision, risk of bias	RR 1.18 (0.81 to 1.73)	21 per 1000	4 more per 1000 (from 4 fewer to 15 more)
Intermediate death (all-cause mortality at 6-12 months)	8915 (8 studies)	⨁⨁⨁⊖ MODERATE[1] due to imprecision	RR 0.88 (0.72 to 1.08)	39 per 1000	5 fewer per 1000 (from 11 fewer to 3 more)
Late death (all-cause mortality at >2 years)	5467 (3 studies)	⨁⨁⊖⊖ LOW[1,3] due to imprecision, risk of bias	RR 0.9 (0.77 to 1.06)	100 per 1000	10 fewer per 1000 (from 23 fewer to 6 more)
All-cause mortality at latest time-point (10 years)	3010 (2 studies)	⨁⨁⨁⊖ MODERATE[3] due to risk of bias	RR 1.04 (0.92 to 1.18)	243 per 1000	10 more per 1000 (from 19 fewer to 44 more)
Cardiovascular mortality (1 year)	313 (1 study)	⨁⨁⊖⊖ LOW[1] due to imprecision	RR 0.97 (0.51 to 1.85)	107 per 1000	3 fewer per 1000 (from 52 fewer to 91 more)
Cardiovascular mortality (2 years)	3010 (2 studies)	⨁⊖⊖⊖ VERY LOW[1,3] due to imprecision, risk of bias	RR 0.95 (0.66 to 1.35)	39 per 1000	2 fewer per 1000 (from 13 fewer to 14 more)
Cardiovascular mortality (5 years)	3634 (2 studies)	⨁⊖⊖⊖ VERY LOW[1,3] due to imprecision, risk of bias	RR 0.99 (0.75 to 1.31)	49 per 1000	0 fewer per 1000 (from 12 fewer to 15 more)
Cardiovascular death at latest time point available (10 years)	3010 (2 studies)	⨁⨁⨁⊖ MODERATE[3] due to risk of bias	RR 1.01 (0.85 to 1.19)	152 per 1000	2 more per 1000 (from 23 fewer to 29 more)

Outcomes (follow up)	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with conservative	Risk difference with routine invasive (95% CI)
Index myocardial infarction (MI in hospital)	8694 (7 studies)	⨁⨀⨀⨀ VERY LOW[1,2] due to inconsistency, imprecision	RR 1.08 (0.65 to 1.8)	31 per 1000	2 more per 1000 (from 11 fewer to 25 more)
Early myocardial infarction (up to 4 months)	4345 (4 studies)	⨁⨁⨁⨀ MODERATE[1] due to imprecision	RR 0.65 (0.49 to 0.88)	48 per 1000	17 fewer per 1000 (from 6 fewer to 24 fewer)
Intermediate myocardial infarction at 6-12 months (intermediate MI)	8915 (8 studies)	⨁⨁⨀⨀ LOW[1,3] due to imprecision, risk of bias	RR 0.78 (0.67 to 0.91)	89 per 1000	20 fewer per 1000 (from 8 fewer to 29 fewer)
Late myocardial infarction (at > 2 years)	5467 (3 studies)	⨁⨁⨀⨀ LOW[1,3] due to imprecision, risk of bias	RR 0.79 (0.67 to 0.93)	65 per 1000	14 fewer per 1000 (from 5 fewer to 21 fewer)
Myocardial infarction at latest time point (10 years)	1200 (1 study)	⨁⨁⨀⨀ LOW[1] due to imprecision	RR 1.03 (0.76 to 1.39)	121 per 1000	4 more per 1000 (from 29 fewer to 47 more)
Procedure-related myocardial infarction	6380 (5 studies)	⨁⨁⨁⨁ HIGH	RR 1.88 (1.48 to 2.39)	29 per 1000	26 more per 1000 (from 14 more to 40 more)
Revascularisation (in hospital)	1513 (2 studies)	⨁⨁⨁⨀ MODERATE[2] due to inconsistency	RR 2.06 (1.64 to 2.57)	312 per 1000	331 more per 1000 (from 200 more to 490 more)
Revascularisation (1 year) – routine glycoprotein IIb/IIa receptor antagonist use	1200 (1 study)	⨁⨁⨁⨁ HIGH	RR 1.46 (1.34 to 1.58)	544 per 1000	250 more per 1000 (from 185 more to 302 more)

Outcomes (follow up)	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with conservative	Risk difference with routine invasive (95% CI)
Revascularisation (1 year) – no routine glycoprotein IIb/IIa receptor antagonist use	2254 (3 studies)	⨁⨁⨁⊖ MODERATE[3] due to risk of bias	RR 2.02 (1.82 to 2.24)	315 per 1000	321 more per 1000 (from 258 more to 391 more)
Revascularisation (2 years)	2457 (1 study)	⨁⨁⨁⊖ MODERATE[3] due to risk of bias	RR 1.72 (1.61 to 1.84)	454 per 1000	327 more per 1000 (from 277 more to 381 more)
Revascularisation (5 years)	2212 (1 study)	⨁⨁⨁⊖ MODERATE[3] due to risk of bias	RR 1.53 (1.44 to 1.64)	520 per 1000	276 more per 1000 (from 229 more to 333 more)
Intermediate refractory angina	8287 (5 studies)	⨁⨁⊖⊖ LOW[2] due to inconsistency	RR 0.64 (0.52 to 0.79)	Moderate	
				129 per 1000	46 fewer per 1000 (from 27 fewer to 62 fewer)
Early stroke (30 days)	184 (1 study)	⨁⨁⊖⊖ LOW[1] due to imprecision	RR 1 (0.06 to 15.75)	11 per 1000	0 fewer per 1000 (from 10 fewer to 162 more)
Intermediate stroke (at 1 year)	184 (1 study)	⨁⨁⊖⊖ LOW[1] due to imprecision	RR 0.67 (0.11 to 3.9)	33 per 1000	11 fewer per 1000 (from 29 fewer to 96 more)
Intermediate rehospitalisation - Routine glycoprotein IIb/IIIa receptor antagonist use	4020 (3 studies)	⨁⨁⨁⊖ MODERATE[1] due to imprecision	RR 0.81 (0.67 to 0.97)	107 per 1000	20 fewer per 1000 (from 3 fewer to 35 fewer)
Intermediate rehospitalisation - No routine glycoprotein IIb/IIIa receptor antagonist use	2901 (3 studies)	⨁⨁⨁⊖ MODERATE[3] due to risk of bias	RR 0.66 (0.61 to 0.72)	170 per 1000	58 fewer per 1000 (from 48 fewer to 66 fewer)
Major bleeding (in hospital)	313 (1 study)	⨁⨁⊖⊖ LOW[1] due to imprecision	RR 4.13 (0.47 to 36.54)	6 per 1000	19 more per 1000 (from 3 fewer to 213 more)

Outcomes (follow up)	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with conservative	Risk difference with routine invasive (95% CI)
Major bleeding (30 days)	184 (1 study)	⨁⨁⨁⨀ MODERATE[1] due to imprecision	RR 8 (1.02 to 62.68)	11 per 1000	77 more per 1000 (from 0 more to 678 more)
Major bleeding (1 year)	5774 (5 studies)	⨁⨁⨁⨀ MODERATE[1] due to imprecision	RR 1.89 (1.2 to 2.99)	10 per 1000	9 more per 1000 (from 2 more to 20 more)
Major bleeding (2 years)	184 (1 study)	⨁⨁⨁⨀ MODERATE[1] due to imprecision	RR 9 (1.16 to 69.61)	11 per 1000	88 more per 1000 (from 2 more to 755 more)
Minor bleeding (1 year)	4677 (2 studies)	⨁⨁⨁⨀ LOW[1,3] due to imprecision, risk of bias	RR 1.42 (1.1 to 1.84)	39 per 1000	16 more per 1000 (from 4 more to 33 more)
Bleeding unspecified (in hospital)	1810 (1 study)	⨁⨁⨁⨀ MODERATE[3] due to risk of bias	RR 2.33 (1.56 to 3.5)	35 per 1000	47 more per 1000 (from 20 more to 87 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 or 2 increments because there is heterogeneity, I2 > 50%, p=0.04, unexplained by subgroup analysis
3 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

See appendix F for full GRADE tables.

1.6 Economic evidence

1.6.1 Included studies

One health economic study was identified with the relevant comparison and has been included in this review.[27, 28] An additional study was identified but has not been summarised as it was a comparative-costing study that informed the included study.[17] The study is summarised in the health economic evidence profile below (Table 5) and the health economic evidence table in Appendix H:.

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: Early invasive versus conservative management

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Henriksson 2008[17, 27, 28] (UK)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Decision tree based on index hospital stay followed by Markov model for post-index stay. Death, MI, QoL and resource use data based on the 5 year follow-up data from RITA-3 RCT[20, 21] • Cost-utility analysis (QALYs) • Population: UA/NSTEMI sub-grouped by risk[(c)] • Comparators ○ Early angiography (routine angiography <72hrs followed by revascularisation if clinically indicated) • Conservative strategy (ischemia or symptom-driven angiography) • Time horizon: lifetime (relative treatment effect	***Basecase:*** *Risk group 1* £4,885[(d)] *Risk group 2* £4,898[(d)] *Risk group 3* £6,045[(d)] *Risk group 4a* £6,538[(d)] *Risk group 4b* £6,530[(d)] ***Pooled treatment effect:*** *Risk group 1* £4,819[(d)] *Risk group 2* £4,852[(d)] *Risk group 3* £5,788[(d)] *Risk group 4a* £6,163[(d)] *Risk group 4b* £6,129[(d)]	***Basecase:*** *Risk group 1* 0.0909 QALYs *Risk group 2* 0.2134 QALYs *Risk group 3* 0.2834 QALYs *Risk group 4a* 0.5468 QALYs *Risk group 4b* 0.5122 QALYs ***Pooled treatment effect:*** *Risk group 1* 0.082 QALYs *Risk group 2* 0.185 QALYs *Risk group 3* 0.240 QALYs *Risk group 4a* 0.452 QALYs *Risk group 4b* 0.418 QALYs	***Basecase:*** *Risk group 1* £53,760 per QALY gained *Risk group 2* £22,949 per QALY gained *Risk group 3* £21,325 per QALY gained *Risk group 4a* £11,957 per QALY gained *Risk group 4b* £12,750 per QALY gained ***Pooled treatment effect:*** *Risk group 1* £58,490 per QALY gained *Risk group 2* £26,265 per QALY gained *Risk group 3* £24,143 per QALY gained *Risk group 4a* £13,646 per QALY gained *Risk group 4b* £14,673 per QALY gained ***Allowing treatment effect to vary with baseline risk:***	*Probability early invasive strategy cost effective (£20,000/£30,000 threshold):* ***Basecase:*** *Risk group 1* = 1%/12% *Risk group 2* = 33%/75% *Risk group 3* = 41%/81% *Risk group 4a* = 95%/98% *Risk group 4b* = 92%/98% ***Pooled treatment effect:*** *Risk group 1* = 0.2%/6% *Risk group 2* = 19%/63% *Risk group 3* = 25%/71% *Risk group 4a* = 87%/96% *Risk group 4b* = 83%/96%

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			assumed to last 5 years)	***Allowing treatment effect to vary with baseline risk:*** *Risk group 1* £4,746[(d)] *Risk group 2* £4,774[(d)] *Risk group 3* £5,574[(d)] *Risk group 4a* £6,552[d)] *Risk group 4b* £7,214[(d)]	***Allowing treatment effect to vary with baseline risk:*** *Risk group 1* -0.019 QALYs *Risk group 2* 0.095 QALYs *Risk group 3* 0.188 QALYs *Risk group 4a* 0.551 QALYs *Risk group 4b* 0.689 QALYs	*Risk group 1* Dominated *Risk group 2* £50,131 per QALY gained *Risk group 3* £29,711 per QALY gained *Risk group 4a* £11,898 per QALY gained *Risk group 4b* £10,476 per QALY gained	***Allowing treatment effect to vary with baseline risk:*** *Risk group 1* = 0.1%/3% *Risk group 2* = 7%/26% *Risk group 3* = 17%/51% *Risk group 4a* = 94%/98% *Risk group 4b* = 98%/99% *See Table 6 for additional scenario analyses*

Abbreviations: ICER = incremental cost-effectiveness ratio; NSTEMI = non-ST-elevation myocardial infarction; QALY = quality-adjusted life years; RCT = randomised controlled trial; UA = unstable angina

(a) UK resource use from 1997-2003 and UK 2003/4 unit costs may not reflect the current UK context (e.g. increased angiography and revascularisation, increased use of drug eluting stents and dual antiplatelet therapy).

(b) Analysis does not reflect full body of available evidence for this area as identified in clinical review; main analysis based on a single study (RITA-3), alternative analysis using pooled data from 5 of 8 RCTs identified in clinical review plus 3 excluded pre-stent era RCTs. Pooled estimates of effect based on clinical review suggest outcomes may be worse than used in this analysis.

(c) A multivariate predictive model for MI or death in RITA-3 was used to calculate a risk score defining quartiles of risk, with the 4th quartile subdivided into two groups due to the much higher event rate in the top quartile (risk groups: 1, 2, 3, 4a, 4b). The primary results of the cost–effectiveness analysis were based on the characteristics of people with the median risk score in each of these five risk groups.

(d) Cost components included: angiography, PCI, CABG, days on wards (for all causes), visits to family doctor/ community nurse/ outpatients, MI, key cardiac medications (aspirin, beta blockers, statins, LA nitrates, CCBs, ACEs, clopidogrel)

Henriksson 2008[27, 28] found that an early invasive strategy, compared to a conservative strategy, was generally increasingly cost–effective as risk increased and reported cost-effectiveness ratios of £53,760, £22,949, £21,325, £11,957, £12,750 per QALY gained for risk groups 1, 2, 3, 4a and 4b respectively (1 = lowest and 4b = highest risk). This analysis is based on relative effectiveness data from the RITA-3 RCT with 5 years follow-up; constant relative treatment effect across risk groups is assumed (although note that absolute differences will still vary due to differences in baseline risk).

The base-case analysis assumed that the relative effect of an early invasive strategy compared to a conservative strategy was constant across risk groups, but a post hoc analysis of RITA-3 suggested that there was an interaction between treatment effect and risk group. Although the interaction was not statistically significant an alternative analysis was undertaken in which the relative benefit of the early invasive strategy varied with risk group. Allowing the relative treatment effect to vary by risk group improved cost effectiveness in risk groups 4a and 4b while reducing it in risk groups 1, 2 and 3. Cost effectiveness was also considerably impacted by variations in the assumption regarding duration of treatment effect: assuming that treatment effect was maintained beyond the observed trial follow-up of five years improved cost–effectiveness.

Using effectiveness inputs from pooled data (TIMI IIIB[15], VANQWISH[6], MATE[45], TACTICS[8], VINO[64], ICTUS[11, 29], RITA-3[20, 21] and FRISC II[33, 38, 39, 71]) instead of from only the RITA-3 trial had a modest impact in terms of reducing cost-effectiveness.

Full results for the basecase analysis and selected alternative scenarios are summarised in Table 6 below.

Table 6: Mean incremental cost–effectiveness ratio for an early invasive strategy compared to a conservative strategy (% of simulations cost–effective at a threshold of £20,000/£30,000)

	Basecase[a]	Basecase with different assumptions re treatment effect duration			Pooled effectiveness data	Interaction between treatment effect and risk[b]	Interaction model with different assumptions re treatment effect duration		
		10 years	15 years	Lifetime			10 years	15 years	Lifetime
Risk group 1	£53,760 (1%/12%)	£34,901	£27,949	£13,920	£58,490 (0.2%/6%)	Dominated (0.1%/3%)	£187,947	£121,044	£45,130
Risk group 2	£22,949 (33%/75%)	£15,410	£11,652	£7,850	£26,265 (19%/63%)	£50,131 (7%/26%)	£28,163	£21,553	£14,354
Risk group 3	£21,325 (41%/81%)	£15,754	£13,159	£10,473	£24,143 (25%/71%)	£29,711 (17%/51%)	£19,681	£16,218	£12,781
Risk group 4a	£11,957 (95%/98%)	£9,631	£8,446	£7,600	£13,646 (87%/96%)	£11,898 (94%/98%)	£9,450	£8,334	£7,600
Risk group 4b	£12,750 (92%/98%)	£9,707	£8,904	£8,270	£14,673 (83%/96%)	£10,476 (98%/99%)	£7,934	£7,348	£6,906

(a) RITA-3 effectiveness, no variation in treatment effect by baseline risk, 5-year duration of treatment effect
(b) RITA-3 analysis

Impact of updated pooled effectiveness estimate

The Henriksson 2008 analysis uses effectiveness data from the RITA-3 trial in the base case analysis but also investigates the impact of using pooled data. The meta–analysis used included trials in the pre-stent era, which were judged not relevant to current practice by the committee (specifically TIMI IIIB[15], VANQWISH[6] and MATE[45]). In addition new studies have also been identified by the clinical review for this update. New pooled estimates that excluded pre-stent trials and included new published data were generated in order to compare to the Henriksson 2008 estimates. Some of the new studies were not included in this pooled estimate as they did not report the combined endpoint of MI or CV death.

Comparing these numbers to the pooled estimates used by Henriksson 2008 show that the relative effect in the index hospitalisation was slightly improved and in the post-discharge period was similar to the pooled analysis (see Table 7 below for figures). As these effects are similar it may not have an impact on the results. Also, in the original analysis using the pooled analysis instead of RITA-3 had a modest impact.

Table 7: Comparison of composite endpoints of MI or CV death for early invasive versus initial conservative strategy

	Composite endpoint of MI or CV death for early invasive versus initial conservative strategy	
	Odds ratio during index hospitalisation	Hazard ratio from hospital discharge to end of trial
Henriksson et al. RITA-3 analysis	1.52 (0.864, 2.675)	0.621 (0.464, 0.830)
Henriksson et al. Pooled effectiveness data (used in alternative analysis)	1.42 (NR)	0.69 (NR)
NGC meta-analysis[(a)]	1.35 (0.80, 2.30)	0.68 (0.50, 0.91)

Abbreviations: MI = CV = cardiovascular; myocardial infarction; NR = not reported
(a) Trials included in the updated pooled estimate were ICTUS, TACTICS-TIMI 18, FRISC-II, RITA-3 and VINO.

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 and interpretation of the published cost-effectiveness analysis. The current NHS reference costs are generally higher than the costs used in the Henriksson 2008 analysis. The cost of hospitalisation for myocardial infarction that was used in the Henriksson 2008 analysis was £1,055, which is less than the current average of £1,403. The average cost of PCI has also increased from £2,402 to £2,819.

Table 8: UK NHS reference costs of myocardial infarction

Currency code	Currency description	Weighted average[(a)]
EB10A-E	Actual or Suspected Myocardial Infarction, with CC Score 0-13+	£1,510

Source: NHS reference costs 2016/17[12]
(a) Includes non-elective short stay, non-elective long stay and excess bed days.

Table 9: UK NHS reference costs for percutaneous coronary interventions

Currency code	Currency description	Weighted average[(a)]
EY41A – D	Standard Percutaneous Transluminal Coronary Angioplasty with CC Score 0-12+	£2,984
EY40A - D	Complex Percutaneous Transluminal Coronary Angioplasty with CC Score 0-12+	£3,864
Overall weighted average		**£3,202**

Source: NHS reference costs 2016/17[12]
(a) Includes non-elective short stay, non-elective long stay and excess bed days.

1.7 Evidence statements

1.7.1 Clinical evidence statements

- There was a clinically important harm in all-cause mortality in hospital (8094 participants in 6 studies, low quality evidence) and in all-cause mortality up to 30 days (4345 participants in 4 studies; low quality evidence) when an early invasive strategy (early angiography) was used compared to conservative management for UA/NMSTEMI.

- There was a clinically important benefit of an early invasive management compared to a conservative strategy for all-cause mortality at 6-12 months (8915 participants in 4 studies; low quality evidence) and for all-cause mortality up to 2 years (5467participants in 3 studies, moderate quality evidence).

- There was a clinically important harm in all case mortality at 10 years (3010 participants in 2 studies; moderate quality evidence) when using an early invasive strategy (early angiography) compared to conservative management for UA/NMSTEMI.

- There was a clinically important benefit of an early invasive management compared to a conservative strategy for cardiac mortality at 1 year (313 participants in 1 study, low quality evidence) and cardiac mortality at 2 years (3010 participants in 2 studies, very low quality evidence).

- There was a clinically important benefit of the invasive strategy compared to a conservative one for early myocardial infarction up to 30 days (4345 participants in 4 studies, moderate quality evidence), for MI at 6-12 months (8915 participants in 8 studies, low quality evidence) and for late MI up to 2 years (1200 participants in 1 study, low quality evidence)

- There was a clinically important harm in the following outcomes when using an invasive strategy compared to a conservative one: procedure-related MI (6380 participants in 5 study, high quality evidence), in hospital revascularisation (1513 participants in 2 studies, moderate quality evidence), revascularisation at 1 year with routine GP IIb/IIa receptor antagonist use (1200 participants in 1 study, high quality evidence), revascularisation at 1 year without routine GP IIb/IIa receptor antagonist use (2254 participants in 3 studies, moderate quality evidence), revascularisation at 2 years (2457 participants in 1 study, moderate quality evidence) and for revascularisation at 5 years (2212 participants in 1 study, moderate quality evidence).

- There was a clinically important benefit if the invasive strategy compared to a conservative one for intermediate refractory angina (8287 participants in 5 studies; low quality evidence), for stroke at 1 year (184 participants in 1 study, low quality evidence), intermediate rehospitalisation with routine GP IIb/IIa receptor antagonist use (4020 participants in 3 studies, moderate quality evidence), intermediate rehospitalisation without routine GP IIb/IIa receptor antagonist use (2901 participants in 3 studies, moderate quality evidence)

- There was a clinically important harm in major bleeding at 30 days (184 participants in 1 study, moderate quality evidence), major bleeding at 2 years (184 participants in 1 study, moderate quality evidence) and in hospital bleeding (1810 participants in 1 study, moderate quality evidence) when using an invasive strategy compared to a conservative one.

- There was no clinically important difference between the invasive and conservative strategies for cardiac mortality at 10 years (3010 participants in 2 studies, moderate quality evidence), myocardial infarction at 10 years (1200 participants in 1 study, low quality evidence), stroke at 30 days (184 participants in 1 study, low quality evidence), major bleeding at 1year (5774 participants in 5 studies, moderate quality evidence), minor bleeding at 1 year (4677 participants in 2 studies, low quality evidence).

- There was no evidence for health related quality of life outcomes or for length of hospital stay.

1.7.2 Health economic evidence statements

- One cost-utility analysis found that an early invasive strategy was increasingly cost effective with increasing risk, with the high risk groups (4a, 4b) being definitely cost effective (ICERs: £13,646 and £14,673 per QALY gained, respectively). Risk groups 2 and 3 were cost effective at a threshold of £30,000 per QALY gained but were not cost-effective at a threshold of £20,000 per QALY gained (ICERs: £26,265 and £24,143 per QALY gained, respectively). An early invasive strategy was not cost effective in the lowest risk group (ICER: £58,490 per QALY gained). This analysis was assessed as partially applicable with potentially serious limitations.

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 the following outcomes were critical for decision making: mortality (all-cause and cardiovascular specific); non-fatal and all (non-fatal and fatal) myocardial re-infarction; unplanned revascularisation; major and minor bleeding. The time points of interest for each outcome were events in hospital, at 30 days and at 1 year. Quality of life at 1 year was also considered a critical outcome.

The committee agreed that other important outcomes for consideration were length of hospital stay, refractory ischaemia, as well as the following outcomes at the latest time point available (> 1 year):stroke; unplanned rehospitalisation; mortality (all-cause and cardiovascular specific); non-fatal and all (non-fatal and fatal) myocardial reinfarction; unplanned revascularisation; major and minor bleeding.

1.8.1.2 The quality of the evidence

The GRADE rating of the evidence ranged from very low to high with the majority rated low or very low. The main reasons for downgrading the quality of the evidence were risk of bias, imprecision and inconsistency. The majority of the studies were judged to be at low risk of allocation bias as they had adequate methods of random sequence generation. All studies were deemed to be at low risk of allocation concealment and attrition bias. Blinding was not carried out in most of the studies. However, some studies had blinded outcome assessors and where outcomes were objective such as mortality; this was not deemed to be a high risk of bias.

There was some inconsistency particularly in the MI outcome. This is thought to be due to the varying definitions of MI used in the trials. Some definitions were more stringent than others and included troponin levels and hence recorded a lower than expected event rate. In addition, because a universal definition of procedural-related MI has only recently been adopted, the included studies did not define it consistently which lead the committee to interpret the results with caution.

This review included the overall data for MI (fatal and non-fata) as the non-fatal MI events were not reported separately.

There was no evidence for length of hospital stay.

1.8.1.3 Benefits and harms

The committee considered the evidence for early invasive management with angiography and follow on PCI if indicated, compared to conservative management (deferred angiography or optimal medical management) with or without GPI use. There was an increase in early mortality rates when using an invasive strategy during index hospitalisation and up to 4 months follow up. However, at intermediate (6-12 months) and late follow up (up to 2 years), this strategy conferred a clinical benefit in reducing all cause and cardiovascular mortality. The committee accepted this as logical given that one might expect there to be short-term risks to performing invasive procedures in people in the early phase of ACS, and attached more importance to the survival benefit which emerges after 4-6 months.

There was no clinical difference in MI rates during index hospitalisation when using an invasive strategy. However, this strategy conferred a clinical benefit of reduction in MI rate at 30 days follow up, as well as at intermediate (6-12 months) and late follow up (up to 2 years).

A clinical benefit in reduction of rehospitalisation and refractory angina was also seen at intermediate follow up when using an invasive strategy. However, this strategy led to an increased number of revascularisation procedures at all time points of interest, although this difference appeared to be established in the index admission, as is predictable, and did not obviously increase over time.

There was no appreciable clinical difference between strategies in the incidence of stroke at 30 days. There was a clinical benefit of the invasive strategy at 1 year although there was uncertainty around the estimate of effect which did not exclude possible harm. There was an increased risk of bleeding using an invasive strategy, inevitably so given the nature of the intervention.

Some evidence was available for up to 10 years follow up. This did not show a continued benefit in reducing the risk of mortality or MI when using an invasive strategy. However, the committee interpreted these results with caution. It was agreed that this length of time may be too long to directly reflect the benefits and harms of the strategies used at index admission in the studies.

The committee noted that the previous guideline recommendations incorporated risk stratification as there is a spectrum of risk in UA/NSTEMI patients and absolute benefits will depend on baseline risk (even if relative risk is considered constant across risk groups). This impacts cost-effectiveness and is discussed in the next section. They also noted the work undertaken by the CG94 guideline committee that mapped risk profile of included clinical trials to the risk profile of the real world population and showed that studies generally had lower risk populations than in the real world.

The committee noted that the interventions in the included studies no longer reflect current practice. There have been significant improvements in relation to PCI. For example, the increased use of drug eluting stents, new pharmacotherapy and the change from predominantly femoral to predominantly radial access. The committee felt that these changes have made PCI more effective; for example, radial access leads to a reduction in bleeding which in turn may improve survival. This is likely to impact outcomes to a greater extent in the early invasive group as rates of PCI are higher than in those who are initially managed conservatively. Improvements in medical management, for example the use of routine dual antiplatelet therapy regimens with a reduction in intravenous glycoprotein inhibitor use, has improved clinical outcomes for both the invasive and medically managed groups.

The majority of the studies were the same as those included in the previous guideline. There was no new evidence to suggest that the previous recommendations should be significantly changed. However, the committee agreed that weaker recommendations are more appropriate, reflecting their lower confidence in the applicability of the evidence to current practice. They also noted that risk was not assessed in the studies in the same way as recommended by the CG94 guideline committee.

The committee agreed that the timeframe of 96 hours specified in CG94 should be reduced to 72 hours. The studies addressing invasive versus conservative management differ in the time within which the invasive strategy had to be implemented, and it is not possible to derive a firm evidence-based time window from this data. The previous guideline had chosen the 96 hours as a conservative estimate which was the higher end of the interval from admission to hospital to having the procedure. At the time, the previous committee had acknowledged that this was not in line with other European Society of Cardiology and that should angiography be deemed to be required in higher risk patients then this should be carried out sooner. A subsequent quality standard recommended that angiography and PCI should be offered within 72 hours and this has become common practice. Recently a best practice tariff was introduced based on this quality standard which is likely to have further standardised practice. The professional members of the Committee agreed that this is achievable, and the lay members were clear that people with UA or NSTEMI who knew that an invasive intervention was indicated would rather have the procedure as quickly as possible. Therefore, the committee agreed that 72 hours is a more appropriate threshold.

1.8.2 Cost effectiveness and resource use

One published economic evaluation was identified comparing an early invasive strategy to a conservative strategy; this informed the previous guideline recommendations. This analysis was based on the RITA-3 trial, that was conducted in the UK from 1997 – 2003 and was included in the clinical review. This analysis using 2003/04 costs found that the early invasive strategy was increasingly cost-effective as patient risk increased and reported cost–effectiveness ratios of £53,760, £22,949, £21,325, £11,957, £12,750 per QALY gained for risk groups 1, 2, 3, 4a and 4b respectively (1 = lowest and 4b = highest risk). Although this analysis was based on a single RCT alternative analyses were also undertaken where relative treatment effect was based on pooled data from a number of trials. The results from this pooled analysis were similar although ICERs increased slightly. However, as the pooled data included three pre-stent era trials that were not considered relevant to current clinical

practice and didn't include newer studies identified in the clinical review we calculated updated equivalent pooled effectiveness estimates to assess whether they were different to those used in the economic analysis. This resulted in similar estimates, suggesting that the updated evidence may not have an impact on cost-effectiveness results. However, three recent trials could not be included in the updated estimate of pooled treatment effect as they did not report the composite endpoint of MI or cardiovascular death that was used in the model. Overall, the pooled effectiveness data showed a similar trend that was seen in the clinical review, that there was an increased risk of MI or death during index stay for the early invasive strategy but that there was a long-term benefit favouring the early invasive strategy following discharge with regards to death and MI. Therefore the studies that were not included were considered unlikely to change the estimates.

The base case analysis in the economic evaluation applied a treatment effect difference for 5 years in line with the longest follow-up data available at the time. Alternative scenarios were also run where a longer treatment effect difference was applied in the model for 10 years, 15 years and over a lifetime. However 10 year clinical follow-up data is now available for RITA 3 and ICTUS and does not support a longer treatment effect difference and so these alternative scenarios were not considered relevant by the committee.

The committee noted the work done by the previous guideline committee in relating the risk subgroups in the RITA-3 economic analysis to the real world risk. This analysis is based on a UK trial and so reflects UK practice, resource use and population – things that can vary considerably between countries in this disease area. However, one of the major limitations of the economic analysis was that it was based on an old trial and used unit costs from 2003/04. As described in the previous sections changes in practice since the trial may affect clinical outcomes; they may also affect costs. It was noted that some key unit costs appear to have increased since the study such as the cost of PCI and an admission for MI. However, it is hard to judge the impact on differences in costs between interventions because costs are likely to have increased with both interventions and downstream savings. In addition, increases in costs may also be associated with improvements in outcomes and so cost effectiveness will not necessarily have worsened. For example, the use of drug-eluting stents has been steadily increasing since 2003 and this may at least partially account for increases in PCI costs. However, the current estimate of the cost of drug-eluting stents is approximately £380, which is similar to the cost of stents used in the analysis (£370). As the use of drug-eluting stents is associated with improved health outcomes cost effectiveness of an early invasive strategy should improve.

Overall the committee agreed that there have been changes in practice that may affect costs and health outcomes and so increase uncertainty in the published economic analysis. However, there was no specific reason to believe that the difference in costs with a routine early invasive strategy would be greater or the difference in health outcomes smaller and so cost effectiveness reduced. Therefore the committee agreed that it was reasonable to maintain the recommendations made by the previous guideline committee recommending an early invasive strategy in those with predicted 6-month mortality above 3.0% where it was considered likely to be clinically and cost effective. In those at lower risk, a conservative strategy (initial medical management with angiography, and PCI if indicated, only in those with evidence of recurrent ischemia) was considered likely to be the most cost effective strategy.

Recent audit data from 2016/17 has shown that 83% of patients with NSTEMI were eligible for angiography and of those eligible, 85% underwent angiography before discharge home. Of those patients who are admitted to a hospital capable of performing angiography 56% received angiography within 72 hours and 69% received angiography within 96 hours. It is likely that since 2016/17 there has been an increase in the percentage of patients undergoing angiography within 72 hours due to the recent introduction of the Best Practice Tariff for angiography in NSTEMI. This means that hospitals receive a higher reimbursement for the service where at least 60% of all NSTEMI patients receive angiography within 72

hours and hence this is incentivised. It was also noted that undertaking angiography (with PCI if indicated) earlier is likely to lead to shorter length of stay in hospital as it is common practice to discharge people once this has taken place. Given this the committee agreed it is unlikely that the recommendations will lead to a substantial resource impact as it is already standard practice to carry out angiography within 72 hours if the patient is deemed to be high risk or clinically unstable and the quality standard already states that angiography should be conducted within 72 hours.

1.8.3 Other factors the committee took into account

Decisions about management are made by clinicians based on risk stratification. When treatment is carried out in an emergency situation, there is little scope for clinicians to explain risk to patients, limiting the opportunity for shared-decision making. However, it would be important to outline the risks of early invasive versus conservative strategies and how they change with time. Once it is known that angiography (with or without revascularisation) is required, waiting for the procedure is likely to induce anxiety in the patient. Equally, conservative management can induce anxiety because of concerns about not having an angiography. The lay members agreed it is important for clinicians to address these anxieties.

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Appendices

Appendix A: Review protocols

Table 10: Clinical review protocol for early invasive management in UA/NSTEMI

ID	Field	Content
0.	PROSPERO registration number	CRD42019147576
1.	Review title	In adults with UA or non-ST elevation MI does early routine invasive investigation (i.e. angiography) with intent to assess for (and in those patients deemed suitable, to perform) revascularization improve outcomes in comparison with conservative or selective treatment, with or without later angiography?
2.	Review question	In adults with UA or non-ST elevation MI does early routine invasive investigation (i.e. angiography) with intent to assess for (and in those patients deemed suitable, to perform) revascularization improve outcomes in comparison with conservative or selective treatment, with or without later angiography?
3.	Objective	To compare the clinical and cost effectiveness of a routine invasive to a conservative or selective invasive strategy for the management of UA/NSTEMI.
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 syndrome

ID	Field	Content
6.	Population	Inclusion: Adults (≥ 18 years old) with UA/NSTEMI Exclusion: None
7.	Intervention/Exposure/Test	Routine invasive strategy (and intervention if indicated) Invasive procedures include: Angiography Stents Angioplasty CABG
8.	Comparator/Reference standard/Confounding factors	Conservative approach including: Deferred or selective angiography in patients with ongoing or recurrent symptoms or ischaemia. Medical management (anti-thrombotic and anti-anginal)
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	Studies with indirect populations will not be considered. Studies with mixed populations will only be considered if at least 50% of patients have UA/NSTEMI We will exclude studies where stents are deployed in <50% of PCI procedures 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)	Outcomes at following time intervals: in hospital, 30 days, 1 year (or closest to 1 year) All-cause mortality Cardiac mortality Non-fatal and all (non-fatal and fatal) myocardial re-infarction Unplanned revascularisation (Where information is available we will record whether index lesion or not) 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 – at 1 year.
13.	Secondary outcomes (important outcomes)	Length of hospital stay Refractory ischaemia

ID	Field	Content
		The following outcomes at latest time point available (>1 year) Stroke Unplanned rehospitalisation for any reason Mortality (all-cause and cardiovascular specific) Non-fatal and all (non-fatal and fatal) myocardial re-infarction Unplanned revascularisation (Where information is available we will record whether index lesion or not) Major and minor bleeding. Intracranial bleeding recorded separately
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

ID	Field	Content	
		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 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	UA and NSTEMI High risk versus low risk patients (including tests for troponin levels) People receiving GPIs with PCI versus no GPIs with PCI. Timing of angiography – within 24, 48, 72 and 96 hours Proportion of patients treated with bare metal vs drug-eluting stents Use/choice of DAPT Rates of revascularisation (both within each study arm and across the different studies) sub-group into > 50% and < 50%) Gender Black and minority ethnic groups People with diabetes People with renal dysfunction	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	

ID	Field	Content		
20.	Country	England		
21.	Anticipated or actual start date	14/09/18		
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 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/Ms 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		

ID	Field	Content	
		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=147576	
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, routine invasive, conservative invasive , unstable angina, NSTEMI	
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 11: 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).[52] **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.[52]

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 12: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	01 January 2008– 19 June 2019	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	01 January 2008 – 19 June 2019	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews 2008 to 2019 Issue 6 of 12 CENTRAL 2008 to 2019 Issue 6 of 12	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.	or/1-7,9-16
37.	36 not 35
38.	limit 37 to English language
39.	randomized controlled trial.pt.
40.	controlled clinical trial.pt.
41.	randomi#ed.ti,ab.
42.	placebo.ab.
43.	randomly.ti,ab.
44.	Clinical Trials as topic.sh.
45.	trial.ti.
46.	or/39-45

47.	Meta-Analysis/
48.	exp Meta-Analysis as Topic/
49.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
50.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
51.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
52.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
53.	(search* adj4 literature).ab.
54.	(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.
55.	cochrane.jw.
56.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
57.	or/47-56
58.	46 or 57
59.	38 and 58
60.	(interven* adj2 (strateg* or therap* or treatment* or management)).ti,ab.
61.	(conservative adj2 (strateg* or therap* or treatment* or management)).ti,ab.
62.	(invasive adj2 (strateg* or therap* or treatment* or management*)).ti,ab.
63.	(early adj2 invasive).ti,ab.
64.	(isch?emi* adj4 (guid* or strateg*)).ti,ab.
65.	(invasive adj4 conservative).ti,ab.
66.	(angiograph* adj4 (invasive or conservative)).ti,ab.
67.	(triage adj4 angiograph*).ti,ab.
68.	or/60-67
69.	59 and 68

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.	or/1-7,9-16
35.	random*.ti,ab.
36.	factorial*.ti,ab.
37.	(crossover* or cross over*).ti,ab.
38.	((doubl* or singl*) adj blind*).ti,ab.
39.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
40.	crossover procedure/
41.	single blind procedure/
42.	randomized controlled trial/
43.	double blind procedure/
44.	or/35-43
45.	systematic review/
46.	meta-analysis/
47.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
48.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
49.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
50.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
51.	(search* adj4 literature).ab.
52.	(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.
53.	((pool* or combined) adj2 (data or trials or studies or results)).ab.
54.	cochrane.jw.
55.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
56.	or/45-55
57.	34 not 33
58.	limit 57 to English language
59.	44 or 56
60.	58 and 59
61.	(interven* adj2 (strateg* or therap* or treatment* or management)).ti,ab.

62.	(conservative adj2 (strateg* or therap* or treatment* or management)).ti,ab.
63.	(invasive adj2 (strateg* or therap* or treatment* or management*)).ti,ab.
64.	(early adj2 invasive).ti,ab.
65.	(isch?emi* adj4 (guid* or strateg*)).ti,ab.
66.	(invasive adj4 conservative).ti,ab.
67.	(angiograph* adj4 (invasive or conservative)).ti,ab.
68.	(triage adj4 angiograph*).ti,ab.
69.	or/61-68
70.	60 and 69

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-#12)
#23.	(or #14-#21)
#24.	#22 or #23
#25.	(interven* near/6 (strateg* or therap* or treatment* or management)):ti,ab
#26.	(conservative near/6 (strateg* or therap* or treatment* or management)):ti,ab
#27.	(invasive near/6 (strateg* or therap* or treatment* or management)):ti,ab
#28.	((ischaemi* or ischemi*) near/6 (guid* or strateg*)):ti,ab
#29.	(early near/6 invasive):ti,ab
#30.	(invasive near/6 conservative):ti,ab
#31.	(angiograph* near/6 (invasive or conservative)):ti,ab
#32.	(triage near/6 angiograph*):ti,ab
#33.	(or #25-#32)

#34.	#24 and #33

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 13: 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

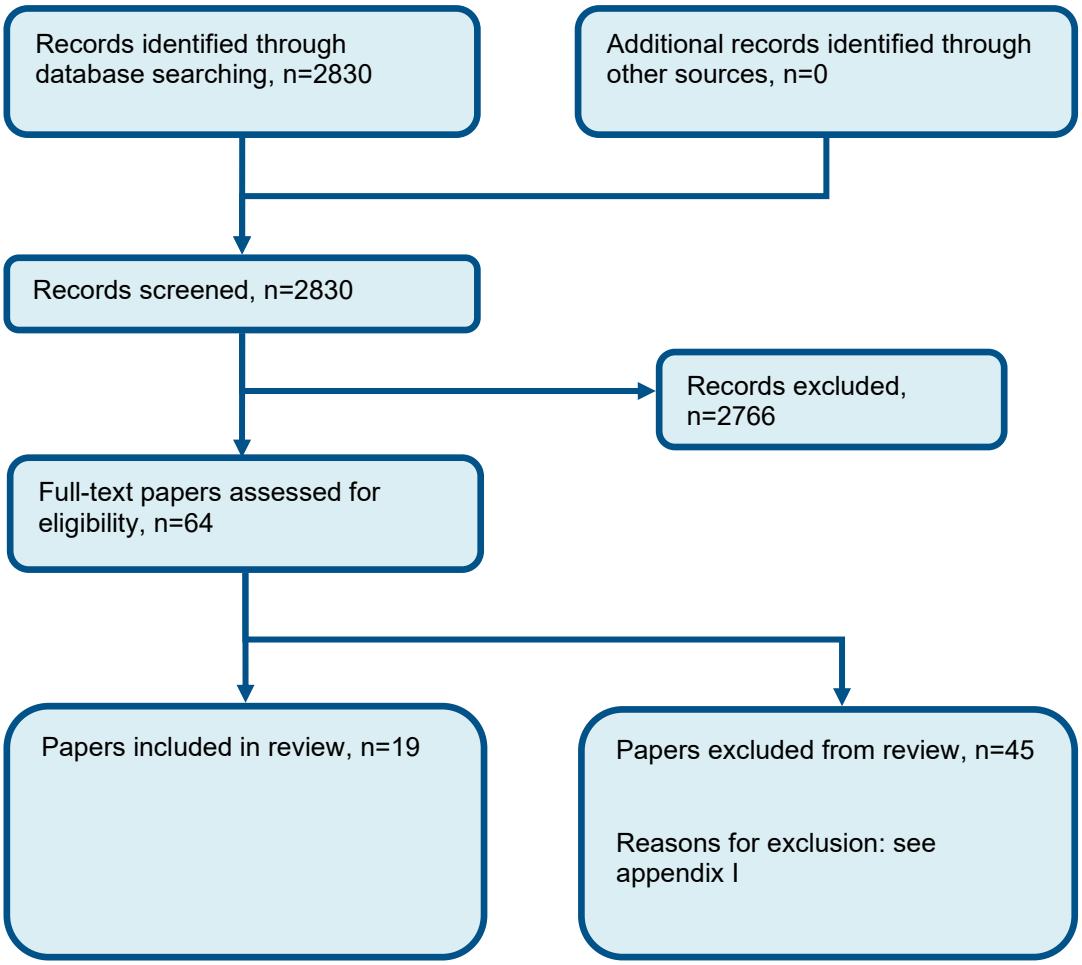
#1.	MeSH DESCRIPTOR Acute Coronary Syndrome
#2.	(MeSH DESCRIPTOR angina pectoris)
#3.	(MeSH DESCRIPTOR Angina, Unstable)
#4.	(MeSH DESCRIPTOR Coronary Thrombosis)
#5.	MeSH DESCRIPTOR Myocardial Infarction EXPLODE ALL TREES
#6.	#1 OR #2 OR #3 OR #4 OR #5
#7.	(MeSH DESCRIPTOR Heart Arrest)
#8.	((acute 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 early vs. conservative management for UA/NSTEMI



Appendix D: Clinical evidence tables

Table 14: Clinical evidence summary table

Study (subsidiary papers)	**Fanning 2016[18] (Anon 1999[33], , Savonitto 2012[60], Savonitto 2008[61], Swahn 2012[65], Thiele 2012[69], Wallentin 2016[72], Cannon 2001[8], De winter 2005[11], Fox 2005[20], Fox 2002[21], Hirsch 2007[29], Lagerqvist 2002[38], Lagerqvist 2006[39], Lagerqvist 2001[40], Spacek 2002[64], Wallentin 2000[71])**
Study type	Systematic Review
Number of studies (number of participants)	8 (n=8915)
Countries and setting	Conducted in Multiple countries; Setting: Hospital
Line of therapy	Mixed line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: For the majority of the included studies, the % of men was between 50%-80%
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	For the review: Men and women, at least 18 years of age, who had an episode of angina with an accelerating pattern of pain at rest. The index episode of pain must have occurred within 72 hours of randomisation. The patients must have exhibited at least one of the following. 1. New ST depression. 2. Transient (< 20 minute) ST elevation. 3. Ischaemic T-wave inversion or T-wave inversion in at least two contiguous leads. 4. Elevated levels of cardiac markers; e.g. troponins or creatine kinase-myocardial band (CK-MB). 5. Coronary artery disease (CAD), as determined by a history of catheterisation, revascularisation, or acute coronary syndromes (ACS).
Exclusion criteria	1. Persistent ST elevation (i.e. > 20 minutes). 2. Secondary causes of acute myocardial ischaemia (e.g. anaemia, thyrotoxicosis, acute pulmonary infection, fever, tachyarrhythmias, uncontrolled hypertension). 3. Secondary causes of cardiac biomarker elevation or altered kinetics (e.g. renal insufficiency, acute non-

Study (subsidiary papers)	Fanning 2016[18] (Anon 1999[33], , Savonitto 2012[60], Savonitto 2008[61], Swahn 2012[65], Thiele 2012[69], Wallentin 2016[72], Cannon 2001[8], De winter 2005[11], Fox 2005[20], Fox 2002[21], Hirsch 2007[29], Lagerqvist 2002[38], Lagerqvist 2006[39], Lagerqvist 2001[40], Spacek 2002[64], Wallentin 2000[71])
	cardiac disease etc.). 4. Serious systemic disease or major co-morbidities that would preclude an invasive approach. 5. Severe congestive heart failure or cardiogenic shock. 6. Arrhythmias that required immediate catheterisation. 7. Refractory symptoms. 8. Intolerance of anticoagulation and anti-platelet therapy. 9. Coronary revascularisation procedure within the previous 30days.
Recruitment/selection of patients	Review included randomised controlled trials (RCTs) that compared invasive and selectively invasive strategies in participants with unstable angina and non-ST elevation myocardial infarction (UA/NSTEMI), and measured at least one of this review's outcomes. The revascularisation approaches in the included studies were percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), as required.
Age, gender and ethnicity	Age - Mean (SD): For the majority of the included studies, the mean age of patients was between approximately 62 and 82 years old.
Further population details	1. Renal function: Systematic review: mixed
Extra comments	The included studies were heterogeneous in their participant selection criteria. The inclusion criteria were comprised of different combinations of the following core criteria: chest pain, electrocardiograph (ECG) changes, increased level(s) of cardiac marker(s) or a documented history of coronary artery disease (CAD). The review investigated the effect of glycoprotein IIb/IIIa receptor antagonist use on outcomes further by undertaking two separate analyses on trials according to routine versus selective use of glycoprotein IIb/IIIa receptor antagonists during PCI. Thus, the analyses conducted were as follows: 1. All studies that deployed stents routinely in revascularisation procedures using PCI, regardless of glycoprotein IIb/IIIa receptor antagonist use. 2. Stents and glycoprotein IIb/IIIa receptor antagonists deployed routinely in revascularisation procedures using PCI. 3. Stents deployed routinely in revascularisation procedures using PCI with selective glycoprotein IIb/IIIa receptor antagonists use. The review applied a restriction of 1996 onwards because of low rates of stent use prior to that year
Indirectness of population	No indirectness
Interventions	Intervention 1 (n=4545): Invasive routine angiography with or without revascularisation - Angiography. Routine invasive strategy: routine angiography with or without revascularisation in all patients. This was performed in all eligible patients unless they had contraindications to angiography. Duration up to 5 years. Concurrent medication/care: Majority of the studies reported the use of following background medications: Aspirin, unfractionated heparin, beta blocker, statin, clopidogrel, calcium channel antagonist, ACE inhibitor Indirectness: No indirectness

Study (subsidiary papers)	**Fanning 2016[18] (Anon 1999[33], , Savonitto 2012[60], Savonitto 2008[61], Swahn 2012[65], Thiele 2012[69], Wallentin 2016[72], Cannon 2001[8], De winter 2005[11], Fox 2005[20], Fox 2002[21], Hirsch 2007[29], Lagerqvist 2002[38], Lagerqvist 2006[39], Lagerqvist 2001[40], Spacek 2002[64], Wallentin 2000[71])**
	Further details: 1. Rate of revascularisation: Systematic review: mixed (n/a). 2. Timing of angiography: Systematic review: mixed (n/a). 3. Type of antiplatelet: Systematic review: mixed (n/a). 4. Use of GpIIb/IIIa: Systematic review: mixed (n/a). Comments: The times to angiography after randomisation in the routine invasive arms were: mean 6.2 hours in VINO, median 22 hours in TACTICS-TIMI 18, median 23 hours in ICTUS, mean 24 hours in the Italian Elderly ACS, median two days in RITA-3, median 51 hours in OASIS 5 and mean four days in FRISC-II. The invasive strategy in the LIPSIA-NSTEMI trial included both an immediate invasive strategy and an early invasive strategy with respective mean randomisation to sheath insertion times of 1.1 and 18.3 hours. Intervention 2 (n=4370): Conservative or 'selective invasive' management - Angiography with or without revascularisation only in eligible patients with evidence of ischemia. Conservative or ’selective invasive’ strategy: angiography with or without revascularisation only in eligible patients with evidence of cardiac ischaemia; e.g. recurrent ischaemia, dynamic electrocardiograph (ECG) changes or a positive stress test. Revascularisation modalities included PCI or CABG, depending on the angiographic findings. CABG is indicated in lieu of PCI when any one of the following criteria was met: Three vessel disease and an ejection fraction (EF) of less than 0.50; Two vessel disease with proximal left anterior descending involvement and EF of less than0.50 or ischaemia; Left main CAD.. Duration NR. Concurrent medication/care: Majority of the studies reported the use of following background medications: Aspirin, unfractionated heparin, beta blocker, statin, clopidogrel, calcium channel antagonist, ACE inhibitor Indirectness: No indirectness Further details: 1. Rate of revascularisation: Systematic review: mixed 2. Timing of angiography: Systematic review: mixed (n/a). 3. Type of antiplatelet: Systematic review: mixed (n/a). 4. Use of GpIIb/IIIa: Systematic review: mixed (n/a). Comments: Angiography is a component of both strategies, and that angiography in the conservative arm did not represent a ’cross-over’, as long as it was preceded by myocardial ischaemia or evidence of CAD.
Funding	The majority of the included studies were funded by industry
FRISC-II	

Study (subsidiary papers)	Fanning 2016[18] (Anon 1999[33], , Savonitto 2012[60], Savonitto 2008[61], Swahn 2012[65], Thiele 2012[69], Wallentin 2016[72], Cannon 2001[8], De winter 2005[11], Fox 2005[20], Fox 2002[21], Hirsch 2007[29], Lagerqvist 2002[38], Lagerqvist 2006[39], Lagerqvist 2001[40], Spacek 2002[64], Wallentin 2000[71])
Protocol outcome 2: All cause mortality at in hospital - Actual outcome: All-cause mortality (6 months); Group: 13/1222, Group 2: 11/1235 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 101; Group 2 Number missing: 67 Protocol outcome 3: All cause mortality at 1 year - Actual outcome: All-cause mortality (6 months); Group 1: 27/1222, Group 2: 48/1235 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 101; Group 2 Number missing: 67 Protocol outcome 3: All cause mortality at latest time point available - Actual outcome: All-cause mortality (12 months); Group 1:, Group 2: Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 101; Group 2 Number missing: 67 Protocol outcome 1: All cause mortality at latest time point available - Actual outcome: All-cause mortality (24 months); Group 1: 117/1222, Group 2: 124/1235 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 101; Group 2 Number missing: 67 Protocol outcome 1: All cause mortality at latest time point available - Actual outcome: All-cause mortality (5 years); Group 1:, Group 2: Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 101; Group 2 Number missing: 67 Protocol outcome 5: All myocardial infarction (fatal and non-fatal) at 1 year - Actual outcome: MI (6 months); Group 1:, Group 2:	

Study (subsidiary papers)	Fanning 2016[18] (Anon 1999[33], , Savonitto 2012[60], Savonitto 2008[61], Swahn 2012[65], Thiele 2012[69], Wallentin 2016[72], Cannon 2001[8], De winter 2005[11], Fox 2005[20], Fox 2002[21], Hirsch 2007[29], Lagerqvist 2002[38], Lagerqvist 2006[39], Lagerqvist 2001[40], Spacek 2002[64], Wallentin 2000[71])
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 101; Group 2 Number missing: 67 Protocol outcome 5: All myocardial infarction (fatal and non-fatal) at 1 year - Actual outcome: MI (12 months); Group 1: 105/1222, Group 2: 143/1235 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 101; Group 2 Number missing: 67 Protocol outcome 6: Myocardial infarction (non-fatal) at latest time-point available - Actual outcome MI (24 months); Group 1: 141/1222, Group 2: 195/1235 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 101; Group 2 Number missing: 67 Protocol outcome 6: Myocardial infarction (non-fatal) at latest time-point available - Actual outcome: MI (5 years); Group 1:, Group 2: Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 101; Group 2 Number missing: 67 Protocol outcome 7: refractory angina at 1 year - Actual outcome: Refractory angina (6 months); Group 1: 256/1222, Group 2: 455/1235 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 101; Group 2 Number missing: 67 Protocol outcome 8: unplanned rehospitalisation for any reason - Actual outcome: Rehospitalisation (6 weeks); Group 1: 451/1222, Group 2: 704/1235	

Study (subsidiary papers)	Fanning 2016[18] (Anon 1999[33], , Savonitto 2012[60], Savonitto 2008[61], Swahn 2012[65], Thiele 2012[69], Wallentin 2016[72], Cannon 2001[8], De winter 2005[11], Fox 2005[20], Fox 2002[21], Hirsch 2007[29], Lagerqvist 2002[38], Lagerqvist 2006[39], Lagerqvist 2001[40], Spacek 2002[64], Wallentin 2000[71])
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 101; Group 2 Number missing: 67 Protocol outcome 8: unplanned rehospitalisation for any reason - Actual outcome: Rehospitalisation (6 months); Group 1:, Group 2: Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 101; Group 2 Number missing: 67 Protocol outcome 8: unplanned rehospitalisation for any reason - Actual outcome: Rehospitalisation (12 months); Group 1:, Group 2: Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 101; Group 2 Number missing: 67 Protocol outcome 9: Myocardial infarction (non-fatal) at during procedure - Actual outcome: Procedural MI (during procedure); Group 1: 66/1222, Group 2: 36/1235 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 101; Group 2 Number missing: 67 Protocol outcome 10: Major bleeding at 30 days - Actual outcome: Bleeding (unclear); Group 1:, Group 2: Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 101; Group 2 Number missing: 67 **ICTUS** Protocol outcome 2: All cause mortality at in hospital - Actual outcome: All-cause mortality (6 months); Group: 6/586, Group 2: 5/577	

Study (subsidiary papers)	Fanning 2016[18] (Anon 1999[33], , Savonitto 2012[60], Savonitto 2008[61], Swahn 2012[65], Thiele 2012[69], Wallentin 2016[72], Cannon 2001[8], De winter 2005[11], Fox 2005[20], Fox 2002[21], Hirsch 2007[29], Lagerqvist 2002[38], Lagerqvist 2006[39], Lagerqvist 2001[40], Spacek 2002[64], Wallentin 2000[71])
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: All cause mortality at 1 year - Actual outcome: Death all causes (1 year); Group 1: 15/604, Group 2: 15/596 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 1: All cause mortality at latest time point available - Actual outcome: Death all causes (3 years); Group 1: 45/604, Group 2: 40/596 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 1: All cause mortality at latest time point available - Actual outcome: Death all causes (4 years); Group 1:, Group 2: Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: All myocardial infarction (fatal and non-fatal) at 1 year - Actual outcome: MI (1 year); Group 1: 22/604, Group 2: 27/596 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 6: Myocardial infarction (non-fatal) at latest time-point available - Actual outcome MI (3 years); Group 1:40/604, Group 2: 39/596	

Study (subsidiary papers)	Fanning 2016[18] (Anon 1999[33], , Savonitto 2012[60], Savonitto 2008[61], Swahn 2012[65], Thiele 2012[69], Wallentin 2016[72], Cannon 2001[8], De winter 2005[11], Fox 2005[20], Fox 2002[21], Hirsch 2007[29], Lagerqvist 2002[38], Lagerqvist 2006[39], Lagerqvist 2001[40], Spacek 2002[64], Wallentin 2000[71])
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 8: unplanned rehospitalisation for any reason - Actual outcome: Rehospitalisation (1 year); Group 1:44/604, Group 2: 64/596 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 8: unplanned rehospitalisation for any reason - Actual outcome: Rehospitalisation (3 years); Group 1:, Group 2: Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 11: Major bleeding during hospitalisation - Actual outcome: Major bleeding (during the index admission); Group 1:, Group 2: Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 **Italian Elderly ACS** Protocol outcome 2: All cause mortality at in hospital - Actual outcome: All-cause mortality (6 months); Group: 8/154, Group 2: 5/159 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: All cause mortality at 1 year - Actual outcome: All-cause death (6 months); Group 1: 19/154, Group 2: 22/159	

Study (subsidiary papers)	Fanning 2016[18] (Anon 1999[33], , Savonitto 2012[60], Savonitto 2008[61], Swahn 2012[65], Thiele 2012[69], Wallentin 2016[72], Cannon 2001[8], De winter 2005[11], Fox 2005[20], Fox 2002[21], Hirsch 2007[29], Lagerqvist 2002[38], Lagerqvist 2006[39], Lagerqvist 2001[40], Spacek 2002[64], Wallentin 2000[71])
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcome 3: All cause mortality at 1 year - Actual outcome: All-cause death (1 year); Group 1:, Group 2: Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcome 5: All myocardial infarction (fatal and non-fatal) at 1 year - Actual outcome: MI (6 months); Group 1:, Group 2: Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcome 5: All myocardial infarction (fatal and non-fatal) at 1 year - Actual outcome: MI (1 year); Group 1:, Group 2: Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcome 8: unplanned rehospitalisation for any reason - Actual outcome: Rehospitalisation (6 month); Group 1: 26/154, Group 2: 27/159 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcome 8: unplanned rehospitalisation for any reason - Actual outcome: Rehospitalisation (1 year); Group 1:, Group 2:	

Study (subsidiary papers)	Fanning 2016[18] (Anon 1999[33], , Savonitto 2012[60], Savonitto 2008[61], Swahn 2012[65], Thiele 2012[69], Wallentin 2016[72], Cannon 2001[8], De winter 2005[11], Fox 2005[20], Fox 2002[21], Hirsch 2007[29], Lagerqvist 2002[38], Lagerqvist 2006[39], Lagerqvist 2001[40], Spacek 2002[64], Wallentin 2000[71])
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 12: Major bleeding at 1 year - Actual outcome: Major bleeding (6 months); Group 1:, Group 2: Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 12: Major bleeding at 1 year - Actual outcome Major bleeding (1 year); Group 1:, Group 2: Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 14: Length of hospitalisation at 1 year - Actual outcome: Days spent in hospital (6 months); Group 1:, Group 2: Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 14: Length of hospitalisation at 1 year - Actual outcome: Days spent in hospital (1 year); Group 1:, Group 2: Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 13: Stroke at 1 year - Actual outcome: Stroke (6 months); Group 1:, Group 2:	

Study (subsidiary papers)	Fanning 2016[18] (Anon 1999[33], , Savonitto 2012[60], Savonitto 2008[61], Swahn 2012[65], Thiele 2012[69], Wallentin 2016[72], Cannon 2001[8], De winter 2005[11], Fox 2005[20], Fox 2002[21], Hirsch 2007[29], Lagerqvist 2002[38], Lagerqvist 2006[39], Lagerqvist 2001[40], Spacek 2002[64], Wallentin 2000[71])
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 13: Stroke at 1 year - Actual outcome: Stroke (1 year); Group 1:, Group 2: Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 **RITA-3** Protocol outcome 2: All cause mortality at in hospital - Actual outcome: All-cause mortality (in hospital); Group: 14/895, Group 2: 6/915 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: All cause mortality at 30 days - Actual outcome: All-cause mortality (4 months); Group 1: 26/895, Group 2: 24/915 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: All cause mortality at 1 year - Actual outcome: All-cause mortality (12 months); Group 1: 41/895, Group 2: 36/915 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 1: All cause mortality at latest time point available - Actual outcome: All-cause mortality (24 months); Group 1:102/895, Group 2: 132/915	

Study (subsidiary papers)	Fanning 2016[18] (Anon 1999[33], , Savonitto 2012[60], Savonitto 2008[61], Swahn 2012[65], Thiele 2012[69], Wallentin 2016[72], Cannon 2001[8], De winter 2005[11], Fox 2005[20], Fox 2002[21], Hirsch 2007[29], Lagerqvist 2002[38], Lagerqvist 2006[39], Lagerqvist 2001[40], Spacek 2002[64], Wallentin 2000[71])
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcome 1: All cause mortality at latest time point available - Actual outcome: All-cause mortality (5 years); Group 1:, Group 2: Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcome 5: All myocardial infarction (fatal and non-fatal) at 30 days - Actual outcome: MI (4 months); Group 1:, Group 2: Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcome 5: All myocardial infarction (fatal and non-fatal) at 1 year - Actual outcome: MI (12 months); Group 1:, Group 2: Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcome 6: Myocardial infarction (non-fatal) at latest time-point available - Actual outcome: MI (24 months); Group 1:, Group 2: Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcome 6: Myocardial infarction (non-fatal) at latest time-point available - Actual outcome: MI (5 years); Group 1:, Group 2:	

Study (subsidiary papers)	Fanning 2016[18] (Anon 1999[33], , Savonitto 2012[60], Savonitto 2008[61], Swahn 2012[65], Thiele 2012[69], Wallentin 2016[72], Cannon 2001[8], De winter 2005[11], Fox 2005[20], Fox 2002[21], Hirsch 2007[29], Lagerqvist 2002[38], Lagerqvist 2006[39], Lagerqvist 2001[40], Spacek 2002[64], Wallentin 2000[71])

Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 7: refractory angina at 1 year

- Actual outcome: Refractory angina (4 months); Group 1:, Group 2:

Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 7: refractory angina at 1 year

- Actual outcome: Refractory angina (12 months); Group 1:, Group 2:

Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

OASIS-5

Protocol outcome 1: All cause mortality at

- Actual outcome: All-cause mortality; Group 1: 4/92, Group 2: 1/92

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 1: All cause mortality at latest time point available

- Actual outcome: All-cause mortality (2 years); Group 1: 8/92, Group 2: 1/92

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 6: Myocardial infarction (non-fatal) at latest time-point available

- Actual outcome: Myocardial infarction (2 years); Group 1:, Group 2:

Study (subsidiary papers)	Fanning 2016[18] (Anon 1999[33], , Savonitto 2012[60], Savonitto 2008[61], Swahn 2012[65], Thiele 2012[69], Wallentin 2016[72], Cannon 2001[8], De winter 2005[11], Fox 2005[20], Fox 2002[21], Hirsch 2007[29], Lagerqvist 2002[38], Lagerqvist 2006[39], Lagerqvist 2001[40], Spacek 2002[64], Wallentin 2000[71])
	Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 14: Stroke at longest time point - Actual outcome Stroke (2 years); Group 1:, Group 2: Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
	VINO Protocol outcome 2: All cause mortality at hospitalisation - Actual outcome: All causes mortality (during hospitalisation); Group 1:1/64, Group 2: 3/67 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: All cause mortality at 30 days - Actual outcome: All-cause mortality (30 days); Group 1:1/64, Group 2: 5/67 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 1: All cause mortality at 1 year - Actual outcome: All-cause mortality (6 months); Group 1: 2/64, Group 2: 9/67 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Study (subsidiary papers)	Fanning 2016[18] (Anon 1999[33], , Savonitto 2012[60], Savonitto 2008[61], Swahn 2012[65], Thiele 2012[69], Wallentin 2016[72], Cannon 2001[8], De winter 2005[11], Fox 2005[20], Fox 2002[21], Hirsch 2007[29], Lagerqvist 2002[38], Lagerqvist 2006[39], Lagerqvist 2001[40], Spacek 2002[64], Wallentin 2000[71])
Protocol outcome 4: All myocardial infarction (fatal and non-fatal) at 30 days - Actual outcome Myocardial infarction (30 days); Group 1:, Group 2: Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: All myocardial infarction (fatal and non-fatal) at 1 year - Actual outcome: Myocardial infarction (6 months); Group 1:, Group 2: Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 8: unplanned rehospitalisation for any reason - Actual outcome: Rehospitalisation (30 days); Group 1:, Group 2: Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 8: unplanned rehospitalisation for any reason - Actual outcome: Rehospitalisation (6 months); Group 1:, Group 2: Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 **TACTICS-TIMI 18** Protocol outcome 2: All cause mortality at hospitalisation - Actual outcome: All causes mortality (during hospitalisation); Group 1:16/1114, Group 2: 8/1106 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	

Study (subsidiary papers)	Fanning 2016[18] (Anon 1999[33], , Savonitto 2012[60], Savonitto 2008[61], Swahn 2012[65], Thiele 2012[69], Wallentin 2016[72], Cannon 2001[8], De winter 2005[11], Fox 2005[20], Fox 2002[21], Hirsch 2007[29], Lagerqvist 2002[38], Lagerqvist 2006[39], Lagerqvist 2001[40], Spacek 2002[64], Wallentin 2000[71])
	Protocol outcome 2: All cause mortality at 30 days - Actual outcome: All causes mortality (30 days); Group 1: 25/1114, Group 2: 18/1106 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
	Protocol outcome 3 All cause mortality at 1 year - Actual outcome: All causes mortality (6 months); Group 1: 37/1114, Group 2: 39/1106 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
	Protocol outcome 7: refractory angina at 1 year - Actual outcome: Refractory angina (6 months); Group 1:, Group 2: Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
	Protocol outcome 8: unplanned rehospitalisation for any reason - Actual outcome: Rehospitalisation (30 days); Group 1:, Group 2: Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
	Protocol outcome 8: unplanned rehospitalisation for any reason - Actual outcome: Rehospitalisation (6 months); Group 1:, Group 2: Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Study (subsidiary papers)	Fanning 2016[18] (Anon 1999[33], , Savonitto 2012[60], Savonitto 2008[61], Swahn 2012[65], Thiele 2012[69], Wallentin 2016[72], Cannon 2001[8], De winter 2005[11], Fox 2005[20], Fox 2002[21], Hirsch 2007[29], Lagerqvist 2002[38], Lagerqvist 2006[39], Lagerqvist 2001[40], Spacek 2002[64], Wallentin 2000[71])
LIPSIA-NSTEMI Protocol outcome 3: All cause mortality at 1 year - Actual outcome: Death (6 months); Group 1: 21/400, Group 2: 13/200 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Myocardial infarction (non-fatal) at 1 year - Actual outcome: Non-fatal infarction (6 months); Group 1:, Group 2: Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 7: refractory angina at 1 year - Actual outcome: Refractory ischaemia (6 months); Group 1:, Group 2: Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 8: unplanned rehospitalisation for any reason - Actual outcome: Rehospitalisation for unstable angina (6 months); Group 1:, Group 2: Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at 1 year; Cardiac mortality at up to 30 days ; Need for revascularisation at 1 year; Re-infarction at 1 year; Length of hospital stay ; Cardiac mortality at 1 year; Unplanned revascularisation at 1 year; Unplanned revascularisation at longest time-point available ; Major bleeding at 1 year; Major bleeding at latest time-point available ; Minor bleeding at 30 days ; Minor bleeding at 1 year ; Minor bleeding at longest time-point available ; Stroke at longest time-point available;

Study	Henderson 2015[26] 10 year follow up of RITA-3 trial
Study type	
Number of studies (number of participants)	RCT (Patient randomised; Parallel)
Countries and setting	n/a (n=1810)
Line of therapy	Conducted in United Kingdom; Setting: Mostly district or community hospitals without revascularisation facilities on site.
Duration of study	Mixed line
Method of assessment of guideline condition	Follow up (post intervention): 10 year follow up
Stratum	Adequate method of assessment/diagnosis
Subgroup analysis within study	Overall:
Inclusion criteria	Not applicable
Exclusion criteria	Patients were randomized within 48 h of an index episode of myocardial ischemia. Patients were eligible for inclusion if they had suspected cardiac chest pain at rest and had documented evidence of coronary artery disease with at least one of the following: evidence of ischaemia on electrocardiograph(ST-segment depression, transient ST elevation,left bundle branch block [documented previously], or T-wave inversion);pathological Q waves suggesting previous myocardial infarction; or arteriographicallyproven coronary artery disease on a previous arteriogram.
Recruitment/selection of patients	Patients were excluded if they had probable evolving myocardial infarction, including those for whom reperfusion therapy wasindicated. Those in whom new pathological Q waves developed, or those with creatine kinase or creatine kinase MB concentrations twice the upper limit of normal before randomisation, were excluded. Those with myocardial infarctionwithin the previous month, PCI in the preceding 12 months, or CABG at any time were also excluded.Patients were excluded if coronary arteriography was planned within 72 h of the index episode of myocardial ischemia or if the ischemia was thought to be due to an arrhythmia, anemia, or noncoronary disease.
Age, gender and ethnicity	Not reported.
Further population details	Age - Mean (SD): Invasive group: 63 years (10);Conservative group: 62 years (11). Gender (M:F): 1128/682. Ethnicity: Not reported
Extra comments	1. Renal function: Not stated / Unclear
Indirectness of population	In all cases, the participating cardiologist had to be uncertain about the optimum treatment strategy and continued medical treatment had to be an acceptable treatment option.
Interventions	No indirectness

Study	Henderson 2015[26] 10 year follow up of RITA-3 trial
Funding	(n=895) Intervention 1: Invasive routine angiography with or without revascularisation - Angiography . Routine angiography as soon as possible after randomisation and ideally within 72 hours. Asprin, antianginal treatment including β-blockers and Enoxaparin (1 mg/kg twice daily subcutaneously for 2-8 days). . Duration 10 years (intervention and follow up). Concurrent medication/care: Glycoprotein 2b/3a inhibitor or other antiplatelet agents could be prescribed if clinically appropriate. . Indirectness: No indirectness Further details: 1. Rate of revascularisation : Not stated / Unclear 2. Timing of angiography: Not stated / Unclear 3. Type of antiplatelet: Not stated / Unclear 4. Use of GpIIb/IIIa : Not stated / Unclear (n=915) Intervention 2: Conservative or 'selective invasive' management - Angiography with or without revascularisation only in eligible patients with evidence of ischemia . Aspirin, antianginal treatment including β-blockers and Enoxaparin (1 mg/kg twice daily subcutaneously for 2-8 days). Coronary arteriography was indicated only for failure of the selective invasive strategy, defined by recurrence of ischemic pain at rest or on minimum exertion, with transient or persistent electrocardiographic evidence of ischemia despite full antianginal medication. Following discharge from hospital coronary arteriography could be performed for exertional angina despite appropriate anginal medication or for evidence of functional ischemia. Duration 10 years (intervention and follow up). Concurrent medication/care: Glycoprotein 2b/3a inhibitor or other antiplatelet agents could be prescribed if clinically appropriate. Indirectness: No indirectness Further details: 1. Rate of revascularisation : Not stated / Unclear 2. Timing of angiography: Not stated / Unclear 3. Type of antiplatelet: Not stated / Unclear 4. Use of GpIIb/IIIa : Not stated / Unclear

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANGIOGRAPHY versus ANGIOGRAPHY WITH OR WITHOUT REVASCULARISATION ONLY IN ELIGIBLE PATIENTS WITH EVIDENCE OF ISCHEMIA

Protocol outcome 1: All cause mortality at latest time-point available
- Actual outcome: Mortality at 10 years at 10 years; Group 1: 225/895, Group 2: 232/915
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics were comparable between the two groups and no significant differences were observed.; Blinding details: Deaths between 5 and 10 years were classified as cardiovascular or noncardiovascular by an investigator blinded to treatment assignment, on the basis of the cause of death recorded on the death certificate.

Study	Henderson 2015[26] 10 year follow up of RITA-3 trial
; Group 1 Number missing: , Reason: Changes in Office of National Statistics in England and General Register office in Scotland prevented collection of mortality data. ; Group 2 Number missing: , Reason: Changes in Office of National Statistics in England and General Register office in Scotland prevented collection of mortality data. Protocol outcome 2: Cardiac mortality at latest time-point available - Actual outcome: Cardiac mortality at 10 years at 10 years; Group 1: 135/895, Group 2: 147/915 Risk of bias: All domain - ; Indirectness of outcome: No indirectness Other (Funded by a competitive grant obtained from the British Heart Foundation (BHF). The BHF received a donation from Aventis Pharma. Additional government support was obtained to reimburse interventional centres for part of the PCI costs. One of the authors had received a support grant from The Medicines Company)	
Protocol outcomes not reported by the study	
	Quality of life at 1 year; Unplanned revascularisation at longest time-point available ; Myocardial infarction (non-fatal) at latest time-point available; Major bleeding at 30 days ; Minor bleeding at 1 year ; Major bleeding at latest time-point available ; All myocardial infarction (fatal and non-fatal) at 30 days; Myocardial infarction (non-fatal) at up to 30 days ; Cardiac mortality at 1 year; Mortality at 1 year at 1 year; All cause mortality at up to 30 days; Unplanned revascularisation at 30 days; Cardiac mortality at up to 30 days ; Minor bleeding at 30 days ; Myocardial infarction (non-fatal) at 1 year; All myocardial infarction (fatal and non-fatal) at 1 year; All myocardial infarction (fatal and non-fatal) at latest time-point available; Re-infarction at 1 year; Major bleeding at 1 year; Need for revascularisation at 1 year; Stroke at longest time-point available; Unplanned revascularisation at 1 year; unplanned rehospitalisation for any reason at Define; Minor bleeding at longest time-point available ; Length of hospital stay at

Study	Hoedemaker 2017[30] 10 year follow up of ICTUS trial
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=1200)
Countries and setting	Conducted in Netherlands; Setting: 42 Dutch hospitals, 12 of which were high-volume centres with facilities for percutaneous coronary intervention and on-site cardiac surgery.
Line of therapy	Mixed line

Study	Hoedemaker 2017[30] 10 year follow up of ICTUS trial
Duration of study	Follow up (post intervention): 10 year follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Eligible patients had to have all three of the following: 1)symptoms of ischemia that were increasing or occurred at rest, with the last episode occurring no more than 24 hours before randomization; 2) an elevated cardiac troponin T level (≥0.03 µg per litre); and 3) either ischemic changes as assessed by electrocardiography (defined as ST-segment depression or transient ST-segment elevation exceeding 0.05 mV, or T-wave inversion of ≥0.2 mV in two contiguous leads) or a documented history of coronary artery disease as evidenced by previous myocardial infarction, findings on previous coronary angiography, or a positive exercise test.
Exclusion criteria	Age younger than 18 years or older than 80 years, myocardial infarction with ST-segment elevation in the past 48 hours, an indication for PCI or fibrinolytic therapy, hemodynamic instability or overt congestive heart failure, the use of oral anticoagulant drugs in the past 7 days, fibrinolytic treatment within the past 96 hours, PCI within the past 14 days, a contraindication to treatment with PCI or glycoprotein IIb/IIIa inhibitors, recent trauma or risk of bleeding, hypertension despite treatment (i.e., systolic pressure >180 mm Hg or diastolic pressure >100 mm Hg), weight greater than 120 kg, or inability to give informed consent.
Age, gender and ethnicity	Age - Median (range): 62 (NR). Gender (M:F): 900/300. Ethnicity: Not reported
Further population details	1. Renal function: Not applicable
Indirectness of population	No indirectness
Interventions	(n=604) Intervention 1: Invasive routine angiography with or without revascularisation - Angiography . Patients were scheduled to undergo angiography within 24 to 48 hours after randomisation and PCI when appropriate on the basis of the coronary anatomy. CABG was recommended in patients with extensive three-vessel disease or severe left main-stem disease and was to be performed as soon as possible during the initial hospitalisation period. The protocol also specified that patients receive daily aspirin, enoxaparin (1 mg/kg twice a day) subcutaneously for at least 48 hours and abciximab during all PCI procedures (given as bolus of 0.25 mg/kg, followed by an infusion of 0.125 mg/kg/min for 12 h, and started 10 to 60

Study	Hoedemaker 2017[30] 10 year follow up of ICTUS trial
	min before the first balloon inflation). Duration 10 year follow up. Concurrent medication/care: The protocol recommended intensive lipid lowering therapy, preferably with 80 mg atorvastatin daily or equivalent started as soon as possible after randomisation. Clopidogrel was also used as necessary.. Indirectness: No indirectness Further details: 1. Rate of revascularisation : Not stated / Unclear 2. Timing of angiography: Not stated / Unclear 3. Type of antiplatelet: Not stated / Unclear 4. Use of GpIIb/IIIa : Not stated / Unclear (n=596) Intervention 2: Conservative or 'selective invasive' management - Angiography with or without revascularisation only in eligible patients with evidence of ischemia . Optimal medical treatment as per invasive strategy. Angiography and subsequent revascularization only if they had refractory angina despite optimal medical treatment, hemodynamic or rhythmic instability, or clinically significant ischemia on the predischarge exercise test. Coronary angiography and revascularization after the initial hospital phase were performed if severe angina symptoms (i.e., Canadian Cardiovascular Society [CCS] class III or IV) persisted despite optimal antianginal medication or if ischemia was documented on subsequent testing. Duration 10 year follow up. Concurrent medication/care: as per invasive management group. Indirectness: No indirectness Further details: 1. Rate of revascularisation : Not stated / Unclear 2. Timing of angiography: Not stated / Unclear 3. Type of antiplatelet: Not stated / Unclear 4. Use of GpIIb/IIIa : Not stated / Unclear
Funding	Study funded by industry (Sponsorship from Eli Lilly, Sanofi-Synthelabo, Aventis, Pfizer and Medtronic. The study states that sponsors had no involvement in the design of the study, data collection or analysis, or the writing of the manuscript.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANGIOGRAPHY versus ANGIOGRAPHY WITH OR WITHOUT REVASCULARISATION ONLY IN ELIGIBLE PATIENTS WITH EVIDENCE OF ISCHEMIA	

Study	Hoedemaker 2017[30] 10 year follow up of ICTUS trial
Protocol outcome 1: All cause mortality at latest time-point available - Actual outcome: All cause mortality at 10 years at 10 years; Group 1: 156/604, Group 2: 138/596 Risk of bias: All domain - --, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Cardiac mortality at latest time-point available - Actual outcome: Cardiovascular death at 10 years at 10 years; Group 1: 97/604, Group 2: 85/596 Risk of bias: All domain - --, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: All myocardial infarction (fatal and non-fatal) at latest time-point available - Actual outcome: MI including spontaneous and procedure related at 10 years; Group 1: 106/604, Group 2: 84/596 Risk of bias: All domain - --, Selection - Low, Blinding - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at 1 year; Unplanned revascularisation at longest time-point available ; Myocardial infarction (non-fatal) at latest time-point available; Major bleeding at 30 days ; Minor bleeding at 1 year ; Major bleeding at latest time-point available ; All myocardial infarction (fatal and non-fatal) at 30 days; Myocardial infarction (non-fatal) at up to 30 days ; Cardiac mortality at 1 year; Mortality at 1 year at 1 year; All cause mortality at up to 30 days; Unplanned revascularisation at 30 days; Cardiac mortality at up to 30 days ; Minor bleeding at 30 days ; Myocardial infarction (non-fatal) at 1 year; All myocardial infarction (fatal and non-fatal) at 1 year; Re-infarction at 1 year; Major bleeding at 1 year; Need for revascularisation at 1 year; Stroke at longest time-point available; Unplanned revascularisation at 1 year; unplanned rehospitalisation for any reason at Define; Minor bleeding at longest time-point available ; Length of hospital stay

Appendix E: Forest plots

E.1 Routine invasive versus conservative management in UA/NSETMI: all studies undertaken in the stent era regardless of glycoprotein

Figure 2: Index death (all-cause mortality in hospital)

Study or Subgroup	Invasive Events	Invasive Total	Conservative Events	Conservative Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FRISC-II	13	1222	11	1235	29.0%	1.19 [0.54, 2.66]
ICTUS	6	586	5	577	13.3%	1.18 [0.36, 3.85]
Italian Elderly ACS	8	154	5	159	13.0%	1.65 [0.55, 4.94]
RITA-3	14	895	6	915	15.7%	2.39 [0.92, 6.18]
TACTICS-TIMI 18	16	1114	8	1106	21.2%	1.99 [0.85, 4.62]
VINO	1	64	3	67	7.8%	0.35 [0.04, 3.27]
Total (95% CI)		**4035**		**4059**	**100.0%**	**1.54 [1.03, 2.31]**
Total events	58		38			

Heterogeneity: Chi² = 3.45, df = 5 (P = 0.63); I² = 0%
Test for overall effect: Z = 2.09 (P = 0.04)

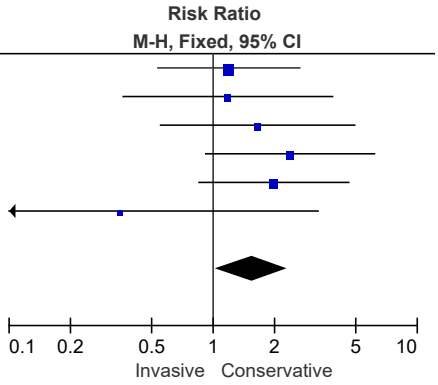
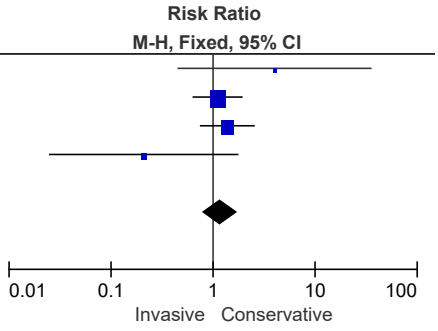


Figure 3: Early death (all-cause mortality up to 30 days)

Study or Subgroup	Invasive Events	Invasive Total	Conservative Events	Conservative Total	Weight	Risk Ratio M-H, Fixed, 95% CI
OASIS 5	4	92	1	92	2.1%	4.00 [0.46, 35.11]
RITA-3	26	895	24	915	49.8%	1.11 [0.64, 1.91]
TACTICS-TIMI 18	25	1114	18	1106	37.9%	1.38 [0.76, 2.51]
VINO	1	64	5	67	10.2%	0.21 [0.03, 1.74]
Total (95% CI)		**2165**		**2180**	**100.0%**	**1.18 [0.81, 1.73]**
Total events	56		48			

Heterogeneity: Chi² = 4.08, df = 3 (P = 0.25); I² = 26%
Test for overall effect: Z = 0.85 (P = 0.40)



RITA-3 data is at up to 4 months

Figure 4: Intermediate death (all-cause mortality at 6-12 months)

Study or Subgroup	Invasive Events	Invasive Total	Conservative Events	Conservative Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FRISC-II	27	1222	48	1235	25.6%	0.57 [0.36, 0.90]
ICTUS	15	604	15	596	8.1%	0.99 [0.49, 2.00]
Italian Elderly ACS	19	154	22	159	11.6%	0.89 [0.50, 1.58]
LIPSIA-NSTEMI	21	400	13	200	9.3%	0.81 [0.41, 1.58]
OASIS 5	8	92	1	92	0.5%	8.00 [1.02, 62.68]
RITA-3	41	895	36	915	19.1%	1.16 [0.75, 1.80]
TACTICS-TIMI 18	37	1114	39	1106	21.0%	0.94 [0.61, 1.47]
VINO	2	64	9	67	4.7%	0.23 [0.05, 1.04]
Total (95% CI)		**4545**		**4370**	**100.0%**	**0.88 [0.72, 1.08]**
Total events	170		183			

Heterogeneity: Chi² = 12.68, df = 7 (P = 0.08); I² = 45%
Test for overall effect: Z = 1.24 (P = 0.21)

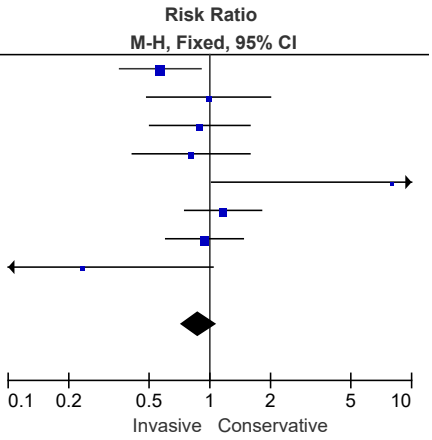


Figure 5: Late death (all-cause mortality at >2 years)

Study or Subgroup	Invasive Events	Invasive Total	Conservative Events	Conservative Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FRISC-II	117	1222	124	1235	41.9%	0.95 [0.75, 1.21]
ICTUS	45	604	40	596	13.7%	1.11 [0.74, 1.67]
RITA-3	102	895	132	915	44.4%	0.79 [0.62, 1.01]
Total (95% CI)		**2721**		**2746**	**100.0%**	**0.90 [0.77, 1.06]**
Total events	264		296			

Heterogeneity: Chi² = 2.35, df = 2 (P = 0.31); I² = 15%
Test for overall effect: Z = 1.28 (P = 0.20)

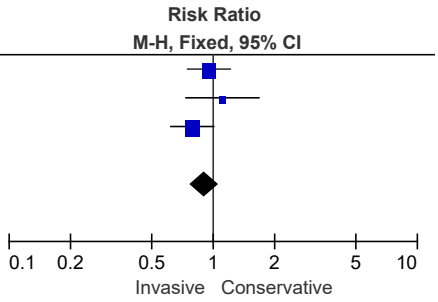


Figure 6: All-cause mortality at latest time point (10 years)

Study or Subgroup	Invasive Events	Invasive Total	Conservative Events	Conservative Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ICTUS	156	604	138	596	37.7%	1.12 [0.91, 1.36]
RITA-3	225	895	232	915	62.3%	0.99 [0.85, 1.16]
Total (95% CI)		**1499**		**1511**	**100.0%**	**1.04 [0.92, 1.18]**
Total events	381		370			

Heterogeneity: Chi² = 0.82, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 0.59 (P = 0.55)

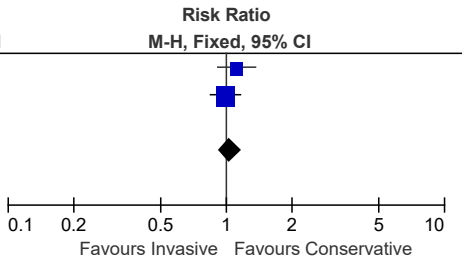


Figure 7: Cardiovascular death (at 1 year)

Study or Subgroup	Invasive Events	Invasive Total	Conservative Events	Conservative Total	Risk Ratio M-H, Fixed, 95% CI
Italian Elderly ACS	16	154	17	159	0.97 [0.51, 1.85]

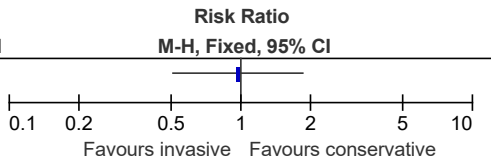


Figure 8: Cardiovascular mortality (at 2 years)

Study or Subgroup	Invasive Events	Invasive Total	Conservative Events	Conservative Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ICTUS	16	604	19	596	31.5%	0.83 [0.43, 1.60]
RITA-3	41	895	42	915	68.5%	1.00 [0.66, 1.52]
Total (95% CI)		**1499**		**1511**	**100.0%**	**0.95 [0.66, 1.35]**
Total events	57		61			

Heterogeneity: Chi² = 0.21, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.31 (P = 0.76)

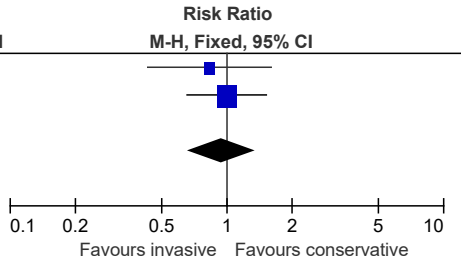


Figure 9: Cardiovascular mortality (at 5 years)

Study or Subgroup	Invasive Events	Invasive Total	Conservative Events	Conservative Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FRISC-II	68	1211	72	1223	75.6%	0.95 [0.69, 1.32]
ICTUS	26	604	23	596	24.4%	1.12 [0.64, 1.93]
Total (95% CI)		**1815**		**1819**	**100.0%**	**0.99 [0.75, 1.31]**
Total events	94		95			

Heterogeneity: Chi² = 0.23, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.05 (P = 0.96)

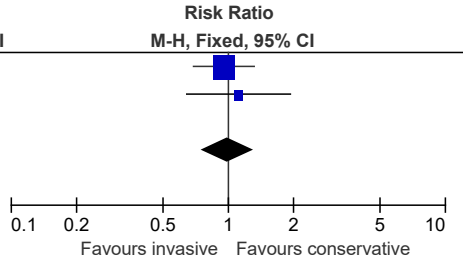


Figure 10: Cardiovascular mortality at latest time point available (10 years)

Study or Subgroup	Invasive Events	Invasive Total	Conservative Events	Conservative Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ICTUS	97	604	85	596	37.1%	1.13 [0.86, 1.47]
RITA-3	135	895	147	915	62.9%	0.94 [0.76, 1.16]
Total (95% CI)		**1499**		**1511**	**100.0%**	**1.01 [0.85, 1.19]**
Total events	232		232			

Heterogeneity: Chi² = 1.07, df = 1 (P = 0.30); I² = 7%
Test for overall effect: Z = 0.10 (P = 0.92)

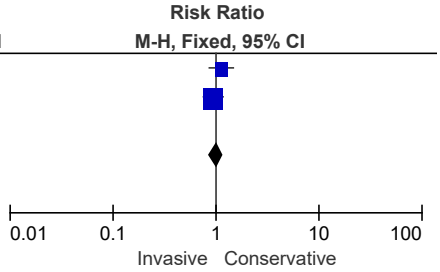


Figure 11: Index myocardial infarction (MI in hospital)

Study or Subgroup	Invasive Events	Invasive Total	Conservative Events	Conservative Total	Weight	Risk Ratio M-H, Random, 95% CI
FRISC-II	68	1222	31	1235	20.7%	2.22 [1.46, 3.36]
ICTUS	9	586	9	577	13.4%	0.98 [0.39, 2.46]
Italian Elderly ACS	3	154	5	159	8.4%	0.62 [0.15, 2.55]
LIPSIA-NSTEMI	44	400	14	200	18.3%	1.57 [0.88, 2.80]
RITA-3	17	895	15	915	16.7%	1.16 [0.58, 2.31]
TACTICS-TIMI 18	27	1114	44	1106	19.9%	0.61 [0.38, 0.98]
VINO	0	64	3	67	2.6%	0.15 [0.01, 2.84]
Total (95% CI)		**4435**		**4259**	**100.0%**	**1.08 [0.65, 1.80]**
Total events	168		121			

Heterogeneity: Tau² = 0.28; Chi² = 19.99, df = 6 (P = 0.003); I² = 70%
Test for overall effect: Z = 0.32 (P = 0.75)

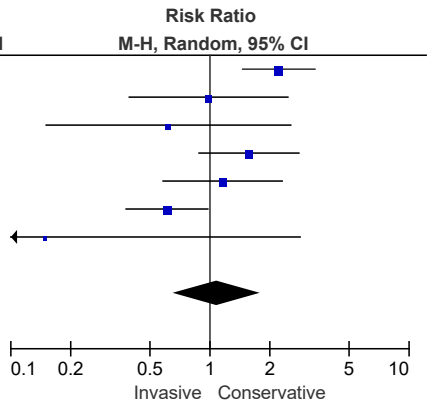
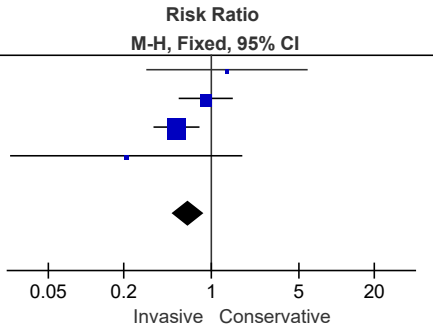


Figure 12: Early myocardial infarction (up to 30 days)

Study or Subgroup	Invasive Events	Invasive Total	Conservative Events	Conservative Total	Weight	Risk Ratio M-H, Fixed, 95% CI
OASIS 5	4	92	3	92	2.8%	1.33 [0.31, 5.79]
RITA-3	30	895	34	915	31.8%	0.90 [0.56, 1.46]
TACTICS-TIMI 18	34	1114	64	1106	60.7%	0.53 [0.35, 0.79]
VINO	1	64	5	67	4.6%	0.21 [0.03, 1.74]
Total (95% CI)		**2165**		**2180**	**100.0%**	**0.65 [0.49, 0.88]**
Total events	69		106			

Heterogeneity: Chi² = 4.79, df = 3 (P = 0.19); I² = 37%
Test for overall effect: Z = 2.79 (P = 0.005)



RITA-3 data is at up to 4 months

Figure 13: Intermediate myocardial infarction at 6-12 months (intermediate MI)

Study or Subgroup	Invasive Events	Invasive Total	Conservative Events	Conservative Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FRISC-II	105	1222	143	1235	41.1%	0.74 [0.58, 0.94]
ICTUS	22	604	27	596	7.9%	0.80 [0.46, 1.40]
Italian Elderly ACS	11	154	17	159	4.8%	0.67 [0.32, 1.38]
LIPSIA-NSTEMI	53	400	16	200	6.2%	1.66 [0.97, 2.82]
OASIS 5	7	92	9	92	2.6%	0.78 [0.30, 2.00]
RITA-3	34	895	44	915	12.6%	0.79 [0.51, 1.22]
TACTICS-TIMI 18	53	1114	76	1106	22.0%	0.69 [0.49, 0.97]
VINO	2	64	10	67	2.8%	0.21 [0.05, 0.92]
Total (95% CI)		**4545**		**4370**	**100.0%**	**0.78 [0.67, 0.91]**
Total events	287		342			

Heterogeneity: Chi² = 11.54, df = 7 (P = 0.12); I² = 39%
Test for overall effect: Z = 3.16 (P = 0.002)

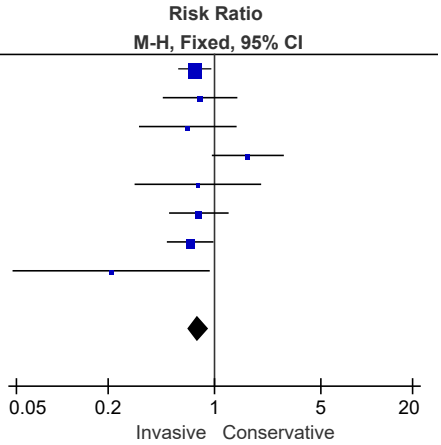


Figure 14: Late myocardial infarction (at > 2 years)

Study or Subgroup	Invasive Events	Invasive Total	Conservative Events	Conservative Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FRISC-II	141	1222	195	1235	67.0%	0.73 [0.60, 0.89]
ICTUS	40	604	39	596	13.6%	1.01 [0.66, 1.55]
RITA-3	46	895	57	915	19.5%	0.83 [0.57, 1.20]
Total (95% CI)		**2721**		**2746**	**100.0%**	**0.79 [0.67, 0.93]**
Total events	227		291			

Heterogeneity: Chi² = 1.92, df = 2 (P = 0.38); I² = 0%
Test for overall effect: Z = 2.86 (P = 0.004)

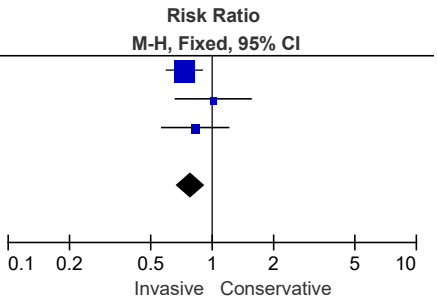


Figure 15: Myocardial infarction at latest time point (10 years)

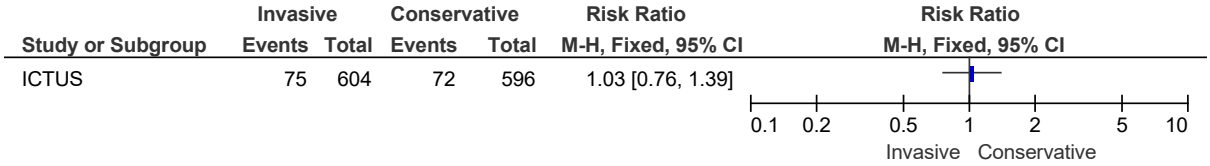


Figure 16: Procedure-related myocardial infarction

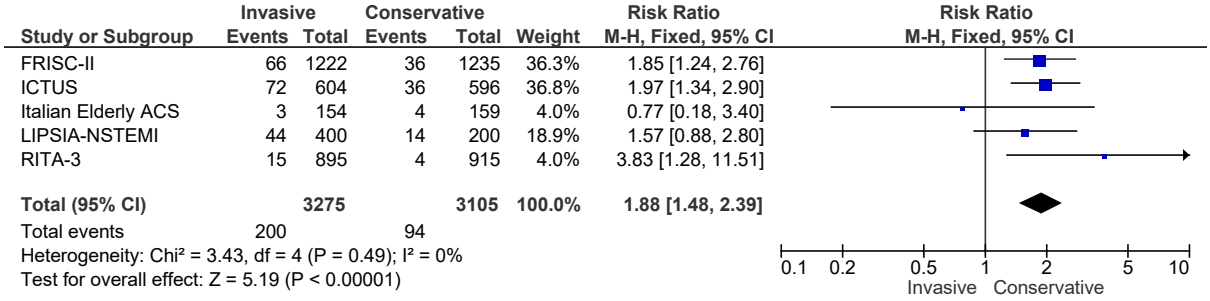


Figure 17: Revascularisation (in hospital)

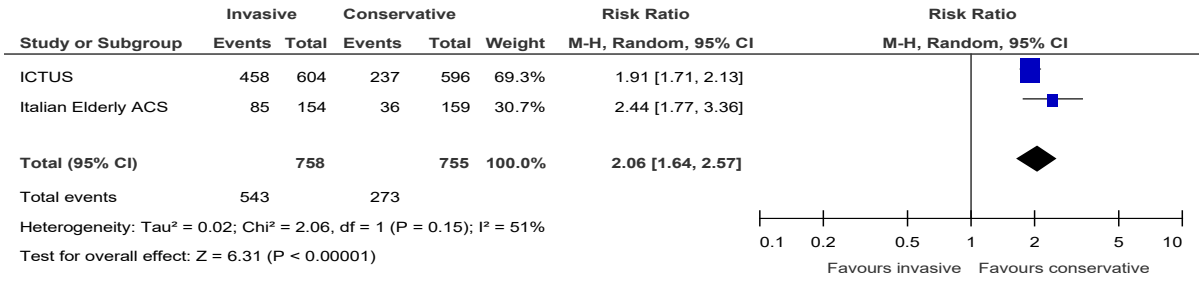


Figure 18: Revascularisation (1 year)

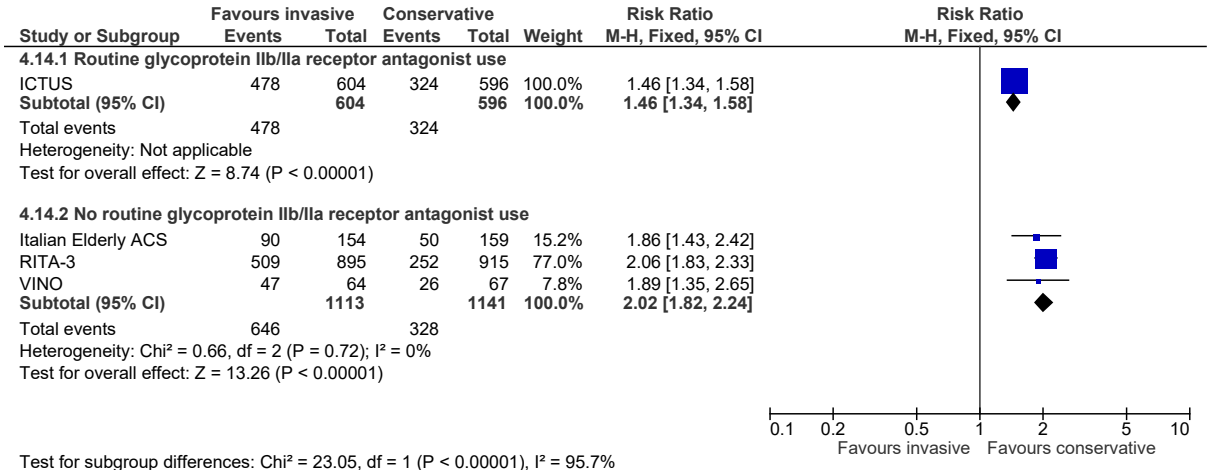


Figure 19: Revascularisation (2 years)

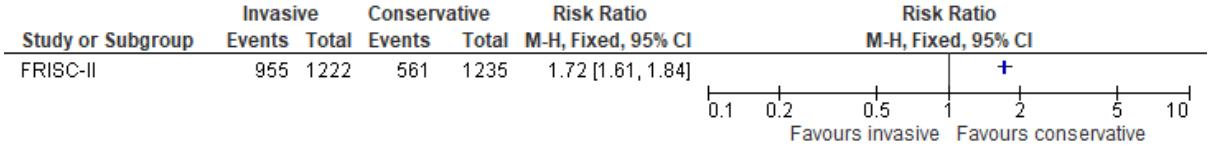


Figure 20: Revascularisation (5 years)

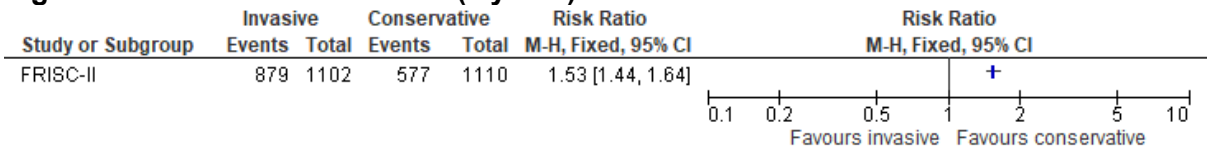


Figure 21: Intermediate refractory angina

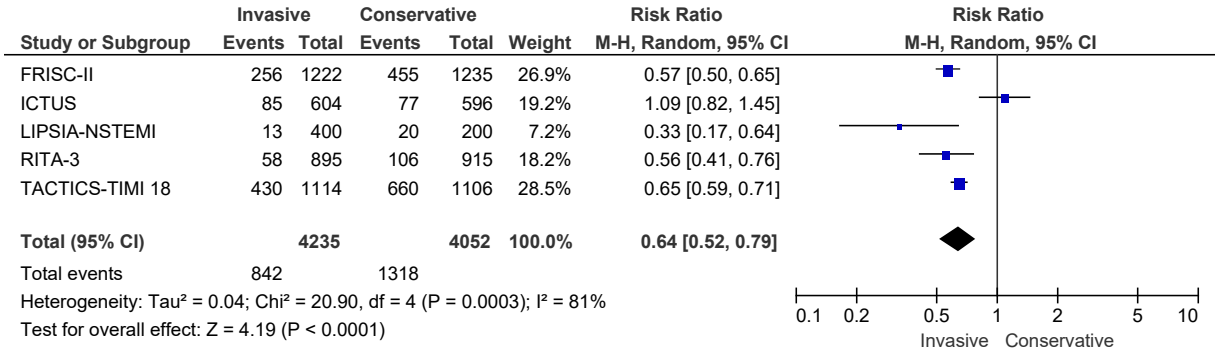


Figure 22: Intermediate rehospitalisation

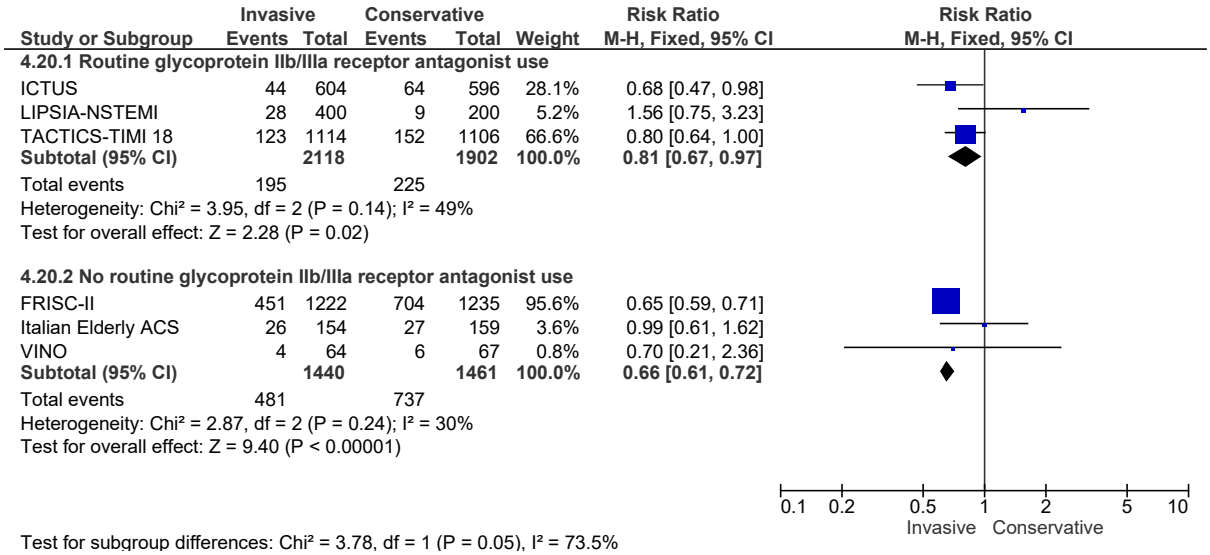


Figure 23: Early stroke (30 days)

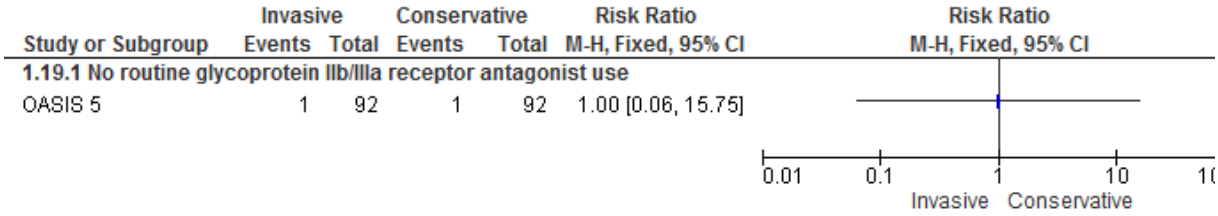


Figure 24: Intermediate stroke (at 1 year)

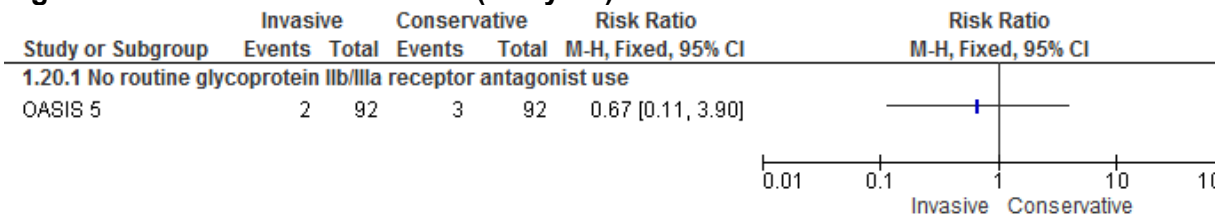


Figure 25: Major bleeding (in hospital)

Study or Subgroup	Invasive Events	Total	Conservative Events	Total	Risk Ratio M-H, Fixed, 95% CI
Italian Elderly ACS	4	154	1	159	4.13 [0.47, 36.54]

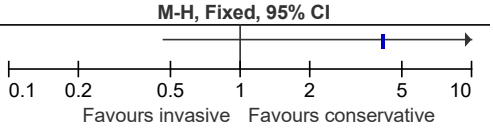


Figure 26: Major bleeding (30 days)

Study or Subgroup	Favours invasive Events	Total	Conservative Events	Total	Risk Ratio M-H, Fixed, 95% CI
OASIS 5	8	92	1	92	8.00 [1.02, 62.68]

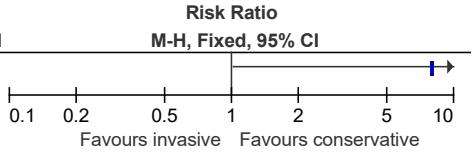


Figure 27: Major bleeding (1 year)

Study or Subgroup	Invasive Events	Total	Conservative Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FRISC-II	19	1222	9	1235	32.4%	2.13 [0.97, 4.70]
Italian Elderly ACS	2	154	1	159	3.6%	2.06 [0.19, 22.54]
LIPSIA-NSTEMI	2	400	2	200	9.6%	0.50 [0.07, 3.52]
OASIS 5	9	92	1	92	3.6%	9.00 [1.16, 69.61]
TACTICS-TIMI 18	21	1114	14	1106	50.8%	1.49 [0.76, 2.91]
Total (95% CI)		**2982**		**2792**	**100.0%**	**1.89 [1.20, 2.99]**
Total events	53		27			

Heterogeneity: Chi² = 4.60, df = 4 (P = 0.33); I² = 13%
Test for overall effect: Z = 2.75 (P = 0.006)

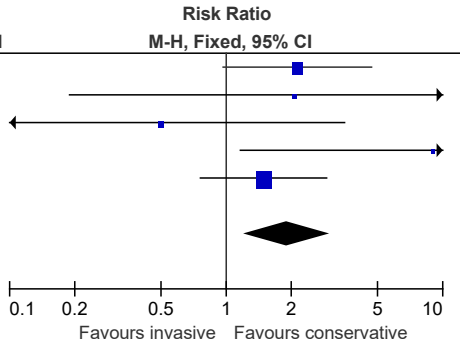


Figure 28: Major bleeding (2 years)

Study or Subgroup	Invasive Events	Total	Conservative Events	Total	Risk Ratio M-H, Fixed, 95% CI
OASIS 5	9	92	1	92	9.00 [1.16, 69.61]

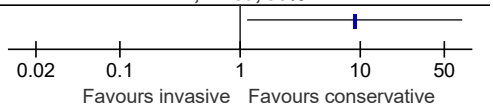


Figure 29: Minor bleeding (at 1 year)

Study or Subgroup	Invasive Events	Total	Conservative Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FRISC-II	93	1222	72	1235	76.4%	1.31 [0.97, 1.76]
TACTICS-TIMI 18	40	1114	22	1106	23.6%	1.81 [1.08, 3.02]
Total (95% CI)		**2336**		**2341**	**100.0%**	**1.42 [1.10, 1.84]**
Total events	133		94			

Heterogeneity: Chi² = 1.15, df = 1 (P = 0.28); I² = 13%
Test for overall effect: Z = 2.69 (P = 0.007)

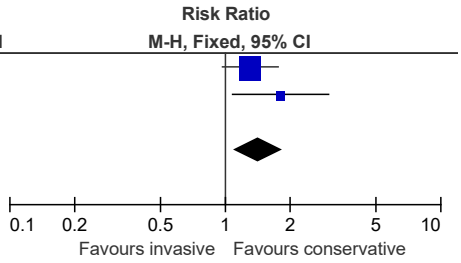
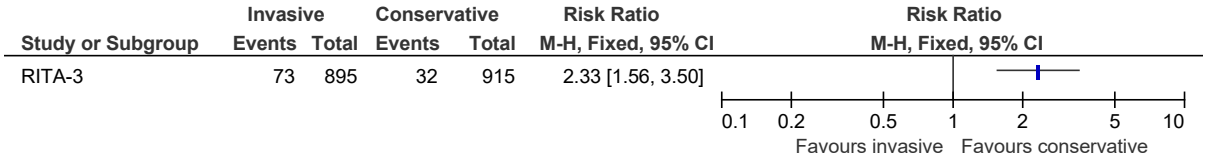


Figure 30: Unspecified bleeding (in hospital)



Appendix F: GRADE tables

Table 15: Clinical evidence profile: Routine invasive versus conservative management in UA/NSTEMI

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early invasive	Conservative	Relative (95% CI)	Absolute		
Index death (all cause mortality in hospital)												
6	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	58/4035 (1.4%)	0.9%	RR 1.54 (1.03 to 2.31)	5 more per 1000 (from 0 more to 12 more)	⊕⊕OO LOW	CRITICAL
Early death (all cause mortality up to 30 days)												
4	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	56/2165 (2.6%)	2.1%	RR 1.18 (0.81 to 1.73)	4 more per 1000 (from 4 fewer to 15 more)	⊕⊕OO LOW	CRITICAL
Intermediate death (all cause mortality at 6-12 months)												
8	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	170/4545 (3.7%)	3.9%	RR 0.88 (0.72 to 1.08)	5 fewer per 1000 (from 11 fewer to 3 more)	⊕⊕⊕O MODERATE	CRITICAL
Late death (all cause mortality at >2 years)												

3	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	264/2721 (9.7%)	10%	RR 0.9 (0.77 to 1.06)	10 fewer per 1000 (from 23 fewer to 6 more)	⊕⊕OO LOW	IMPORTANT
All cause mortality at latest time point (10 years)												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	381/1499 (25.4%)	24.3%	RR 1.04 (0.92 to 1.18)	10 more per 1000 (from 19 fewer to 44 more)	⊕⊕OO LOW	IMPORTANT
Cardiovascular mortality (1 year)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	16/154 (10.4%)	10.7%	RR 0.97 (0.51 to 1.85)	3 fewer per 1000 (from 52 fewer to 91 more)	⊕⊕OO LOW	CRITICAL
Cardiovascular mortality (2 years)												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[1]	none	57/1499 (3.8%)	3.9%	RR 0.95 (0.66 to 1.35)	2 fewer per 1000 (from 13 fewer to 14 more)	⊕OOO VERY LOW	IMPORTANT
Cardiovascular mortality (5 years)												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[1]	none	94/1815 (5.2%)	4.9%	RR 0.99 (0.75 to 1.31)	0 fewer per 1000 (from 12 fewer to 15 more)	⊕OOO VERY LOW	IMPORTANT
Cardiovascular death at latest time point available (10 years)												
2	randomised trials	serious[13]	no serious inconsistency	no serious indirectness	no serious imprecision	none	232/1499 (15.5%)	15.2%	RR 1.01 (0.85 to 1.19)	2 more per 1000 (from 23 fewer to 29 more)	⊕⊕⊕O MODERATE	IMPORTANT

Index myocardial infarction (MI in hospital)												
7	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	very serious[1]	none	168/4435 (3.8%)	3.1%	RR 1.08 (0.65 to 1.8)	2 more per 1000 (from 11 fewer to 25 more)	⊕OOO VERY LOW	
Early myocardial infarction (up to 30 days)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	69/2165 (3.2%)	4.8%	RR 0.65 (0.49 to 0.88)	17 fewer per 1000 (from 6 fewer to 24 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Intermediate myocardial infarction at 6-12 months (intermediate MI)												
8	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	287/4545 (6.3%)	8.9%	RR 0.78 (0.67 to 0.91)	20 fewer per 1000 (from 8 fewer to 29 fewer)	⊕⊕OO LOW	CRITICAL
Late myocardial infarction (at > 2 years)												
3	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	227/2721 (8.3%)	6.5%	RR 0.79 (0.67 to 0.93)	14 fewer per 1000 (from 5 fewer to 21 fewer)	⊕⊕OO LOW	IMPORTANT
Myocardial infarction at latest time point (10 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	75/604 (12.4%)	12.1%	RR 1.03 (0.76 to 1.39)	4 more per 1000 (from 29 fewer to 47 more)	⊕⊕OO LOW	IMPORTANT
Procedure-related myocardial infarction												

5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	200/3275 (6.1%)	2.9%	RR 1.88 (1.48 to 2.39)	26 more per 1000 (from 14 more to 40 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Revascularisation (in hospital)												
2	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	543/758 (71.6%)	31.2%	RR 2.06 (1.64 to 2.57)	331 more per 1000 (from 200 more to 490 more)	⊕⊕⊕O MODERATE	CRITICAL
Revascularisation (1 year) - Routine glycoprotein IIb/IIa receptor antagonist use												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	478/604 (79.1%)	54.4%	RR 1.46 (1.34 to 1.58)	250 more per 1000 (from 185 more to 316 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Revascularisation (1 year) - No routine glycoprotein IIb/IIa receptor antagonist use												
3	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	646/1113 (58%)	31.5%	RR 2.02 (1.82 to 2.24)	321 more per 1000 (from 258 more to 391 more)	⊕⊕⊕O MODERATE	CRITICAL
Revascularisation (2 years)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	955/1222 (78.2%)	45.4%	RR 1.72 (1.61 to 1.84)	327 more per 1000 (from 277 more to 381 more)	⊕⊕⊕O MODERATE	IMPORTANT
Revascularisation (5 years)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	879/1102 (79.8%)	52%	RR 1.53 (1.44 to 1.64)	276 more per 1000 (from 229 more to 333 more)	⊕⊕⊕O MODERATE	IMPORTANT

Intermediate refractory angina												
5	randomised trials	no serious risk of bias	very serious[2]	no serious indirectness	no serious imprecision	none	842/4235 (19.9%)	12.9%	RR 0.64 (0.52 to 0.79)	46 fewer per 1000 (from 27 fewer to 62 fewer)	⊕⊕OO LOW	CRITICAL
Early stroke (30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/92 (1.1%)	1.1%	RR 1 (0.06 to 15.75)	0 fewer per 1000 (from 10 fewer to 162 more)	⊕⊕OO LOW	CRITICAL
Intermediate stroke (at 1 year)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/92 (2.2%)	3.3%	RR 0.67 (0.11 to 3.9)	11 fewer per 1000 (from 29 fewer to 96 more)	⊕⊕OO LOW	CRITICAL
Intermediate rehospitalisation - Routine glycoprotein IIb/IIIa receptor antagonist use												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	195/2118 (9.2%)	10.7%	RR 0.81 (0.67 to 0.97)	20 fewer per 1000 (from 3 fewer to 35 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Intermediate rehospitalisation - No routine glycoprotein IIb/IIIa receptor antagonist use												
3	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	481/1440 (33.4%)	17%	RR 0.66 (0.61 to 0.72)	58 fewer per 1000 (from 48 fewer to 66 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Major bleeding (in hospital)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	4/154 (2.6%)	0.6%	RR 4.13 (0.47 to 36.54)	19 more per 1000 (from 3 fewer to 213 more)	⊕⊕OO LOW	CRITICAL
Major bleeding (30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	8/92 (8.7%)	1.1%	RR 8 (1.02 to 62.68)	77 more per 1000 (from 0 more to 678 more)	⊕⊕⊕O MODERATE	CRITICAL
Major bleeding (1 year)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	53/2982 (1.8%)	1%	RR 1.89 (1.2 to 2.99)	9 more per 1000 (from 2 more to 20 more)	⊕⊕⊕O MODERATE	CRITICAL
Major bleeding (2 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	9/92 (9.8%)	1.1%	RR 9 (1.16 to 69.61)	88 more per 1000 (from 2 more to 755 more)	⊕⊕⊕O MODERATE	IMPORTANT
Minor bleeding (1 year)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	133/2336 (5.7%)	3.9%	RR 1.42 (1.1 to 1.84)	16 more per 1000 (from 4 more to 33 more)	⊕⊕⊕O MODERATE	CRITICAL
Bleeding unspecified (in hospital)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	73/895 (8.2%)	3.5%	RR 2.33 (1.56 to 3.5)	47 more per 1000 (from 20 more to 87 more)	⊕⊕⊕O MODERATE	CRITICAL

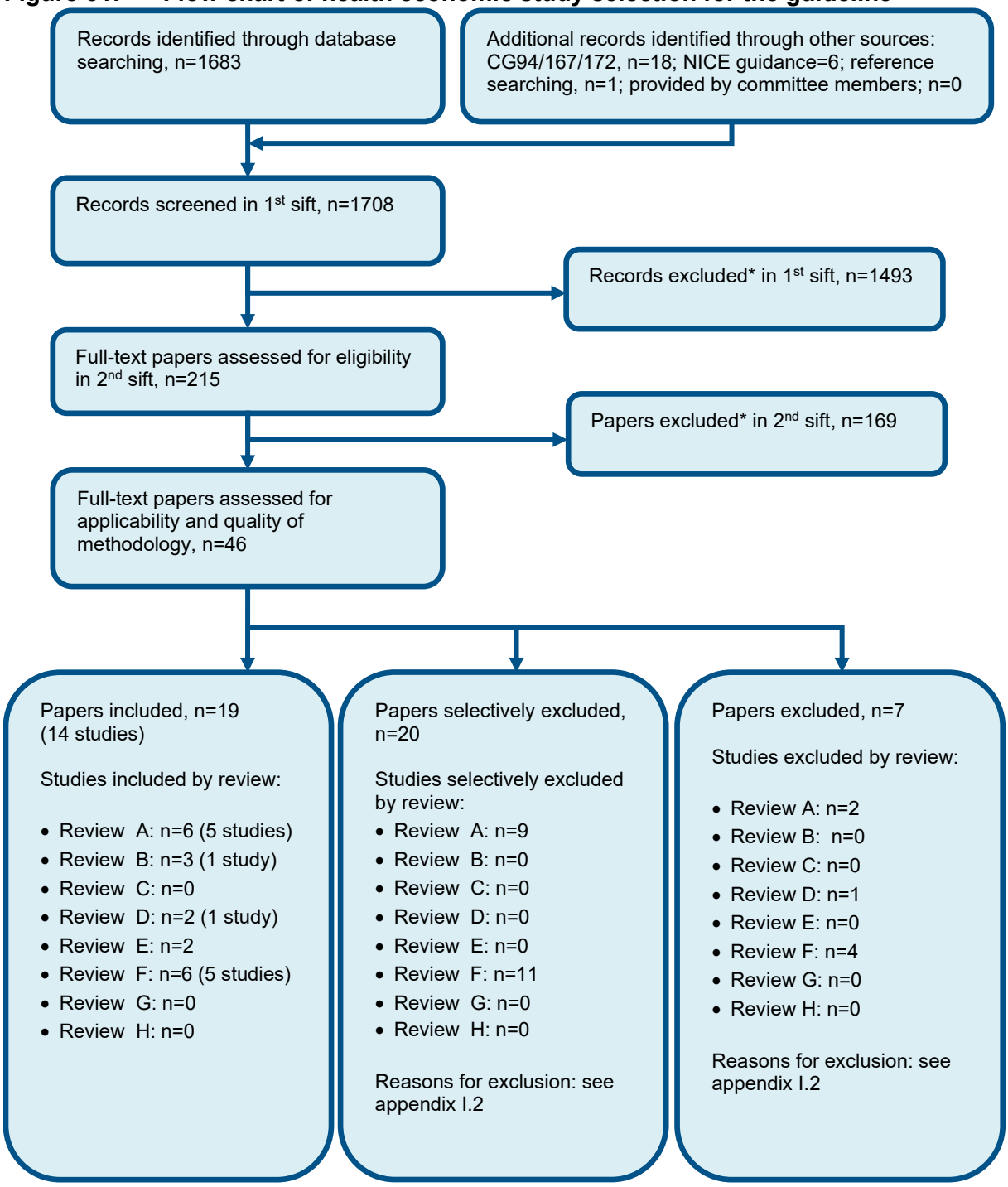
[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

[2] Downgraded by 1 or 2 increments because there is heterogeneity, I2 > 50%, p=0.04, unexplained by subgroup analysis

[3] 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

Appendix G: Health economic evidence selection

Figure 31: 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

Table 16: Health economic evidence tables

Study	Henriksson 2008[27, 28]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** A cost-effectiveness model which was based on a short-term decision tree for index hospitalisation and a long-term Markov model representing the post-index period. The model was based primarily on effectiveness, QoL and resource use data from the RCT RITA-3 5 year follow-up[20, 21]. A series of statistical models were estimated to determine the rates of cardiovascular death or non-fatal MI during the	**Population:** UA/NSTEMI RITA 3: N = 1810 Median age = 63 Male = 61% UK setting Results analysed by risk group (1, 2, 3, 4a, 4b – quartiles of risk in RITA-3 with highest risk split into two) **Intervention 1:** Conservative strategy (ischemia or symptom-driven angiography) **Intervention 2:** Early angiography (routine angiography <72hrs of index episode of pain,	**Total costs (mean):** Mean per patient per group not reported Incremental (Intvn 2 –Intvn 1): ***Base case:*** Risk group 1[(a)] = £4885 Risk group 2[(a)] = £4898 Risk group 3[(a)] = £6045 Risk group 4a[(a)] = £6538 Risk group 4b[(a)] = £6530 ***Pooled effectiveness data:*** Risk group 1[(a)] = £4819 Risk group 2[(a)] = £4852 Risk group 3[(a)] = £5788 Risk group 4a[(a)] = £6163 Risk group 4b[(a)] = £4746 ***Allowing treatment effect to vary with baseline risk:***	**Health outcomes incorporated:** Death, MI, quality of life **Primary outcome measure:** *QALYs (mean)* Mean per patient per group not reported Incremental (Intvn 2 – Intvn 1): ***Base case:*** Risk group 1[(a)] = 0.091 Risk group 2[(a)] = 0.213 Risk group 3[(a)] = 0.283 Risk group 4a[(a)] = 0.547 Risk group 4b[(a)] = 0.512 ***Pooled effectiveness data:*** Risk group 1[(a)] = 0.082 Risk group 2[(a)] = 0.185 Risk group 3[(a)] = 0.240 Risk group 4a[(a)] = 0.452	**Base case ICER (Intvn 2 vs Intvn 1):** *Patient level analysis for RITA-3 patients:* Results only presented graphically. Early interventional strategy cost-effective for more patients as risk increased but with a considerable spread of ICERs within each risk group. Probability CE at £20,000/£30,000 threshold: ***Base case:*** Risk group 1[(a)] = £53,760 (1%/12%) Risk group 2[(a)] = £22,949 (33%/75%) Risk group 3[(a)] = £21,325 (41%/81%) Risk group 4a[(a)] = £11,957 (95%/98%) Risk group 4b[(a)] = £12,750 (92%/98%) ***Pooled effectiveness data:*** Risk group 1[(a)] = £58,490 (0.2%/6%) Risk group 2[(a)] = £26,265 (19%/63% Risk group 3[(a)] = £24,143 (25%/71%) Risk group 4a[(a)] = £13,646 (87%/96%) Risk group 4b[(a)] = £14,673 (83%/96%)

index hospitalisation and the remainder of the trial follow-up period. These estimates of effectiveness were then incorporated into the model. **Perspective:** UK NHS **Time horizon:** Lifetime **Treatment effect duration:**[(a)] 5 years (different durations of treatment effect explored in alternative scenarios) **Discounting:** Costs: 3.5%; Outcomes: 3.5%	followed by revascularisation if clinically indicated)	Risk group 1[(a)] = £4746 Risk group 2[(a)] = £4774 Risk group 3[(a)] = £5574 Risk group 4a[(a)] = £6552 Risk group 4b[(a)] = £7214 *Alternative durations of effect of treatment:* Not reported **Currency & cost year:** 2003/04 UK pounds **Cost components incorporated:** Angiography, PCI, CABG, days on wards (for all causes), visits to family doctor/ community nurse/ outpatients, MI, key cardiac medications (aspirin, beta blockers, statins, LA nitrates, CCBs, ACEs, clopidogrel) Cost analyses accounted for covariates. NB: resource use collected in trial for 1 year; costs are extrapolated past this.	Risk group 4b[(a)] = 0.418 ***Allowing treatment effect to vary with baseline risk:*** Risk group 1[(a)] = -0.019 Risk group 2[(a)] = 0.095 Risk group 3[(a)] = 0.188 Risk group 4a[(a)] = 0.551 Risk group 4b[(a)] = 0.689 *Alternative durations of effect of treatment:* Not reported	***Allowing treatment effect to vary with baseline risk:*** Risk group 1[(a)] = Dominated (0.1%/3%) Risk group 2[(a)] = £50,131 (7%/26%) Risk group 3[(a)] = £29,711 (17%/51%) Risk group 4a[(a)] = £11,898 (94%/98%) Risk group 4b[(a)] = £10,476 (98%/99%) *Alternative durations of effect of treatment (base case = 5 years (trial follow-up)):* 10 yrs / 15 yrs / Lifetime *Constant RITA-3 treatment effect* 1: £34,901 / £27,949 / £13,920 2: £15,410 / £11,652 / £7,850 3: £15,754 / £13,159 / £10,473 4a: £9,631 / £8,446 / £7,600 4b: £9,707 / £8,904 / £8,270 *Interaction between treatment effect and risk at randomisation* 1: £187,947 / £121,044 / £45,130 2: £28,163 / £21,553 / £14,354 3: £19,681 / £16,218 / £12,781 4a: £9,450 / £8,334 / £7,600 4b: £7,934 / £7,348 / £6,906 *Other:* Results were robust to other sensitivity analyses
Data sources				

Health outcomes: Base case: Baseline effectiveness and relative treatment effect were derived from the RITA-3 trial[20, 21] – various statistical analyses were undertaken using RITA-3 patient level data accounting for covariates; lifetables were used for non-cv death rate. Pooled effectiveness data for alternative scenario: Pooled treatment effect was estimated using Mehta 2005[46] meta-analysis and updating with ICTUS trial[11] data, long-term results from RITA-3[20] and FRISC III[39] **Quality-of-life weights:** EQ-5D data from RITA-3 collected at randomisation, 4 months and 1 year. **Cost sources:** Resources use data from RITA-3 with unit costs applied from national sources or collected from hospital in RITA 3 or RITA 2 published previously.[17]
Comments
Source of funding: RITA-3 funded by British Heart Foundation (who received a donation from Aventis Pharma); additional governmental support also obtained. Analysis and preparation of manuscript undertaken independently. **Limitations:** UK resource use from 1997-2002 and UK 2003/2004 unit costs may not reflect the current UK context (e.g. increased angiography and revascularisation, increased use of drug eluting stents and dual antiplatelet therapy). Analysis does not reflect full body of available evidence for this area as identified in clinical review; main analysis based on a single study (RITA-3), alternative analysis using pooled data from 5 of 8 RCTs identified in clinical review plus 3 excluded pre-stent era RCTs. Pooled estimates of effect based on clinical review suggest outcomes may be worse than used in this analysis.
Overall applicability:(b) Partially applicable **Overall quality:**(c) Potentially serious limitations

Abbreviations: ACEs = angiotensin-converting enzyme inhibitors; CABG = coronary artery bypass graft; CCBs = calcium channel blockers; CUA = cost-utility analysis; EQ-5D = Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER = incremental cost-effectiveness ratio; LA = long-acting; MI = myocardial infarction; NSTEMI = non-ST-segment-elevation myocardial infarction; PCI = percutaneous coronary intervention; QALY = quality-adjusted life year; QoL = quality of life; RCT = randomised controlled trial; RITA-3= Randomized Intervention Trial of unstable Angina 3; UA = unstable angina

(a) Illustrative patients based on predicted risk of death or MI as defined in RITA-3 represent each risk group

(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 17: Studies excluded from the clinical review

Study	Exclusion reason
Abdel-Gadir 2015[1]	Less than minimum duration. Not Studies with mixed populations will only be considered if at least 50% of patients have UA/NSTEMI Define. Not Only studies conducted in the stent era (1998 onwards). Incorrect interventions. Systematic review: quality assessment is inadequate
Angeli 2014[2]	Systematic review: methods are not adequate/unclear
Badings 2013[4]	Inappropriate comparison
Badings 2017[3]	Inappropriate comparison
Barthelemy 2013[5]	Inappropriate comparison
Bonello 2016[7]	Systematic review: quality assessment is inadequate
Damman 2012[10]	Systematic review: quality assessment is inadequate
Damman 2012[9]	IPD analysis
Diderholm 2002[13]	Inappropriate comparison
Diderholm 2002[14]	Inappropriate comparison
Elgendy 2016[16]	Systematic review: quality assessment is inadequate
Fox 2010[19]	Inappropriate comparison. IPD analysis
Garg 2018[22]	Systematic review: quality assessment is inadequate
Giannitsis 2017[23]	Inappropriate comparison. Optimal use of antithrombotic medication
Hahn 2017[24]	Not guideline condition
Henderson 2017[25]	Commentary
Holmvang 2003[31]	Inappropriate comparison
Huang 2008[32]	Systematic review: methods are not adequate/unclear
Javat 2017[34]	Systematic review: quality assessment is inadequate
Jobs 2017[35]	Systematic review: quality assessment is inadequate

Katritsis 2011[36]	Inappropriate comparison
Kugelmass 2006[37]	Report on TACTICS TIMI 18
Lemesle 2018[41]	Inappropriate comparison
Li 2017[42]	Systematic review: quality assessment is inadequate
Ma 2018[43]	Systematic review: quality assessment is inadequate
Manfrini 2016[44]	Systematic review: quality assessment is inadequate
Mehta 2009[47]	Not Studies with mixed populations will only be considered if at least 50% of patients have UA/NSTEMI
Milasinovic 2015[48]	Systematic review: quality assessment is inadequate
Milosevic 2016[49]	Inappropriate comparison
Montalescot 2009[50]	Inappropriate comparison
Morrow 2001[51]	Inappropriate comparison
Navarese 2011[53]	Systematic review: quality assessment is inadequate
Navarese 2013[54]	Systematic review: quality assessment is inadequate
O'Donoghue 2012[55]	Systematic review: quality assessment is inadequate
Reuter 2015[56]	Inappropriate comparison
Sabatine 2006[57]	Inappropriate comparison
Sanchis 2019[58]	Inappropriate comparison
Saraswat 2018[59]	Systematic review: quality assessment is inadequate
Sciahbasi 2010[62]	Inappropriate comparison
Shaw 2016[63]	Systematic review: quality assessment is inadequate
Tegn 2016[66]	Studies where stents are deployed in <50% of PCI procedures. Unclear percentage of stents used
Tegn 2018[67]	Studies where stents are deployed in <50% of PCI procedures.
Tekin 2013[68]	Inappropriate comparison
Tricoci 2008[70]	Systematic review is not relevant to review question or unclear PICO
Yan 2011[73]	Inappropriate comparison

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 18: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	