National Institute for Health and Care Excellence

Final

Acute Coronary Syndromes

[E] Evidence review for culprit vessel only compared to complete revascularisation

NICE guideline NG185

Intervention evidence review

November 2020

Final

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

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1.1 Review question: What is the clinical and cost effectiveness of multi-vessel PCI compared to culprit vessel-only PPCI in people with ST-segment elevation myocardial infarction and multi-vessel coronary disease undergoing primary PCI (PPCI)?

1.2 Introduction

Patients who undergo coronary angiography following presentation with an ST-segment elevation myocardial infarction (STEMI) will often be seen to have atherosclerotic disease in more than one vessel with estimates suggesting that 30% to 50% of patients will have angiographic evidence of multi-vessel disease. Historical practice supported revascularisation of culprit vessels alone in STEMI. However, other clinical studies have suggested a potential benefit of multi-vessel intervention. A detailed review of the available evidence has therefore been performed.

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 STEMI and multi-vessel coronary disease
Intervention	Culprit vessel only PPCI. Plus standard adjunctive pharmacotherapies (for example, antiplatelet and antithrombin agents). Culprit vessel only PPCI defined as PPCI confined to the culprit vessel lesions only.
Comparisons	• Multi-vessel PCI during the index procedure. Plus standard adjunctive pharmacotherapies (for example, antiplatelet and antithrombin agents). Multi-vessel PCI defined as PCI in which lesions in the culprit vessel as well as the ≥ 1 non culprit vessel were treated during the same procedure. • Staged multi-vessel PCI. Plus standard adjunctive pharmacotherapies (for example, antiplatelet and antithrombin agents). Staged PCI defined as PCI confined to the culprit vessel only after which ≥ 1 non-culprit vessel were treated during planned secondary procedures. The timing of staged PCI procedures will be defined as reported in each study.
Outcomes	CRITICAL • All-cause mortality at 30 days • Cardiovascular mortality at 30 days • All-cause mortality at 1 year

	• Cardiovascular mortality at 1 year
	• All (fatal and non-fatal) myocardial reinfarction at 30 days
	• Fatal myocardial reinfarction at 30 days
	• All (fatal and non-fatal) myocardial reinfarction at 1 year
	• Fatal myocardial reinfarction at 1 year
	• Health-related quality of life including EQ5D and SF-36. All data for the stated quality of life measures will be collected. Only overall scores will be reported for meta-analysis and GRADE.
	
	IMPORTANT
	• Stroke any type – at 1 year
	• Contrast-induced nephropathy (also note population that goes onto dialysis/renal replacement therapy)
	• Hospitalisation for heart failure – 1 year
	• Unplanned revascularisation – 1 year
	• Complications related to bleeding including haemorrhagic stroke – up to 30 days (access bleeding and non-access bleeding need to be differentiated) – the following hierarchy of bleeding scales will be used:
	  ○ BARC
	  ○ Author's definition
	  ○ TIMI
	  ○ GUSTO
	
	• Where possible, bleeding outcomes will be categorised into
	  ○ Major bleeding (including BARC 3-5 and as reported by author)
	  ○ Minor bleeding (including BARC 2, TIMI and as reported by author)
	• Note intracranial bleeding separately – during index hospitalisation
	• Length of hospital stay

Study design	• Randomised Controlled Trials (RCT) • 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. [65] 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 trials comparing the effectiveness of multi-vessel (either staged or during index procedure) versus culprit vessel only PCI for people with STEMI and multi-vessel coronary disease.

One Cochrane review[12] was identified and has been updated within the review. Nine studies (18 papers) were included in this review.[19, 22, 27, 32, 35, 39, 45, 46, 58, 59, 62, 63, 71-73, 75, 76, 83] Evidence from these studies is summarised in the clinical evidence summary below (Table 2).

Staged multi-vessel PCI was used in 3 studies,[19, 27, 63] and multi-vessel PCI during the index procedure was used in 5 studies[22, 32, 35, 76, 83]. One study[72] included both a staged procedure arm and index procedure arm compared to culprit only arm.

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

1.5.2 Excluded studies

See the excluded studies list in appendix I.

1.5.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Dambrink 2010[19]	Culprit vessel only PCI: conservative management, further treatment after primary PCI was left to the treating physician Multi-vessel PCI: staged intervention on significant stenotic non-culprit lesions	121 people with multi-vessel disease who underwent successful primary angioplasty for STEMI Netherlands	All-cause mortality (6 months), myocardial infarction (6 months), major bleeding (unclear)	Funded by industry. Study was terminated early due to poor recruitment
HELP AMI Di Mario 2004 [22]	Culprit vessel only PCI: culprit lesion treated with primary angioplasty Multi-vessel PCI: during index procedure. Immediate multi-vessel treatment with revascularisation of all suitable lesions Elective abciximab was encouraged in all participants	69 people with ischaemic chest pain	All-cause mortality (1 year), myocardial infarction (1 year)	Funding unclear
DANAMI 3 PRIMULTI Engstrom 2015,[27] Sadjadieh 2016 [, 75] Høfsten 2015[39]	Culprit vessel only PCI: done with a deferred strategy of stent implantation or mechanical postconditioning versus conventional treatment consisting of conventional primary PCI.	627 people presenting with chest pain and ST segment elevation, with successful treatment of culprit lesion and with stenosis greater than 50% in one or more non-infarct related arteries	All-cause mortality (median 27 months), cardiovascular mortality (median 27 months), non-fatal myocardial infarction (median 27 months), stroke (median 27 months), contrast induced nephropathy (median 27	

Study	Intervention and comparison	Population	Outcomes	Comments
	Multi-vessel PCI: Staged. FFR-guided complete revascularisation, using drug eluting stents. This occurred 2 days after initial PCI		months), ischemia driven revascularisation (median 27 months), bleeding (median 27 months)	
CVLPRIT Gershlick 2015[32] Kelion 2015[45], Kelly 2013[46], Mccann 2015[62]	Culprit vessel only PCI: primary PCI was undertaken according to guideline recommendations and routine practice. Drug eluting stents were recommended Multi-vessel PCI: it was recommended that the IRA be treated first, and complete revascularisation was recommended at the same sitting	296 people with myocardial infarction and ST elevation, scheduled for primary PCI	All-cause mortality (1 year), cardiovascular mortality (1 year), myocardial infarction (1 year), stroke (1 year), contrast induced nephropathy (1 year), repeat revascularisation (1 year), major bleed (1 year)	
Hamza 2016[35]	Culprit vessel only PCI: primary PCI was undertaken according to guideline recommendations and routine practice. Drug eluting stents were used Multi-vessel PCI: the IRA was treated first, and complete revascularisation was recommended at the same sitting	100 people with diabetes and diagnosis of acute STEMI presenting within 12 hours of symptoms and with planned primary PCI	All-cause mortality (6 months), recurrent myocardial infarction (6 months), stroke (6 months), contrast induced nephropathy (6 months), repeat revascularisation (6 months), minor bleeding (6 months), major bleeding (6 months)	Funding not stated
COMPLETE Mehta 2019[63]	Culprit vessel only PCI: guideline based medical therapy with no further revascularisation	4041 people with STEMI and multi-vessel coronary disease who had undergone successful culprit legion PCI	All-cause mortality (3 years). Cardiovascular mortality (3 years), myocardial infarction (3 years), ischemia driven revascularisation (3 years),	

Study	Intervention and comparison	Population	Outcomes	Comments
	Multi-vessel PCI: routine staged PCI of all suitable non culprit lesions either during the index hospitalisation or after discharge but no later than 45 days after randomisation		stroke (3 years), major bleeding (3 years)	
Politi 2009[72] Politi 2009[71], Politi 2014[73]	Culprit vessel only PCI: the IRA only was dilated and the other arteries were left untreated. Multi-vessel PCI: Staged (30.4% of participants). The IRA was treated during the primary intervention and complete revascularisation was planned in a second procedure. Multi-vessel PCI: during index procedure (30.4% of participants). The IRA was followed by dilation of other significantly narrowed arteries in the same procedure Post PCI medical oral treatment with aspirin, statins and clopidogrel	214 people with prolonged chest pain and ST elevation	All-cause mortality (mean 2.5 years), cardiovascular mortality (mean 2.5 years), reinfarction (mean 2.5 years), repeat revascularisation (mean 2.5 years)	Funding not stated
COMPARE-ACUTE Smits 2017[76]	Culprit vessel only PCI: after successful primary PCI of the infarct-related coronary artery there were no further procedures	885 people with STEMI and multi-vessel disease. Only hemodynamically stable patients with non–infarct-related lesions for which FFR and PCI were	All-cause mortality (1 year), cardiovascular death (1 year), myocardial infarction (1 year), revascularisation (1 year), major bleeding (1 year)	

Study	Intervention and comparison	Population	Outcomes	Comments
	Multi-vessel PCI: FFR measurements were used to guide the decision as to whether percutaneous revascularization. If appropriate, PCI was performed during the same intervention or during the index hospitalisation within 72 hours	deemed appropriate were eligible		
PRAMI Wald 2013[83] Mangion 2015[59], Mangion 2015[58]	Culprit vessel only PCI: all participants had PCI in the infarct artery and underwent no further procedures Multi-vessel PCI: during the index procedure. Immediate preventative PCI in non-infarct arteries	465 people with STEMI and multi-vessel disease with a successfully treated infarct artery and stenosis deemed to be treatable by PCI	All-cause mortality (mean 23 months), cardiovascular mortality (mean 23 months), non-fatal myocardial infarctions (mean 23 months), stroke (mean 23 months), repeat revascularisation (mean 23 months), major bleeding (mean 23 months)	Early termination of study

See appendix D for full evidence tables.

1.5.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: multi-vessel versus culprit vessel only

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Culprit	Risk difference with Multi (95% CI)
All-cause mortality (30 days)	696 (2 studies) 3 days/in hospital	⊕⊖⊖⊖ VERY LOW[1,3] due to risk of bias, imprecision	Peto OR 0.56 (0.03 to 10.86)	2 per 1000	1 fewer per 1000 (from 2 fewer to 20 more)
All-cause mortality (1 year)	6818 (9 studies) 6 months - 3 years	⊕⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, imprecision	RR 0.84 (0.68 to 1.04)	52 per 1000	8 fewer per 1000 (from 17 fewer to 2 more)
Cardiovascular mortality (1 year)	6528 (6 studies) 6 months - 3 years	⊕⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, imprecision	RR 0.74 (0.56 to 0.99)	37 per 1000	10 fewer per 1000 (from 0 fewer to 16 fewer)
All myocardial infarction (30 days)	696 (2 studies) 3 days/in hospital	⊕⊖⊖⊖ VERY LOW[1,5] due to risk of bias, imprecision	N/A[4]	9 per 1000	3 fewer per 1000 (from 20 fewer to 10 more)
All myocardial infarction (1 year)	6818 (9 studies) 6 months - 3 years	⊕⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, imprecision	RR 0.68 (0.56 to 0.83)	51 per 1000	16 fewer per 1000 (from 9 fewer to 22 fewer)
Stroke (1 year)	5529 (5 studies) 6 months - 3 years	⊕⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, imprecision	RR 1.38 (0.89 to 2.15)	14 per 1000	5 more per 1000 (from 2 fewer to 16 more)
Complications related to bleeding (30 days) - Minor bleeding	627 (1 study) median 5 days	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 1.27 (1.1 to 1.47)	479 per 1000	129 more per 1000 (from 48 more to 225 more) HARM

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Culprit	Risk difference with Multi (95% CI)
Complications related to bleeding (30 days) - Major bleeding	627 (1 study) median 5 days	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.72 (0.30 to 1.78)	35 per 1000	10 fewer per 1000 (from 25 fewer to 27 more)
Complications related to bleeding (30 days) – any bleeding	885 (1 study)	⊕⊖⊖⊖ VERY LOW[1, 3] due to risk of bias, imprecision	RR 1.25 (0.41 to 3.79)	14 per 1000	3 more per 1000 (from 8 fewer to 39 more)
Complications related to bleeding (1 year) - Minor bleeding	727 (2 studies) 6-27 months	⊕⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	RR 1.21 (1.06 to 1.39)	272 per 1000	57 more per 1000 (from 16 more to 106 more)
Complications related to bleeding (1 year) - Major bleeding	6535 (7 studies) 6 months - 3 years	⊕⊖⊖⊖ VERY LOW[1,2,5] due to risk of bias, indirectness, imprecision	N/A[4]	25 per 1000	3 more per 1000 (from 0 fewer to 10 more)
Complications related to bleeding (1 year) – any bleeding	885 (1 study)	⊕⊖⊖⊖ VERY LOW[1, 3] due to risk of bias, imprecision	RR 0.64 (0.31 to 1.34)	48 per 1000	17 fewer per 1000 (from 33 more to 16 more)
Contrast induced nephropathy	1488 (4 studies) 6-27 months	⊕⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	RR 0.92 (0.42 to 1.99)	17 per 1000	1 fewer per 1000 (from 10 fewer to 17 more)
Unplanned revascularisation (1 year)	6697 (8 studies) 6 months - 3 years	⊕⊕⊖⊖ LOW[1,3] due to risk of bias	RR 0.28 (0.23 to 0.34)	121 per 1000	87 fewer per 1000 (from 80 fewer to 93 fewer)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Culprit	Risk difference with Multi (95% CI)
2 Downgraded for indirectness due to length of follow up 3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs 4 No relative effect due to 0 events. Risk difference calculated in Review Manager 5 Imprecision was assessed by calculating the optimal information size and graded as follows: <80% - very serious imprecision, 80-90%- serious imprecision, >90%– no imprecision					

See appendix F for full GRADE tables.

1.6 Economic evidence

1.6.1 Included studies

Two health economic studies with the relevant comparison were included in this review.[10, 22] These are summarised in the health economic evidence profile below (Table 4) and the health economic evidence tables in Appendix H:.

1.6.2 Excluded studies

No relevant health economic studies 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 4: Health economic evidence profile: multi-vessel PCI versus culprit-vessel PCI

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Barton 2017[10] (UK)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Within-trial analysis of CvLPRIT RCT[32] with multiple imputation to impute missing data • Cost-utility analysis (QALYs); also looked at major adverse cardiac event (MACE) • Population: people with multi-vessel disease undergoing primary PCI for STEMI • Comparators: ○ Culprit vessel PCI ○ Multi-vessel PCI • Follow-up: 1 year	-£216[(c)]	**QALYs (mean per patient):** 0.011 **MACE (mean per patient):** -0.170	Multi-vessel PCI dominant (for QALYs and MACEs)	**QALY analysis** Probability multi-vessel PCI cost effective (£20K/30K threshold): 72%/NR Multi-vessel PCI remained dominant when people that did not receive the intervention they were allocated to were excluded. Complete-case only analysis resulted in an ICER of £21,496 per QALY gained for multi-vessel PCI with a probability of it being cost-effective at 20K threshold of 45.3%.
Di Mario 2004[22] (Italy)	Partially applicable[(d)]	Very serious limitations[(e)]	• Within-trial analysis of HELP-AMI RCT • Cost-consequence analysis (mortality; reinfarction; repeat revascularisation) • Population: people admitted to hospital with ischemic chest pain and/or STEMI with arteriography showing lesions in	-£1,412[(f)]	From clinical review – same paper All-cause mortality (30 days): Peto OR 3.77 (CI: 0.04, 356.19); ARD 19 per 1000 All-cause mortality (1	Not applicable	No sensitivity analysis was undertaken

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			multiple coronary arteries • Comparators: ○ Culprit-vessel PCI ○ Multi-vessel PCI • Follow-up: 1 year		year): RR 1.02 (CI: 0.13, 52.78); ARD 19 per 1000 All (fatal, non-fatal) MI (1 year): RR 0.33 (CI: 0.02, 4.95); ARD -40 per 1000 Unplanned revascularisation (1 year): RR 0.44 (CI: 0.18, 1.08) ARD -355 per 1000		

Abbreviations: ARD = absolute risk difference; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years; PCI = percutaneous coronary intervention; RCT = randomised controlled trial; STEMI = ST segment elevation myocardial infarction

(a) UK resource use from 2011-2013 and costs from 2012-2013 may not reflect current UK context. Use of bivalirudin higher in the trial than compared to current context and use of DAPT is different with current prasugrel usage lower and current ticagrelor usage higher than reported in the study (see Table 5 below for details).

(b) Analysis based on a single study (CvLPRIT RCT) and so does not reflect full body of available evidence for this area. Time horizon of 1 year may not fully capture differences in costs and outcomes however as the intervention is dominant this might not make a difference.

(c) Cost components included: culprit and multi-vessel PCI index admission procedure cost (procedure time, consumables, equipment and hospital length of stay), hospital readmissions for revascularisation and follow-up staff costs.

(d) Italian resource use and unit costs from pre-2004 (exact years not stated) may not reflect current UK context. Intervention used heparin-coated stents which are not routinely used in current practice. Contradictory descriptions of study population – not clear whether all patients had STEMI. Study arms had unbalanced proportions of patients with diabetes (culprit-vessel arm = 41.2%; multi-vessel arm = 11.5%). Measure of effect is not in line with NICE reference case methods as does not use QALYs (CCA instead of CUA).

(e) Time horizon of 1 year may not fully capture differences in costs and health outcomes. Analysis based on a single study (HELP-AMI) and so does not reflect full body of available evidence for this area. Unclear if all relevant costs are included, and some unit cost sources are unclear. No sensitivity analysis undertaken. Funding not reported but one author worked for Cordis.

(f) 2004 Italian Euros converted to UK pounds.[70] Cost components included: initial procedure costs including all materials, stay in hospital including intensive care and cardiology wards; downstream cost including additional revascularisation procedures (PCI or CABG).

To aid interpretation Table 5 below compares the resource use in the Barton 2017[10] study and current resource use reported by the British Cardiovascular Intervention Society (BCIS)[56] 2106 audit results.

Table 5: Comparison of resource use in Barton 2017 compared to current practice

Resource use	Barton 2017	BCIS 2017
Use of bivalirudin	Multi-vessel: 56.8%; culprit-vessel: 50.8%	0.7%
Use of glycoprotein inhibitors	Multi-vessel: 31.7%; culprit-vessel: 31.7%	37.4%
Use of clopidogrel	Multi-vessel: 41.0%; culprit-vessel: 39.1%	NR (assume remaining 45.8%)
Use of prasugrel	Multi-vessel: 40.3%; culprit-vessel: 46.4%	7.2%
Use of ticagrelor	Multi-vessel: 13.2%; culprit-vessel: 13.3%	47.5%
Use of drug eluting stents	Multi-vessel: 95.9%; culprit-vessel: 90.7%	91.0%
Radial access	Multi-vessel: 76.7%; culprit-vessel: 70.7%	87.2%

Table 6 below summarises the unit costs reported in Barton 2017[10] and current UK NHS unit costs.

Table 6: Comparison of current UK unit costs and unit costs in Barton 2017

Resource use	Barton 2017 unit costs	Current UK unit costs
Myocardial infarction	£1,710[(a)]	£1,509[(d)]
Revascularisation post-index admission – PCI	£2,017[(a)]	£2,795/£3,864[(d)]
Revascularisation post-index admission– CABG	£9,002[(a)]	£10,559[(d)]
High dependency unit (bed day)	£852[(a)]	£565[(d)]
Intensive care unit (bed day)	£1,236[(a)]	£1,241[(d)]
Bare metal stent	£98[(b)]	£75[(e)]
Drug-eluting stent	£302[(b)]	£380[(f)]
Cardiologist visit	£126[(a)]	£163[(d)]
Hospital nurse per hour	£45[(c)]	£55[(g)]
General practitioner cost per consultation	£25[(c)]	£37[(g)]

Sources:
(a) Based on NHS reference costs 2012/13 as reported in Barton 2017[10]
(b) Survey to participating centres in the RCT as reported in Barton 2017[10]
(c) Based on Personal Social Services Research Unit Costs 2013 as reported in Barton 2017[10]
(d) NHS reference costs 2017/18[21], weighted averages are calculated and cost of PCI is provided for standard PCI and complex PCI as shown in Table 7.
(e) Obtained from NHS Supply Chain 2018[68]
(f) Costs calculated based on weighted average of stents used across NHS, obtained from BCIS audit data, and the cost of drug-eluting stent reported in NHS Supply Chain 2018[68]

(g) Personal Social Services Research Unit Costs 2018[17]

1.6.4 Health economic modelling

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

1.6.5 Unit costs

There a number of different approaches that are considered multi-vessel PCI – these include undertaking a multi-vessel PCI at the time of PPCI or routinely bringing patients back to undertake revascularisation of other vessels, which in turn could be within the index hospital stay or a later readmission. The upfront cost of multi-vessel PCI is likely to be higher than for a culprit-vessel only strategy either because a longer procedure is required (if it is undertaken at the time of PPCI) or because additional procedures and potentially length of stay are required (if undertaken as a staged procedure). If patients are discharged and then readmitted for the staged procedure it may be that costs will be higher than if staged in the same admission as there will be costs associated with admitting and discharging someone on two occasions rather than one. More stents will also be required for multi-vessel PCI.

The included studies showed that the upfront costs associated with the procedure were higher with multi-vessel PCI. Barton 2017 reported that the multi-vessel procedure resulted in over £200 additional costs compared to the culprit-vessel only procedure.[10] Di Mario 2004 reported an additional £500 associated with the multi-vessel procedure compared to the culprit-vessel only PCI.[22]

Unit costs of PCI are provided below to aid consideration of cost effectiveness. Standard percutaneous transluminal coronary angioplasty is based on the insertion of 1-2 stents. Complex transluminal coronary angioplasty is based on the insertion of 3 or more stents.

Table 7: UK NHS reference costs 2017/18 for percutaneous coronary interventions

Currency code	Currency description	Admission	Number of FCEs	National average unit cost	Weighted average
EY40A	Complex Percutaneous Transluminal Coronary Angioplasty with CC Score 12+	Non-elective long stay	752	£7,572	£6,336
		Non-elective short stay	292	£3,152	
EY40B	Complex Percutaneous Transluminal Coronary Angioplasty with CC Score 8-11	Non-elective long stay	1,335	£5,447	£4,632
		Non-elective short stay	476	£2,346	
EY40C	Complex Percutaneous Transluminal Coronary Angioplasty with CC Score 4-7	Non-elective long stay	3,165	£4,485	£3,733
		Non-elective short stay	1,579	£2,228	
EY40D	Complex Percutaneous Transluminal Coronary Angioplasty with CC Score 0-3	Non-elective long stay	3,061	£3,969	£3,232
		Non-elective short stay	2,236	£2,224	
Overall weighted average of Complex Percutaneous Transluminal Coronary Angioplasty with CC Score 0-12+					**£3,864**
EY41A	Standard Percutaneous Transluminal Coronary Angioplasty with CC Score 12+	Non-elective long stay	1,307	£6,826	£5,762
		Non-elective short stay	427	£2,507	

Currency code	Currency description	Admission	Number of FCEs	National average unit cost	Weighted average
EY41B	Standard Percutaneous Transluminal Coronary Angioplasty with CC Score 8-11	Non-elective long stay	2,802	£4,577	£3,827
		Non-elective short stay	1,127	£1,963	
EY41C	Standard Percutaneous Transluminal Coronary Angioplasty with CC Score 4-7	Non-elective long stay	9,037	£3,649	£3,009
		Non-elective short stay	5,137	£1,884	
EY41D	Standard Percutaneous Transluminal Coronary Angioplasty with CC Score 0-3	Non-elective long stay	10,510	£3,185	£2,545
		Non-elective short stay	8,843	£1,784	
Overall weighted average of Standard Percutaneous Transluminal Coronary Angioplasty with CC Score 0-12+					**£2,707**

Source: NHS reference costs, 2017/18[21], non-elective long stay calculations include excess bed days.
Abbreviations: FCE = finished consultant episodes

1.7 Evidence statements

1.7.1 Clinical evidence statements

- For the comparison of a multi-vessel PPCI compared to a culprit only procedure in patients with STEMI and multi-vessel disease, there was a clinically important benefit of multi-vessel PPCI for all-cause mortality and myocardial infarction at 1 year (6818 participants in 9 studies, very low quality evidence), cardiovascular mortality at 1 year (6528 participants in 6 studies, very low quality evidence) and unplanned revascularisation at 1 year (6697 participants in 8 studies, low quality evidence).
- There was a clinically important harm in minor bleeding at 30 days (627 participants in 1 study, low quality evidence) and at 1 year (727 participants in 2 studies, very low quality evidence) when using multi-vessel PPCI.
- There was no clinically important difference in all-cause mortality and MI at 30 days/in hospital (696 participants in 2 studies, very low quality evidence), stroke at 1 year (5529 participants in 5 studies, very low quality evidence), complications related to major bleeding at 30 days (627 participants in 1 study, very low quality evidence) and at 1 year (6535 participants in 7 studies, very low quality evidence),any bleeding at 30 days and 1 year (885 participants in 1 study, very low quality evidence) and contrast induced nephropathy (1488 participants in 4 studies, very low quality evidence).

1.7.2 Health economic evidence statements

- One cost–utility analysis found that multi-vessel PCI was dominant (less costly and more effective) compared to culprit-vessel PCI for treating people with multi-vessel disease undergoing PCI for STEMI. This analysis was assessed as partially applicable with potentially serious limitations.
- One cost–consequence analysis found that multi-vessel PCI was less costly than culprit vessel PCI for treating people with multi-vessel disease undergoing PCI for STEMI (£1,412 less per patient). Multi-vessel PCI had more deaths per patient, but fewer myocardial infarctions and unplanned revascularisations per patient. This analysis was assessed as partially applicable with very 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 outcomes critical for decision making were all-cause and cardiovascular mortality, myocardial re-infarction (fatal, non-fatal and all) reported at 30 days and 1 year. Health-related quality of life was also considered critical for decision making.

Stroke, hospitalisation for heart failure and unplanned revascularisation reported at 1 year, contrast-induced nephropathy, length of hospital stay and complications related to bleeding (up to 30 days) were considered to be important outcomes.

1.8.1.2 The quality of the evidence

Evidence from 9 randomised controlled trials were included in this review. In five of those studies, complete revascularisation was recommended during the index procedure. Three studies undertook staged multi-vessel procedures. One study had 3 arms comparing culprit only to staged multivessel and multivessel during index procedure. For the purposes of this review the 2 multivessel arms were combined and analysed together. Subgroup analyses including timing of complete revascularisation (staged compared to index procedure) was planned in case of significant heterogeneity but this was not necessary as no heterogeneity was detected.

GRADE assessment for all outcomes was either low or very low due to risk of bias and imprecision.

The committee had some concerns about how well the trials represent real world practice. Multi-vessel disease in STEMI is present in about 30% of STEMI patients and STEMI is a common condition, yet some of the studies took several years to recruit. It is possible that some clinical selection bias was operating, for example being less willing to enter patients into the trial when it was known that there was a queue of patients also waiting for the catheter lab, since randomisation might mandate a lengthier multi-vessel procedure; or being less willing to randomise patients and potentially commit them and the PPCI clinical team to longer more complex procedures during the night. Such reluctance can be clinically justified; the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) reports in other surgical domains have highlighted the additional risk of performing complex procedures outside normal working hours. The committee also noted that the risk of any procedure-related complication is inevitably related to the duration of the procedure, which further explains why many PCI operators are reluctant to intentionally prolong PPCI procedures in patients who are already critically unwell with STEMI. However, the largest of the studies, COMPLETE, accrued patients at a more reassuring rate and its results were in keeping with those of the overall data. The committee were therefore happy that the research data could be applied to clinical practice.

It was also noted that the proportion of patients with diabetes was lower than seen in practice and most studies excluded patients with cardiogenic shock suggesting that lower risk population were entered into the trials.

There was no evidence available for cardiovascular mortality at 30 days, length of hospital stay or for quality of life outcomes.

1.8.1.3 Benefits and harms

The committee accepted that there were clinical benefits of conducting multi-vessel procedures for cardiovascular mortality, all MI and unplanned revascularisation up to 1 year.

For the outcome of all-cause mortality at 30 days, the committee did not feel confident that there was a meaningful difference between the interventions in that the evidence had a very low GRADE rating and a control event rate of just 2 per 1000. The all-cause mortality difference at 1 year was thought to show a small benefit in the multi-vessel arm although it was noted that this was from very low quality GRADE rated evidence with confidence intervals which also encompass the possibility of clinical harm. The committee also noted that the all-cause mortality rate in the studies was compatible with the mortality rates in the national MINAP database, which allays some of the concerns about the representativeness of these data.

The evidence suggested that there was no clinically important difference when conducting a multi-vessel procedure compared to culprit vessel only for outcomes such as all MI and major bleeding up to 30 days, stroke at 1 year and contrast-induced nephropathy (the committee had been concerned about this as a possible adverse effect of multi-vessel procedures which are lengthier and require more imaging of the coronary vasculature).

The only outcome in which there was a clinically important benefit of culprit only procedures over multi-vessel was in the rate of minor bleeding complications. There was some discussion over this since the difference was in the opposite direction to that seen for major bleeding, and because there was a big difference between studies for this outcome. This might result from variance in the classification of major versus minor bleeding, although there are other plausible explanations such as differences in the use of additional anti-platelet agents. The committee agreed however that minor bleeding would be unlikely to have long term implications for the patient and the main impact would be a possible resource use of managing the bleed or possibly increased length of stay.

The committee discussed potential practical issues with performing multi- vessel procedures. These clearly take longer, more contrast is required, and risk of complications is increased. They also noted concerns around having to delay other patients from receiving revascularisation or having to cancel other procedures and of clinician performance when the procedure is being carried out late at night and / or after a long shift when the clinician and support staff are fatigued, with the potential increased risk of harmful mistakes. It was felt important to make recommendations which allow the clinical team to factor in these considerations when deciding the need for, and the timing of, any intervention in non-culprit vessels.

1.8.2 Cost effectiveness and resource use

Two economic evaluations were identified for this review. One was a cost-consequences analysis and one was a cost-utility analysis.

Di Mario 2004 conducted a cost-consequences analysis from an Italian healthcare perspective. This was a within-trial analysis of the HELP-AMI randomised controlled trial. This analysis using 2004 Italian Euros found that multi-vessel PCI was cost-saving. Initial procedure costs were more costly in the multi-vessel arm however it led to a reduction in repeat revascularisation procedures, leading to cost savings over the 12 month follow-up. The overall average cost saving per person was £1,412. It was noted that there were several limitations of this study including the details on resource use and unit costs not being reported. Also, the trial was undertaken in 2004 and used heparin-coated stents which have never been used routinely in UK practice. Comparing the estimates of effect size from the meta-analysis of all studies undertaken as part of the clinical evidence review to those just from the HELP-AMI study this analysis was based on, they were greater for mortality and

unplanned revascularisation, which would increase savings based on the reduction in repeat revascularisations. However the effect size for repeat MI was smaller, but it was unclear if this study attributed additional costs to this outcome.

Barton 2017 conducted a cost-utility analysis from a UK NHS perspective. This was a within-trial analysis of the CvLPRIT randomised controlled trial which was conducted in the UK. This analysis using 2012/13 costs found that multi-vessel PCI had lower costs and higher QALYs and so was cost effective compared to culprit-only PCI. Initial procedure costs were more costly in the multi-vessel arm but it led to a reduction in repeat admissions including MI and revascularisation which lead to cost savings over the 12-month follow-up. The base-case analysis involved undertaking multiple imputations to account for missing data. Different scenarios were explored where multiple imputations was not conducted. One scenario excluding patients that did not receive the intervention they were allocated to resulted in the same outcome, with multi-vessel PCI being dominant. A complete case analysis which only included patients that had all data available resulted in the multi-vessel procedure having higher costs and higher QALYs with an ICER just above the NICE threshold of £21,496. The probability of multi-vessel PCI being cost-effective at a £20,000 threshold was 72% in the base-case analysis but dropped to 45.3% in the complete case analysis. Estimates of effect size in the meta-analysis of all available studies were greater for unplanned revascularisation which would lead to more savings in repeat procedures. However, they were worse for mortality and repeat MI which would reduce QALY gains. Current resource use in England and the resource use reported in the study were similar, with the only main differences being that the use of bivalirudin was much higher in the trial compared to current practice. Although the analysis used 2012/13 costs the committee agreed that they were similar to current unit costs.

In both of these studies multi-vessel PCI was undertaken as part of the initial procedure (that is at the time of PPCI) or during the index admission. They did not look at the cost-effectiveness of a procedure where the patient is discharged and brought back at a later date or where multi-vessel PCI was mandated to be at the time of PPCI. The committee discussed that having PPCI in their index admission, being discharged and then being scheduled to come in at a later date to have the rest of the multi-vessel procedure could result in additional costs to the NHS as people are being admitted to hospital twice. The committee also highlighted that there may be increased healthcare resource use while people are waiting for the second procedure after discharge due to people visiting their GP or A&E as a result of concern that symptoms indicate ischemia or another acute event. It was also noted that it could result in a delay in starting cardiac rehabilitation until after the second procedure. Also, the effectiveness of coming back at a later date may be different which could impact resource use (although the committee noted this was not the case in the COMPLETE RCT where people randomised to complete revascularisation could have a second procedure in the index admission or within 45 days of discharge). Mandating multi-vessel PCI at the time of PPCI could also result in additional costs as it could result in a need to expand PPCI services to accommodate longer procedure times without delaying urgent PPCI procedures. Therefore, it was felt that conclusions regarding cost effectiveness could only relate to the clinical scenario where multi-vessel could be at the time of PPCI or staged within the same admission and could not be extrapolated to staged multi-vessel procedures where patients are discharged and return at a later date or multi-vessel PCI specifically at the time of PPCI.

There may be circumstances when it is not considered safe to undertake the procedure, for example, when it is felt that the patient is too high risk to undergo a long procedure, and therefore should not have multi-vessel PCI. The committee felt that the studies included would have potentially avoided conducting multi-vessel PCI in high risk patients where it is not safe, and therefore it would not be considered cost-effective under these situations. Therefore, a recommendation to consider culprit vessel only PCI in people with cardiogenic

shock ensures that multi-vessel PCI is only conducted in accordance with the results from the studies.

Current practice is variable across centres and also within centres. Some offer multi-vessel PCI during the first procedure but other operators may postpone (either within the index admission or post-discharge) or only operate on the culprit vessel. The committee agreed that recommending multi-vessel PCI would result in a change in current practice for some centres or operators and this is likely to increase resource use in terms of initial PCI procedures. However, the reduction in downstream revascularisations is likely to be cost-saving. Overall this may result in savings to the NHS in England.

1.8.3 Other factors the committee took into account

The health-care professionals on the committee were concerned about the effects on people experiencing a STEMI who might be told that they had disease in more than one coronary artery, but that only a single vessel had been treated. The lay members agreed that knowing there are further occlusions would be a source of anxiety, although they were not overly concerned about this, pointing out that having a STEMI induces general anxiety about numerous features of one's health, for example the worry that various future symptoms might be due to ACS even if logically the person knows they are not. It was also noted that people cannot access cardiac rehabilitation classes when waiting for a further coronary procedure, and delaying the benefits of rehabilitation was seen as a negative aspect of multi-vessel interventions unless they were performed quickly during the index admission.

The question of whether multi-vessel procedures should be done during the initial stenting procedure, later but during the same admission, or as a staged procedure during a subsequent planned admission, cannot be directly assessed from this review. Three of the included studies performed staged procedures, and the relative benefits of multi-vessel treatment appears less than in those studies which completed the procedure in the index admission, but this does not represent a formal comparison of these alternatives since other factors also differed between the studies. In the COMPLETE study of over 4,000 patients operators were given the option of performing multi-vessel procedures in either the index admission or during a second elective admission, providing this was done within 45 days. This is not a randomised comparison, and the data are not given in the currently published paper, but the authors comment that there was no substantial difference in the results from the 2 approaches. The GC were also aware of a post-hoc analysis of the CVLPRIT study which showed early divergence of the outcome curves suggesting that at least some of the benefit of multi-vessel intervention is derived quickly, but the authors of the COMPLETE study could not confirm this finding. The committee noted possible cost consequences of having procedures spread across two admissions and felt that their recommendations should favour providing the treatment during the index admission.

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Appendices

Appendix A: Review protocols

Table 8: Review protocol: Culprit only versus multi-vessel PPCI in people with STEMI

ID	Field	Content
0.	PROSPERO registration number	CRD42019131663
1.	Review title	What is the clinical and cost effectiveness of multi-vessel PCI compared to culprit-only PPCI in people with STEMI and multi-vessel coronary disease undergoing primary PCI (PPCI)?
2.	Review question	What is the clinical and cost effectiveness of multi-vessel PCI compared to culprit-only PPCI in people with STEMI and multi-vessel coronary disease undergoing primary PCI (PPCI)?
3.	Objective	To compare the clinical and cost effectiveness of multi-vessel coronary artery, primary percutaneous revascularisation and culprit-only primary percutaneous revascularisation in people with STEMI and multi-vessel coronary disease. Rationale for including this question: The original guideline (CG 167) did not include any recommendations as the evidence was of poor quality. The surveillance report identified new evidence. Topic experts also highlighted that large studies are ongoing. Additionally, they mentioned that American guidelines indicate that multi-vessel PCI can be used when deemed appropriate. As a result, experts felt that the potential impact of any changes to practice need to be explored.
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.

ID	Field	Content
		The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant. The full search strategy will be published in the final review.
5.	Condition or domain being studied	Acute coronary syndrome
6.	Population	Inclusion: Adults (≥ 18 years old) with STEMI and multi-vessel coronary disease undergoing PPCI. Exclusion: None
7.	Intervention/Exposure/Test	Culprit vessel only PPCI. Plus standard adjunctive pharmacotherapies (for example, antiplatelet and anti-thrombin agents). Culprit vessel only PPCI defined as PPCI confined to culprit vessel lesions only.
8.	Comparator/Reference standard/Confounding factors	Multi-vessel PCI during the index procedure). Plus standard adjunctive pharmacotherapies (for example, antiplatelet and anti-thrombin agents). Multi-vessel PCI defined as PCI in which lesions in the culprit vessel as well as ≥ 1 non-culprit vessel were treated during the same procedure. Staged multi-vessel PCI. Plus standard adjunctive pharmacotherapies (for example, antiplatelet and anti-thrombin agents). Staged PCI defined as PCI confined to the culprit vessel only during index procedure after which ≥ 1 non-culprit vessel were treated during planned secondary procedures. The timing of staged PCI procedures will be defined as reported in each study but should not exceed 3 months.
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 STEMI 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

ID	Field	Content
12.	Primary outcomes (critical outcomes)	• All-cause mortality at 30 days • Cardiovascular mortality at 30 days • All-cause mortality at 1 year • Cardiovascular mortality at 1 year • All (fatal and non-fatal) myocardial re-infarction at 30 days • Non-fatal myocardial re-infarction at 30 days • All (fatal and non-fatal) myocardial re-infarction at 1 year • Fatal myocardial re-infarction at 1 year • Non-fatal myocardial re-infarction at 1 year • Health-related quality of life including EQ5D and SF-36
13.	Secondary outcomes (important outcomes)	• Stroke any type – at 1 year • Contrast-induced nephropathy (also note population that goes onto dialysis/renal replacement therapy) • Hospitalisation for heart failure – 1 year • Unplanned revascularisation – 1 year • Complications related to bleeding including haemorrhagic stroke – up to 30 days (access bleeding and non-access bleeding need to be differentiated)- the following hierarchy of bleeding scales will be used: o BARC o Author's definition o TIMI o GUSTO Where possible, bleeding outcomes will be categorised into: • Major bleeding (including BARC 3-5 and as reported by author) • Minor bleeding (including BARC 2, TIMI and as reported by author). Note intracranial bleeding separately – during index hospitalisation • Length of hospital stay
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

ID	Field	Content
		An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB (2.0) Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be 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.

ID	Field	Content
		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	Gender People with diabetes People aged over 75 years. Timing of complete revascularisation As part of index procedure Delayed but during index admission Staged Staging of intervention: Up to 1 week > 1 week and up to 1 month > 1 month and up to 3 months
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	19/10/18
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: ☐ / ☑

ID	Field	Content
		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 Carisle [Senior Systematic Reviewers] Ms Annabelle Davies/Ms Kate Lovibond [Health economist; Health economists lead] Ms Agnes Cuyas/Ms Jill Cobb [Information specialists]
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
29.	Other registration details	
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=131663
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

ID	Field	Content	
		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, culprit , multi-vessel coronary disease, primary PCI, STEMI	
33.	Details of existing review of same topic by same authors	N/A	
34.	Current review status	☐	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	N/A	
36.	Details of final publication	www.nice.org.uk	

Table 9: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2003 that were included in the previous guidelines will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[65] **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.[65]

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

B.1 Clinical search literature search strategy

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

Table 10: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	01 January 1998 – 22 July 2019	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	01 January 1998 – 22 July 2019	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews 1998 to 2019 Issue 7 of 12 CENTRAL 1998 to 2019 Issue 7 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.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.	(culprit or non-culprit or nonculprit).ti,ab.
39.	((infarct-related or infarct related or non-infarct-related) adj2 (artery or arteries)).ti,ab.
40.	(complete adj2 revasc*).ti,ab.
41.	((multi-vessel* or multi-vessel* or single-vessel*) adj3 (percutaneous coronary intervention* or PCI or PPCI or PTCA or stent* or revasc* or recanali* or angioplast*)).ti,ab.
42.	or/38-41
43.	37 and 42
44.	randomized controlled trial.pt.
45.	controlled clinical trial.pt.
46.	randomi#ed.ti,ab.
47.	placebo.ab.
48.	randomly.ti,ab.
49.	Clinical Trials as topic.sh.
50.	trial.ti.
51.	or/44-50
52.	Meta-Analysis/
53.	exp Meta-Analysis as Topic/
54.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
55.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
56.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
57.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.

58.	(search* adj4 literature).ab.
59.	(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.
60.	cochrane.jw.
61.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
62.	or/52-61
63.	43 and (51 or 62)

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.	(culprit or non-culprit or nonculprit).ti,ab.

37.	((infarct-related or infarct related or non-infarct-related) adj2 (artery or arteries)).ti,ab.
38.	(complete adj2 revasc*).ti,ab.
39.	((multi-vessel* or multi-vessel* or single-vessel*) adj3 (percutaneous coronary intervention* or PCI or PPCI or PTCA or stent* or revasc* or recanali* or angioplast*)).ti,ab.
40.	or/36-39
41.	35 and 40
42.	random*.ti,ab.
43.	factorial*.ti,ab.
44.	(crossover* or cross over*).ti,ab.
45.	((doubl* or singl*) adj blind*).ti,ab.
46.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
47.	crossover procedure/
48.	single blind procedure/
49.	randomized controlled trial/
50.	double blind procedure/
51.	or/42-50
52.	systematic review/
53.	meta-analysis/
54.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
55.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
56.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
57.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
58.	(search* adj4 literature).ab.
59.	(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.
60.	((pool* or combined) adj2 (data or trials or studies or results)).ab.
61.	cochrane.jw.
62.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
63.	or/52-62
64.	41 and (51 or 63)

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:ti,ab
#19.	(subendocardial near/3 infarct*):ti,ab
#20.	((unstable or variant) near/2 angina*):ti,ab
#21.	(unstable near/2 coronary):ti,ab
#22.	(or #6-#21)
#23.	(culprit or non-culprit or nonculprit):ti,ab
#24.	((infarct-related or infarct related or non-infarct-related) near/2 (artery or arteries)):ti,ab
#25.	(complete near/2 revasc*):ti,ab
#26.	((multi-vessel* or multi-vessel* or single-vessel*) near/3 (percutaneous coronary intervention* or PCI or PPCI or PTCA or stent* or revasc* or recanali* or angioplast*)):ti,ab
#27.	(or #23-#26)
#28.	#22 and #27

B.2 Health Economics literature search strategy

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

Table 11: Database date parameters and filters used

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

Medline (Ovid) search terms

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

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

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

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

Embase (Ovid) search terms

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

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

52.	angiocardiography/
53.	coronary angiography/
54.	Angiograph*.ti.
55.	Arteriograph*.ti.
56.	Angiocardiograph*.ti,ab.
57.	Coronary Angiograph*.ti,ab.
58.	Angiogram*.ti,ab.
59.	Cardioangiograph*.ti,ab.
60.	Angiocardiogram.ti,ab.
61.	Angio Cardiograph*.ti,ab.
62.	Coronary Arteriogra*.ti,ab.
63.	Coronarograph*.ti,ab.
64.	*heart muscle revascularization/
65.	transluminal coronary angioplasty/
66.	(Myocardial adj revasculari?ation).ti,ab.
67.	PCI.ti,ab.
68.	Percutaneous coronary intervention.ti,ab.
69.	Percutaneous Transluminal Coronary Angioplasty.ti,ab.
70.	PTCA.ti,ab.
71.	*angioplasty/
72.	Blunt microdissection.ti,ab.
73.	((laser or patch) adj angioplasty).ti,ab.
74.	Percutaneous Transluminal Angioplasty.ti,ab.
75.	Transluminal Coronary Angioplasty.ti,ab.
76.	(Balloon adj3 coronary).ti,ab.
77.	(Balloon adj3 angioplasty).ti,ab.
78.	exp STENTS/
79.	stent*.ti,ab.
80.	Or/51-79
81.	acetylsalicylic acid/
82.	(aspirin or acetylsalicylic acid).ti,ab.
83.	(clopidogrel or plavix).ti,ab.
84.	(ticagrelor or brilique).ti,ab.
85.	(prasugrel or efient or effient or prasita).ti,ab.
86.	prasugrel/
87.	antithrombocytic agent/
88.	(Glycoproteins IIb-IIIa or GPIIb-IIIa Receptors or Integrin alpha-IIb beta-3 or Integrin alphaIIbbeta3 or GPIIB IIIA).ti,ab.
89.	exp fibrinogen receptor/
90.	(Abciximab or Reopro or Eptifibatide or Integrelin or Integrilin or Intrifiban or Tirofiban or Aggrastat).ti,ab.

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

NHS EED and HTA (CRD) search terms

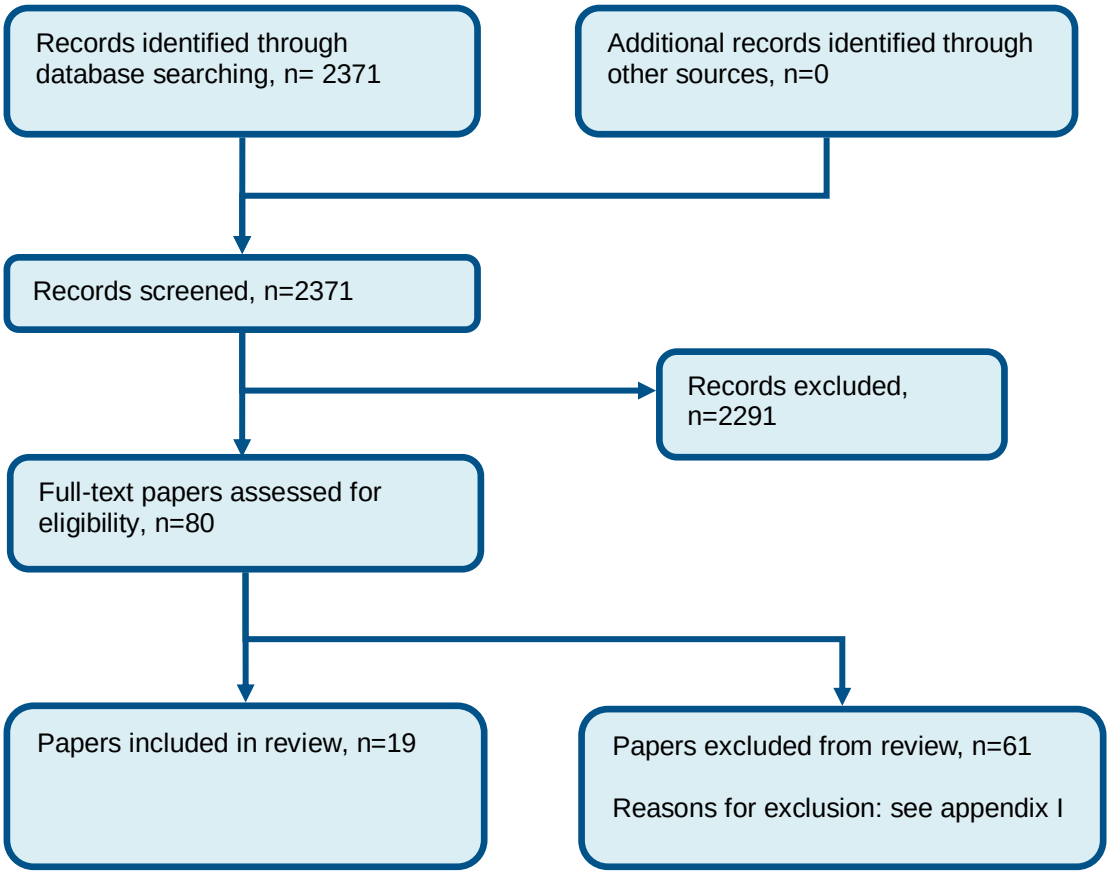
#1.	MeSH DESCRIPTOR Acute Coronary Syndrome
#2.	(MeSH DESCRIPTOR angina pectoris)
#3.	(MeSH DESCRIPTOR Angina, Unstable)
#4.	(MeSH DESCRIPTOR Coronary Thrombosis)
#5.	MeSH DESCRIPTOR Myocardial Infarction EXPLODE ALL TREES
#6.	#1 OR #2 OR #3 OR #4 OR #5
#7.	(MeSH DESCRIPTOR Heart Arrest)
#8.	((acute coronary adj2 syndrome*))
#9.	(((myocardial or heart) adj infarct*))
#10.	((heart adj (attack* or event*)))
#11.	(((heart or cardiac) adj arrest*))
#12.	((coronary adj2 thrombos*))
#13.	((stemi or st-segment or st segment or st-elevation or st elevation))
#14.	("non-ST-segment elevation")
#15.	((non-STEMI or NSTEMI or nonSTEMI))
#16.	("Q wave myocardial infarction")
#17.	("non Q wave MI")
#18.	(NSTE-ACS)
#19.	(STE-ACS)
#20.	(((subendocardial adj3 infarct*)))

#21.	((((unstable or variant) adj2 angina*)))
#22.	(((unstable adj2 coronary)))
#23.	(#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22)
#24.	(MeSH DESCRIPTOR Angiography)
#25.	(MeSH DESCRIPTOR Angiocardiography)
#26.	((MeSH DESCRIPTOR Coronary Angiography))
#27.	((Angiograph*))
#28.	((Arteriograph*))
#29.	((Angiocardiograph*))
#30.	((Coronary Angiograph*))
#31.	((Angiogram*))
#32.	((Cardioangiograph*))
#33.	((Angiocardiogram))
#34.	((Angio Cardiograph*))
#35.	((Coronary Arteriogra*))
#36.	((Coronarograph*))
#37.	(MeSH DESCRIPTOR Myocardial Revascularization)
#38.	(MeSH DESCRIPTOR Angioplasty, Balloon, Coronary)
#39.	(((Myocardial adj revasculari?ation)))
#40.	((PCI))
#41.	((Percutaneous coronary intervention))
#42.	((Percutaneous Transluminal Coronary Angioplasty))
#43.	((PTCA))
#44.	(MeSH DESCRIPTOR Angioplasty EXPLODE ALL TREES)
#45.	((Blunt microdissection))
#46.	((((laser or patch) adj angioplasty)))
#47.	((Percutaneous Transluminal Angioplasty))
#48.	((Transluminal Coronary Angioplasty))
#49.	(((Balloon adj3 coronary)))
#50.	((Balloon adj3 angioplasty))
#51.	(MeSH DESCRIPTOR Stents EXPLODE ALL TREES)
#52.	((stent*))
#53.	(#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52)
#54.	(MeSH DESCRIPTOR Aspirin)
#55.	((aspirin or acetylsalicylic acid))
#56.	((clopidogrel or plavix))
#57.	((ticagrelor or brilique))
#58.	((prasugrel or efient or effient or prasita))
#59.	MeSH DESCRIPTOR Prasugrel Hydrochloride
#60.	MeSH DESCRIPTOR Platelet Aggregation Inhibitors
#61.	((Glycoproteins IIb-IIIa or GPIIb-IIIa Receptors or Integrin alpha-IIb beta-3 or Integrin alphaIIbbeta3 or GPIIB IIIA))
#62.	MeSH DESCRIPTOR Platelet Glycoprotein GPIIb-IIIa Complex EXPLODE ALL TREES

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

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of Culprit only versus multi-vessel PPCI in people with STEMI



Appendix D: Clinical evidence tables

Study	COMPARE-ACUTE trial: Smits 2017[76]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=885)
Countries and setting	Conducted in Czech Republic, Germany, Hungary, Netherlands, Poland, Singapore, Sweden; Setting: Hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall:
Subgroup analysis within study	Not applicable
Inclusion criteria	People 18 through 85 years of age who presented with STEMI within 12 hours after symptom onset and who had an indication for primary PCI were eligible for enrolment if the non–infarct-related coronary arteries (or their major side branches of at least 2.0 mm in diameter) showed lesions with stenosis of 50% or more according to quantitative coronary angiography or visual assessment and were determined to be appropriate candidates for PCI by the interventional cardiologist (who performed the PCI). Non–infarct-related coronary artery lesions were those identified as not being responsible for the acute myocardial infarction on the basis of their appearance on electrocardiography (ECG) and angiography.
Exclusion criteria	The most important criteria for study exclusion were left main coronary artery disease, chronic total occlusion, severe stenosis, with a Thrombolysis in Myocardial Infarction (TIMI) flow grade of 2 or less in the non–infarct-related coronary artery, a suboptimal result or complications after treatment of an infarct-related coronary artery, severe valve dysfunction, and Killip class III or IV
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Complete: 62 (10); culprit: 61 (10). Gender (M:F): 683/202. Ethnicity: Not reported
Further population details	1. Age: Not stated / Unclear (Mixed, mean age 61.5 years). 2. Gender: Not stated / Unclear (Mixed, not reported separately). 3. People with diabetes : Not stated / Unclear (Mixed, 15% with diabetes). 4. Timing of complete revascularisation: as part of index procedure (83.4% during index procedure).
Indirectness of population	No indirectness

Interventions	(n=590) Intervention 1: Culprit vessel only PPCI - During the index procedure. In patients receiving infarct-related-artery treatment only (the infarct-artery-only group), the procedure was stopped after FFR measurements were obtained. Each patient was referred to his or her treating cardiologist. Both the patient and the treating cardiologist were unaware of the findings on FFR but were aware of the angiography. A management plan based on current practice guidelines was recommended, but further investigations and management of care were carried out at the discretion of the treating cardiologist. Thus, the treating cardiologist could decide whether revascularization of non–infarct-related coronary arteries was needed on the basis of tests conducted to detect ischemia, symptoms, or clinical judgment. Elective, clinically indicated revascularizations performed within 45 days after the primary intervention were not counted as events, in accordance with the protocol. Urgent revascularizations performed within 45 days or further revascularizations performed thereafter were counted as events. Additional patient care, including the implementation of anticoagulant and antithrombotic regimens, was performed in accordance with contemporary guidelines.. Duration N/A. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=295) Intervention 2: Multi-vessel PPCI - During index procedure. In the complete-revascularization group, FFR measurements were used to guide the decision as to whether percutaneous revascularization was appropriate. In the case of non–infarct-related coronary arteries with flow-limiting lesions (FFR, ≤0.80), PCI — preferably with everolimus-eluting stents — was performed, generally during the same intervention; this step could be delayed at the operator's discretion (e.g., for complex lesions or logistical problems) but had to be performed during the index hospitalization and preferably within 72 hours. Duration N/A. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Academic or government funding (Supported by Maasstad Cardiovascular Research, which received unconditional grants from Abbott Vascular and St. Jude Medical)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DURING THE INDEX PROCEDURE (CULPRIT) versus DURING INDEX PROCEDURE (MULTI)

Protocol outcome 1: All-cause mortality at at 1 year
- Actual outcome: All-cause mortality at 1 year; Group 1: 10/590, Group 2: 4/295
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Cardiovascular mortality at at 1 year
- Actual outcome: Cardiovascular mortality at 1 year; Group 1: 6/590, Group 2: 3/295
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: All (fatal and non-fatal) myocardial reinfarction at at 1 year - Actual outcome: Myocardial infarction at 1 year; Group 1: 28/590, Group 2: 7/295 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Unplanned revascularisation at at 1 year - Actual outcome: Revascularisation at 1 year; Group 1: 103/590, Group 2: 18/295 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Complications related to bleeding including haemorrhagic stroke at up to 30 days - Actual outcome: Major bleeding at 1 year; Group 1: 8/590, Group 2: 3/295 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Any bleeding at 48 hours; Group 1: 8/590, Group 2: 5/295 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Any bleeding at 12 months; Group 1: 28/590, Group 2: 9/295 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - 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 ; Hospitalisation ; All-cause mortality at at 30 days; Cardiovascular mortality at at 30 days; All (fatal and non-fatal) myocardial reinfarction at at 30 days; Non-fatal myocardial reinfarction at at 30 days; Non-fatal myocardial reinfarction at at 1 year; Stroke - any type at at 1 year; Contrast-induced nephropathy ; Hospitalisation for heart failure at at 1 year; Length of stay

Study	COMPLETE trial: Mehta 2019[63]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=4041)
Countries and setting	Conducted in Brazil, Canada, France, Italy, Serbia, United Kingdom, USA; Setting: Hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Eligible patients were required to have multi-vessel coronary artery disease, defined as the presence of at least one angiographically significant non–infarct-related (nonculprit) lesion that was amenable to successful treatment with PCI and was located in a vessel with a diameter of at least 2.5 mm that was not stented as part of the index culprit-lesion PCI. Nonculprit lesions were deemed angiographically significant if they were associated with at least 70% stenosis of the vessel diameter on visual estimation or with 50 to 69% stenosis accompanied by a fractional flow reserve (FFR) measurement of 0.80 or less
Exclusion criteria	The main exclusion criteria were an intention before randomization to revascularize a nonculprit lesion, a planned surgical revascularization, or previous coronary-artery bypass grafting surgery.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Complete: 61.6±10.7; culprit: 62.4±10.7. Gender (M:F): 3325/716. Ethnicity: Not reported
Further population details	1. Age: Not stated / Unclear (Mixed, mean age 62). 2. Gender: Not stated / Unclear (Mixed). 3. People with diabetes : Not stated / Unclear (19% had diabetes). 4. Timing of complete revascularisation: Not stated / Unclear (PCI during a procedure separate from the index procedure. Procedure could be during index hospitalisation or after discharge (but no more than 45 days)).
Indirectness of population	No indirectness
Interventions	(n=2025) Intervention 1: Culprit vessel only PPCI - During the index procedure. Patients who were randomly assigned to the culprit-lesion-only PCI strategy received guideline-based medical therapy with no further revascularization, regardless of whether there was evidence of ischemia on noninvasive testing.. Duration N/A. Concurrent medication/care: Guideline-based medical therapy was recommended in both treatment groups. Dual antiplatelet therapy with aspirin and ticagrelor for at least 1 year was recommended. Beyond 1 year, aspirin was recommended for all patients, and ticagrelor (60 mg twice daily) was recommended for patients who were not at high risk for bleeding. High-dose statin therapy, angiotensin-converting–enzyme inhibitors or angiotensin-receptor blockers, mineralocorticoid-receptor antagonists, and beta-blockers were

	recommended.. Indirectness: No indirectness (n=2016) Intervention 2: Multi-vessel PPCI - Staged. Patients who were randomly assigned to the complete-revascularization strategy were to have routine staged PCI (i.e., PCI during a procedure separate from the index PCI procedure for STEMI) of all suitable nonculprit lesions, regardless of whether there were clinical symptoms or there was evidence of ischemia. Investigators specified before randomization whether they intended to perform nonculprit-lesion PCI during the index hospitalization or after hospital discharge (no later than 45 days after randomization). Everolimus-eluting stents were strongly recommended for all PCI procedures. It was recommended that PCI of chronic total occlusions be attempted only by operators who had experience in treating chronic total occlusions and only when there was a high likelihood of successful PCI.. Duration N/A. Concurrent medication/care: Guideline-based medical therapy was recommended in both treatment groups. Dual antiplatelet therapy with aspirin and ticagrelor for at least 1 year was recommended. Beyond 1 year, aspirin was recommended for all patients, and ticagrelor (60 mg twice daily) was recommended for patients who were not at high risk for bleeding. High-dose statin therapy, angiotensin-converting–enzyme inhibitors or angiotensin-receptor blockers, mineralocorticoid-receptor antagonists, and beta-blockers were recommended.. Indirectness: No indirectness
Funding	Academic or government funding (Canadian Institutes of Health Research)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DURING THE INDEX PROCEDURE (CULPRIT) versus STAGED (MULTI)

Protocol outcome 1: All-cause mortality at at 1 year
- Actual outcome: All-cause mortality at Mean 3 years; Group 1: 106/2015, Group 2: 96/2016
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Cardiovascular mortality at at 1 year
- Actual outcome: Cardiovascular mortality at Mean 3 years; Group 1: 64/2025, Group 2: 59/2016
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: All (fatal and non-fatal) myocardial reinfarction at at 1 year
- Actual outcome: Myocardial infarction at Mean 3 years; Group 1: 160/2015, Group 2: 109/2016
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Stroke - any type at at 1 year

- Actual outcome: Stroke at Mean 3 years; Group 1: 29/2025, Group 2: 38/2016 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Unplanned revascularisation at at 1 year - Actual outcome: Ischemia driven revascularisation at Mean 3 years; Group 1: 160/2015, Group 2: 29/2016 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: Complications related to bleeding including haemorrhagic stroke at up to 30 days - Actual outcome: Major bleeding at Mean 3 years; Group 1: 44/2025, Group 2: 58/2016 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - 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 ; Hospitalisation ; All-cause mortality at at 30 days; Cardiovascular mortality at at 30 days; All (fatal and non-fatal) myocardial reinfarction at at 30 days; Non-fatal myocardial reinfarction at at 30 days; Non-fatal myocardial reinfarction at at 1 year; Contrast-induced nephropathy ; Hospitalisation for heart failure at at 1 year; Length of stay

Study (subsidiary papers)	CvLPRIT trial: Gershlick 2015[32] (Kelion 2015[45], Kelly 2013[46], Mccann 2015[62])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=296)
Countries and setting	Conducted in United Kingdom; Setting: 7 U.K. interventional centres
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ECG
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Suspected or proven acute myocardial infarction; Significant ST elevation or left bundle branch block (LBBB) on ECG (in cases of LBBB, angiographic confirmation of IRA occlusion is required); < 12 hrs of symptom onset; scheduled for Primary PCI for clinical reasons; provision of verbal assent followed by written informed consent; multi-vessel coronary artery disease at angiography defined as: Infarct related artery (IRA) plus at least one non-infarct related epicardial artery (N-IRA) with at least one lesion deemed angiographically significant (>70% diameter stenosis in one plane or > 50% in 2 planes). The N-IRA should be a major (>2mm) epicardial coronary artery or branch (>2mm) and be suitable for stent implantation.
Exclusion criteria	Any exclusion criteria for P-PCI; <18 years; clear indication for, or contraindication to, multi vessel P-PCI according to operator judgement; previous Q wave myocardial infarction; patients with prior CABG; Cardiogenic Shock; VSD or moderate/severe mitral regurgitation; Chronic kidney disease (Cr>200µmol/l or eGFR<30ml/min/1.73m2); Suspected or confirmed thrombosis of a previously stented artery; where the only significant N-IRA lesion is a chronic total occlusion
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Multi-vessel PCI group: 64.6±11.2; culprit only PCI group: 65.3±11.9. Gender (M:F): 240/56. Ethnicity: Not reported
Further population details	1. Age: Not stated / Unclear (Mixed). 2. Gender: Not stated / Unclear (Mixed). 3. People with diabetes : Not stated / Unclear (Mixed (<150%)). 4. Timing of complete revascularisation: Not stated / Unclear (Mixed though complete revascularization was recommended at the same sitting).
Indirectness of population	No indirectness
Interventions	(n=146) Intervention 1: Culprit vessel only PPCI - During the index procedure. P-PCI was undertaken according to current guideline recommendations and operators' routine practice and could include aspiration thrombectomy, heparin, bivalirudin, or glycoprotein IIb/IIIa inhibitor. To reduce risk of in-stent restenosis,

	unless clinically contraindicated, drug-eluting stents (DES) were recommended. . Duration N/A. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=150) Intervention 2: Multi-vessel PPCI - During index procedure. As above. For complete revascularization, it was mandated that the IRA be treated first. If there were no clinical contraindications, complete revascularization was recommended at the same sitting to reduce multiple vascular punctures, avoid prolonged hospitalization, and attenuate potential patient dropout. If the operator decided for clinical reasons that the procedure be staged, it was mandated that the N-IRA be treated during the index admission.. Duration N/A. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Academic or government funding (The British Heart Foundation, support from the National Institute of Health Research and the Medical Research Council)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DURING THE INDEX PROCEDURE (CULPRIT VESSEL) versus DURING INDEX PROCEDURE (MULTI-VESSEL)

Protocol outcome 1: All-cause mortality at at 1 year
- Actual outcome: All-cause mortality at 1 year; Group 1: 10/146, Group 2: 4/150
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Cardiovascular mortality at at 1 year
- Actual outcome: Cardiovascular mortality at 1 year; Group 1: 7/146, Group 2: 2/150
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: All (fatal and non-fatal) myocardial reinfarction at at 1 year
- Actual outcome: Myocardial infarction at 1 year; Group 1: 4/146, Group 2: 2/150
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Stroke - any type at at 1 year
- Actual outcome: Stroke at 1 year; Group 1: 2/146, Group 2: 2/150
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Contrast-induced nephropathy
- Actual outcome: contrast induced neuropathy at 1 year; Group 1: 2/146, Group 2: 2/150

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: Unplanned revascularisation at at 1 year - Actual outcome: Repeat revascularisation at 1 year; Group 1: 16/146, Group 2: 8/150 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 7: Complications related to bleeding including haemorrhagic stroke at up to 30 days - Actual outcome: Major bleed at 1 year; Group 1: 7/146, Group 2: 4/150 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - 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 ; Hospitalisation ; All-cause mortality at at 30 days; Cardiovascular mortality at at 30 days; All (fatal and non-fatal) myocardial reinfarction at at 30 days; Non-fatal myocardial reinfarction at at 30 days; Non-fatal myocardial reinfarction at at 1 year; Hospitalisation for heart failure at at 1 year; Length of stay

Study	Dambrink 2010[19]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=121)
Countries and setting	Conducted in Netherlands; Setting: Single tertiary referral centre
Line of therapy	1st line
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients with multi-vessel disease who underwent successful primary angioplasty for STEMI
Exclusion criteria	urgent indication for additional revascularisation, aged > 80 years, chronic occlusion of 1 of the non-culprit artery(ies), prior CABG, left main stenosis of ≥ 50%, restenotic lesions in non-culprit artery(ies), chronic atrial fibrillation, limited life-expectancy, or other factors that made complete follow-up unlikely
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Culprit only group: 61 (11); multi-vessel group: 62 (10). Gender (M:F): 97/24. Ethnicity: Not reported
Further population details	1. Age: Not stated / Unclear (Mixed). 2. Gender: Not stated / Unclear (Mixed). 3. People with diabetes : Not stated / Unclear (Mixed (5.65%)). 4. Timing of complete revascularisation: during index hospitalisation
Indirectness of population	No indirectness
Interventions	(n=41) Intervention 1: Culprit vessel only PPCI - During the index procedure. Successful PCI was defined as a residual diameter stenosis of <50% and TIMI 3 flow. Further treatment after primary PCI was left to the treating physician. Aggressive revascularisation without symptoms was discouraged. If symptoms did occur, a strategy of ischaemia guided additional revascularisation was followed. Exercise testing, dobutamine stress echocardiography or myocardial scintigraphy were considered acceptable means to demonstrate ischaemia . Duration N/A. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=80) Intervention 2: Multi-vessel PPCI - Staged. staged intervention on significant stenotic non-culprit lesions compatible with ischaemia (FFR < 0.75) with plain angioplasty, BMS, or DES. Duration N/A. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Study funded by industry (Partly funded by an unrestricted grant from RADI Medical Systems AB, Uppsala, Sweden)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DURING THE INDEX PROCEDURE (CULPRIT) versus STAGED (MULTI)

Protocol outcome 1: All-cause mortality at at 1 year
- Actual outcome: Death at 6 months; Group 1: 0/41, Group 2: 2/80
Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow-up; Baseline details: Difference in hypertensive participants (26.3% vs 42.5%); Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: All (fatal and non-fatal) myocardial reinfarction at at 1 year
- Actual outcome: Myocardial infarction at 6 months; Group 1: 0/41, Group 2: 11/80
Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow-up, unclear if fatal or non-fatal; Baseline details: Difference in hypertensive participants (26.3% vs 42.5%); Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Complications related to bleeding including haemorrhagic stroke at up to 30 days
- Actual outcome: Major bleeding at Unclear; Group 1: 1/41, Group 2: 5/80
Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in hypertensive participants (26.3% vs 42.5%); Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; All-cause mortality at at 30 days; Cardiovascular mortality at at 30 days; Cardiovascular mortality at at 1 year ; All (fatal and non-fatal) myocardial reinfarction at at 30 days; Non-fatal myocardial reinfarction at at 30 days; Non-fatal myocardial reinfarction at at 1 year; Stroke - any type at at 1 year; Contrast-induced nephropathy ; Hospitalisation for heart failure at at 1 year; Unplanned revascularisation at at 1 year; Length of stay

Study (subsidiary papers)	DANAMI-3—PRIMULTI trial: Engstrøm 2015[27] (Høfsten 2015[39], Sadjadieh 2016[75])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=627)
Countries and setting	Conducted in Denmark; Setting: Four large primary PCI centres
Line of therapy	1st line
Duration of study	Intervention + follow up: Within 2 days + minimum 1 year
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Individuals presenting with chest pain of less than 12 h duration and ST-segment elevation greater than 0·1 mV in at least two contiguous leads. After successful treatment of the culprit lesion in the infarct-related artery, those with angiographic diameter stenosis of greater than 50% in one or more non-infarct-related arteries were asked to participate
Exclusion criteria	Intolerance of contrast media or of relevant anticoagulant or antithrombotic drugs, unconsciousness or cardiogenic shock, stent thrombosis, indication for coronary-artery bypass grafting, or increased bleeding risk
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Median (range): Culprit only group: 63 (34–92); complete revascularisation group: 64 (37–94) . Gender (M:F): 506/121. Ethnicity: Not reported
Further population details	1. Age: Not stated / Unclear (Mixed). 2. Gender: Not stated / Unclear (Mixed). 3. People with diabetes : Not stated / Unclear (Mixed (11.3%)). 4. Timing of complete revascularisation: during index hospitalisation
Indirectness of population	No indirectness
Interventions	(n=313) Intervention 1: Culprit vessel only PPCI - During the index procedure. PCI was done with a deferred strategy of stent implantation or mechanical postconditioning versus conventional treatment consisting of conventional primary PCI. The culprit lesion in the infarct-related artery was defined as a thrombolysis in myocardial infarction [TIMI] flow of 2–3 and residual stenosis <30%.. Duration N/a. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=314) Intervention 2: Multi-vessel PPCI - Staged. FFR-guided complete revascularisation involved additional PCI procedures, preferably with everolimus-eluting stents because they are proven safe and efficient. This occurred 2 days after the initial PCI procedure before discharge, according to local routines. Complete revascularisation was defined as revascularisation of all coronary lesions not related to the initial

	infarct-related artery with a greater than 50% diameter stenosis in coronary artery branches of 2 mm or larger in diameter. FFR values were calculated across the lesions by intravenous adenosine infusion; FFR values of 0·80 or lower were classed as significant and treated those lesions, in addition to visually estimated stenoses greater than 90%. In patients with lesions deemed unsuitable for treatment with PCI (eg, chronic total occlusions of long duration, heavy calcification, or extreme tortuosity), coronary-artery bypass surgery was considered. Duration N/a. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Academic or government funding (Danish Agency for Science, Technology and Innovation and the Danish Council for Strategic Research)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DURING THE INDEX PROCEDURE (CULPRIT) versus STAGED (MULTI)

Protocol outcome 1: All-cause mortality at at 30 days
- Actual outcome: All cause mortality at 3 days; Group 1: 1/313, Group 2: 0/314
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: All-cause mortality at at 1 year
- Actual outcome: All cause mortality at Median 27 months; Group 1: 11/313, Group 2: 15/314
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Cardiovascular mortality at at 1 year
- Actual outcome: Cardiac death at Median 27 months; Group 1: 9/313, Group 2: 5/314
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: All (fatal and non-fatal) myocardial reinfarction at at 30 days
- Actual outcome: Reinfarction at 3 days;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Non-fatal myocardial reinfarction at at 1 year
- Actual outcome: Non fatal reinfarction at Median 27 months; Group 1: 16/313, Group 2: 15/314
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up; Group 1 Number missing: ; Group 2 Number missing:

	Protocol outcome 6: Stroke - any type at at 1 year - Actual outcome: Stroke at Median 27 months; Group 1: 1/313, Group 2: 4/314 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 7: Contrast-induced nephropathy - Actual outcome: Contrast induced neuropathy at Median 27 months; Group 1: 7/313, Group 2: 6/314 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 8: Unplanned revascularisation at at 1 year - Actual outcome: Ischemia driven revascularisation at Median 27 months; Group 1: 52/313, Group 2: 17/314 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 9: Complications related to bleeding including haemorrhagic stroke at up to 30 days - Actual outcome: Bleeding requiring transfusion or surgery at Median 27 months; Group 1: 4/313, Group 2: 1/314 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: TIMI bleeding during admission (major + minor) at Median 5 days; Group 1: 7/313, Group 2: 6/314 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: TIMI bleeding during admission (minimal + medical attention) at Median 5 days; Group 1: 155/313, Group 2: 193/314 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: BARC bleeding during admission (BARC 3 + BARC 5) at Median 5 days; Group 1: 11/313, Group 2: 8/314 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: BARC bleeding during admission (BARC 1 + BARC 2) at Median 5 days; Group 1: 150/313, Group 2: 191/314 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - 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 ; Hospitalisation ; Cardiovascular mortality at at 30 days; All (fatal and non-fatal) myocardial reinfarction at at 1 year; Non-fatal myocardial reinfarction at at 30 days; Hospitalisation for heart failure at at 1 year; Length of stay

Study	Hamza 2016[35]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in USA
Line of therapy	1st line
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: electrocardiographic confirmation
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	diabetic patients with diagnosis of acute ST elevation myocardial infarction presenting within 12 hours of symptom and planned primary PCI
Exclusion criteria	Define
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Culprit only group: 52.2 (10.6); complete revascularisation group: 56.4 (11.5). Gender (M:F): 84/16. Ethnicity: Not reported
Further population details	1. Age: Not stated / Unclear (Mixed). 2. Gender: Not stated / Unclear (Mixed). 3. People with diabetes : with diabetes 4. Timing of complete revascularisation: as part of index procedure
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Culprit vessel only PPCI - During the index procedure. Primary PCI was undertaken according to current guideline recommendations and opterators' routine practice and could include aspiration thrombectomy, heparin, or glycoprotein IIb/IIIa inhibitor unless clinically contraindicated. Drug eluting stents were used. Duration N/A. Concurrent medication/care: Patients were pretreated with oral antiplatlets. Indirectness: No indirectness (n=50) Intervention 2: Culprit vessel only PPCI - During the index procedure. The IRA was treated first. Complete revascularisation was recommended at the same sitting to reduce multiple vascular punctures and avoid prolonged hospitalisation. Duration N/A. Concurrent medication/care: Patients were pretreated with oral antiplatlets. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DURING THE INDEX PROCEDURE (CULPRIT) versus DURING THE	

INDEX PROCEDURE (MULTI) Protocol outcome 1: All-cause mortality at 1 year - Actual outcome: Mortality at 6 months; Group 1: 4/50, Group 2: 1/50 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: All (fatal and non-fatal) myocardial reinfarction at 1 year - Actual outcome: Recurrent MI at 6 months; Group 1: 2/50, Group 2: 1/50 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up, unclear if fatal or non-fatal; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Stroke - any type at 1 year - Actual outcome: Stroke at 6 months; Group 1: 1/50, Group 2: 0/50 Risk of bias: All domain - ; Indirectness of outcome: Serious indirectness, Comments: Length of follow up Protocol outcome 4: Contrast-induced nephropathy - Actual outcome: Contrast nephropathy at 6 months; Group 1: 1/50, Group 2: 3/50 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Unplanned revascularisation at 1 year - Actual outcome: Repeat revascularisation at 6 months; Group 1: 6/50, Group 2: 1/50 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: Complications related to bleeding including haemorrhagic stroke at up to 30 days - Actual outcome: Minor bleeding at 6 months; Group 1: 1/50, Group 2: 2/50 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Major bleeding at 6 months; Group 1: 0/50, Group 2: 0/50 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; All-cause mortality at at 30 days; Cardiovascular mortality at at 30 days; Cardiovascular mortality at at 1 year ; All (fatal and non-fatal) myocardial reinfarction at at 30 days; Non-

fatal myocardial reinfarction at at 30 days; Non-fatal myocardial reinfarction at at 1 year; Hospitalisation for heart failure at at 1 year; Length of stay	

Study	HELP AMI trial: Di Mario 2004[22]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=69)
Countries and setting	Conducted in Italy; Setting: Multicentre
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 month follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnostic coronary arteriography
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Ischaemic chest pain started < 12 hours before hospital admission with or without ST-segment elevation of ≥1 mmin ≥2 contiguous electrocardiographic leads (peripheral leads) or 2 mm in the precordial leads. MVD amenable to angioplasty of at least 2 lesions (culprit artery and ≥ 1 (maximum 3) lesions in a major non-culprit coronary artery(ies))
Exclusion criteria	Presence of significant lesions in vein grafts or arterial conduits or in segments previously treated with angioplasty or stent, recent thrombolysis (< 1 week) , cardiogenic shock, defined as hypotension with systolic blood pressure < 90 mmHg and tachycardia > 100 beats/minute, not due to hypovolaemia or requiring inotropic support or balloon counter pulsation. Single-vessel disease, left main stenosis of ≥ 50%, intention to treat > 1 totally occluded major epicardial vessel, diffuse calcification or severe tortuosity in the culprit and non-culprit arteries preventing the implantation of the study stents. A sided branch > 2 mm which required being covered by the stent, unless the operator was willing and technically able to maintain patency of this side branch with either further balloon angioplasty or stent placement
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Culprit only group 65.3 (7.4); complete group 63.5 (12.4). Gender (M:F): 60/9. Ethnicity: Not reported
Further population details	1. Age: Not stated / Unclear (Mixed). 2. Gender: Not stated / Unclear (Mixed). 3. People with diabetes : Not stated / Unclear (26.2% had diabetes). 4. Timing of complete revascularisation: as part of index procedure
Indirectness of population	No indirectness
Interventions	(n=17) Intervention 1: Culprit vessel only PPCI - During the index procedure. Culprit lesion treatment (primary angioplasty). Patients were stented using one or more heparin coated Bx Velocity stents. Noncompliant balloons were used it required. Sequent interventions on the non-culprit lesions were performed at the investigators discretion. Duration N/A. Concurrent medication/care: Elective abciximab was highly encouraged but left to the operator's discretion. Indirectness: No indirectness

	(n=52) Intervention 2: Multi-vessel PPCI - During index procedure. Immediate multi-vessel treatment, completed with revascularisation of all suitable lesions, with the use of heparin coated Bx velocity stents. Duration N/A. Concurrent medication/care: Elective abciximab was highly encouraged but left to the operator's discretion. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DURING THE INDEX PROCEDURE (CULPRIT) versus DURING INDEX PROCEDURE (MULTI) Protocol outcome 1: All-cause mortality at 1 year - Actual outcome: Death at 1 year; Group 1: 0/17, Group 2: 1/52 Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Pre-CABG (9.6% vs 23.5%), smoking history (81% vs 66.6%), hypertension (58.8% vs 36.5%); Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: All (fatal and non-fatal) myocardial reinfarction at 1 year - Actual outcome: Myocardial Infarction at 1 year; Group 1: 1/17, Group 2: 1/52 Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Pre-CABG (9.6% vs 23.5%), smoking history (81% vs 66.6%), hypertension (58.8% vs 36.5%); Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; All-cause mortality at at 30 days; Cardiovascular mortality at at 30 days; Cardiovascular mortality at at 1 year ; All (fatal and non-fatal) myocardial reinfarction at at 30 days; Non-fatal myocardial reinfarction at at 30 days; Non-fatal myocardial reinfarction at at 1 year; Stroke - any type at at 1 year; Contrast-induced nephropathy ; Hospitalisation for heart failure at at 1 year; Unplanned revascularisation at at 1 year; Complications related to bleeding including haemorrhagic stroke at up to 30 days ; Length of stay

Study (subsidiary papers)	Politi 2010[72] (Politi 2009[71], Politi 2014[73])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=214)
Countries and setting	Conducted in Italy
Line of therapy	1st line
Duration of study	Follow up (post intervention): Mean 2.5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with the presence of prolonged (more than 30 minutes) chest pain, started less than 12 h before hospital arrival and ST elevation of at least 1 mm in two or more contiguous limb electrocardiographic leads or 2 mm in precordial leads.
Exclusion criteria	Patients with cardiogenic shock at presentation (systolic blood pressure #90 mm Hg despite drug therapy), left main coronary disease ($50% diameter stenosis), previous coronary artery bypass grafting (CABG) surgery, severe valvular heart disease and unsuccessful procedures
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Culprit only group: 66.5 (13.2); staged group: 64.1 (11.1); complete revascularization group: 64.5 (11.7). Gender (M:F): 166/48. Ethnicity: Not reported
Further population details	1. Age: Not stated / Unclear (Mixed). 2. Gender: Not stated / Unclear (Mixed). 3. People with diabetes : Not stated / Unclear (Mixed (19%)). 4. Timing of complete revascularisation: Not stated / Unclear (Both (separate groups)).
Indirectness of population	No indirectness
Interventions	(n=84) Intervention 1: Culprit vessel only PPCI - During the index procedure. The IRA only was dilated and the other arteries were left untreated. Duration N/A. Concurrent medication/care: Before the procedure patients were treated with aspirin, unfractioned heparin and abciximab bolus followed by 12 h infusion. In addition, the protocol included a bolus of N-acetylcysteine 1200 mg and hydration with saline for12 haftercontrastexposureataninfusionrateof1 ml/kgper hour. Iodixanol (Visipaque) was used as contrast media in all patients. Post-PCI medical oral treatment included aspirin, statins and clopidogrel, unless contraindicated, which was recommended for 30 days in case of bare metal stent implantation and for 12 months in case of drug-eluting stents . Indirectness: No indirectness

	(n=65) Intervention 2: Multi-vessel PPCI - During index procedure. the IRA was opened followed by dilatation of other significantly narrowed arteries during the same procedure.. Duration N/A. Concurrent medication/care: Before the procedure patients were treated with aspirin, unfractioned heparin and abciximab bolus followed by 12 h infusion. In addition, the protocol included a bolus of N-acetylcysteine 1200 mg and hydration with saline for12 haftercontrastexposureataninfusionrateof1 ml/kgper hour. Iodixanol (Visipaque) was used as contrast media in all patients. Post-PCI medical oral treatment included aspirin, statins and clopidogrel, unless contraindicated, which was recommended for 30 days in case of bare metal stent implantation and for 12 months in case of drug-eluting stents. Indirectness: No indirectness (n=65) Intervention 3: Multi-vessel PPCI - Staged. The IRA only was treated during the primary intervention while the complete revascularisation was planned in a second procedure.. Duration N/A. Concurrent medication/care: Before the procedure patients were treated with aspirin, unfractioned heparin and abciximab bolus followed by 12 h infusion. In addition, the protocol included a bolus of N-acetylcysteine 1200 mg and hydration with saline for12 haftercontrastexposureataninfusionrateof1 ml/kgper hour. Iodixanol (Visipaque) was used as contrast media in all patients. Post-PCI medical oral treatment included aspirin, statins and clopidogrel, unless contraindicated, which was recommended for 30 days in case of bare metal stent implantation and for 12 months in case of drug-eluting stents. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DURING THE INDEX PROCEDURE (CULPRIT ONLY) versus DURING INDEX PROCEDURE (MULTI COMPLETE)

Protocol outcome 1: All-cause mortality at 1 year
- Actual outcome: Death at Mean 2.5 years; Group 1: 13/84, Group 2: 6/65
Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up; Baseline details: Difference in number of people with diabetes (24% vs 14%); Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Cardiovascular mortality at 1 year
- Actual outcome: Cardiac death at Mean 2.5 years; Group 1: 10/84, Group 2: 4/65
Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up; Baseline details: Difference in number of people with diabetes (24% vs 14%); Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Non-fatal myocardial reinfarction at 1 year
- Actual outcome: Reinfarction at Mean 2.5 years; Group 1: 7/84, Group 2: 2/65
Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up, unclear if fatal or non-fatal; Baseline details: Difference in number of people with diabetes (24% vs 14%); Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Unplanned revascularisation at 1 year - Actual outcome: Repeat revascularisation at Mean 2.5 years; Group 1: 28/84, Group 2: 6/65 Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up, unclear if fatal or non-fatal; Baseline details: Difference in number of people with diabetes (24% vs 14%); Group 1 Number missing: ; Group 2 Number missing: RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DURING THE INDEX PROCEDURE (CULPRIT ONLY) versus STAGED (MULTI) Protocol outcome 1: All-cause mortality at 1 year - Actual outcome: Death at Mean 2.5 years; Group 1: 13/84, Group 2: 4/65 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Cardiovascular mortality at 1 year - Actual outcome: Cardiac death at Mean 2.5 years; Group 1: 10/84, Group 2: 2/65 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Non-fatal myocardial reinfarction at 1 year - Actual outcome: Reinfarction at Mean 2.5 years; Group 1: 7/84, Group 2: 4/65 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up, unclear if fatal or non-fatal; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Unplanned revascularisation at 1 year - Actual outcome: Repeat revascularisation at Mean 2.5 years; Group 1: 28/84, Group 2: 8/65 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up, unclear if fatal or non-fatal; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; All-cause mortality at at 30 days; Cardiovascular mortality at at 30 days; All (fatal and non-fatal) myocardial reinfarction at at 30 days; All (fatal and non-fatal) myocardial reinfarction at at 1 year; Non-fatal myocardial reinfarction at at 30 days; Stroke - any type at at 1 year; Contrast-induced

	nephropathy ; Hospitalisation for heart failure at at 1 year; Complications related to bleeding including haemorrhagic stroke at up to 30 days ; Length of stay

Study (subsidiary papers)	PRAMI trial: Wald 2013[83] (Mangion 2015[59], Mangion 2015[58])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=465)
Countries and setting	Conducted in United Kingdom; Setting: Five centres in the United Kingdom
Line of therapy	1st line
Duration of study	Follow up (post intervention): Mean follow up 23 months
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Participants were deemed to be eligible if the infarct artery had been treated successfully and there was stenosis of 50% or more in one or more coronary arteries other than the infarct artery and the stenosis was deemed to be treatable by PCI. The treating cardiologist had to consider that both infarctartery-only PCI and preventive PCI would be acceptable treatment options.
Exclusion criteria	Participants were ineligible if they were in cardiogenic shock, were unable to provide consent for any other reason, had undergone previous coronary-artery bypass grafting (CABG), had a non-infarct-artery stenosis of 50% or more in the left main stem or the ostia of both the left anterior descending and circumflex arteries (because these are indications for CABG), or if the only noninfarct stenosis was a chronic total occlusion (because it was felt that PCI in such circumstances was contraindicated owing to a low success rate).
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): Preventative PCI group: 62 (32-92); Non-preventative PCI group: 62 (33-90). Gender (M:F): 363/102. Ethnicity: Not reported
Further population details	1. Age: Not stated / Unclear (Mixed). 2. Gender: Not stated / Unclear (Mixed). 3. People with diabetes : Not stated / Unclear (Mixed (17.85%)). 4. Timing of complete revascularisation: as part of index procedure ("immediate preventive PCI").
Indirectness of population	No indirectness
Interventions	(n=231) Intervention 1: Culprit vessel only PPCI - During the index procedure. All participants had a PCI in the infarct artery, eligible patients were randomly assigned to undergo no further PCI procedures or to undergo immediate preventive PCI in noninfarct arteries with more than 50% stenoses (preventive PCI).. Duration N/A. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=234) Intervention 2: Multi-vessel PPCI - During index procedure. All participants had a PCI in the infarct artery, eligible patients were randomly assigned to undergo no further PCI procedures or to undergo

	immediate preventive PCI in noninfarct arteries with more than 50% stenoses (preventive PCI). Staged PCI (i.e., treatment of stenoses that were not treated during the initial procedure) in patients without angina was discouraged.. Duration N/A. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Other (Supported by Barts and the London Charity)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DURING THE INDEX PROCEDURE (CULPRIT VESSEL) versus DURING INDEX PROCEDURE (MULTI-VESSEL)

Protocol outcome 1: All-cause mortality at at 1 year
- Actual outcome: Death (cardiac + non-cardiac) at Mean 23 months; Group 1: 16/231, Group 2: 12/234
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Cardiovascular mortality at at 1 year
- Actual outcome: Cardiac death at Mean 23 months; Group 1: 10/231, Group 2: 4/234
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Non-fatal myocardial reinfarction at at 1 year
- Actual outcome: Non-fatal myocardial infarction at Mean 23 months; Group 1: 20/231, Group 2: 7/234
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Stroke - any type at at 1 year
- Actual outcome: Stroke at Mean 23 months; Group 1: 0/231, Group 2: 2/234
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Contrast-induced nephropathy
- Actual outcome: Contrast induced neuropathy at Mean 23 months; Group 1: 3/231, Group 2: 1/234
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 6: Unplanned revascularisation at at 1 year
- Actual outcome: Repeat revascularisation at Mean 23 months; Group 1: 46/231, Group 2: 16/234
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 7: Complications related to bleeding including haemorrhagic stroke at up to 30 days - Actual outcome: Bleeding requiring transfusion or surgery at Mean 23 months; Group 1: 6/231, Group 2: 7/234 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Length of follow up; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; All-cause mortality at at 30 days; Cardiovascular mortality at at 30 days; All (fatal and non-fatal) myocardial reinfarction at at 30 days; All (fatal and non-fatal) myocardial reinfarction at at 1 year; Non-fatal myocardial reinfarction at at 30 days; Hospitalisation for heart failure at at 1 year; Length of stay

Appendix E: Forest plots

E.1 Multi-vessel versus culprit vessel

Figure 2: All-cause mortality (< 30 days: in hospital – 3 days)

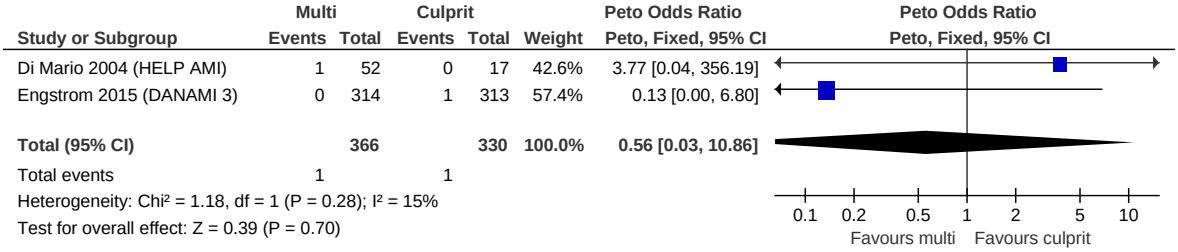
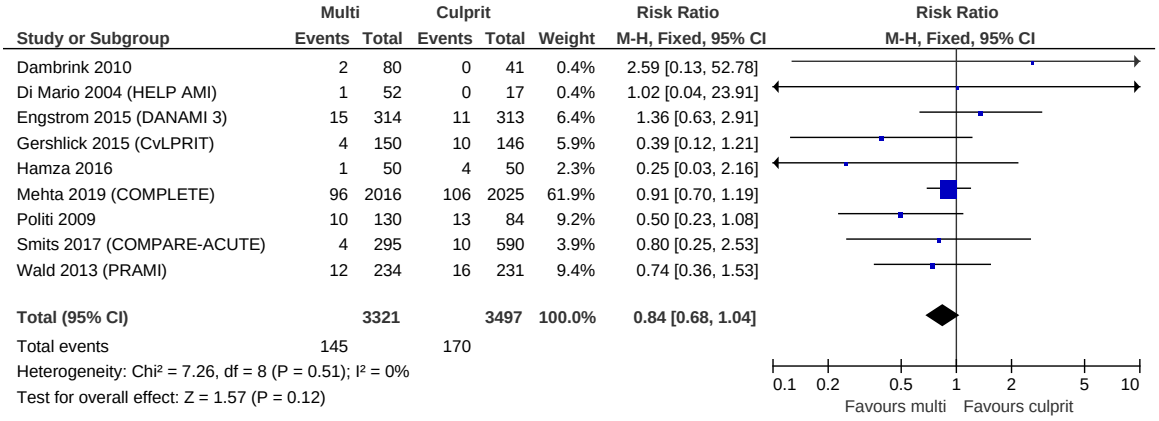
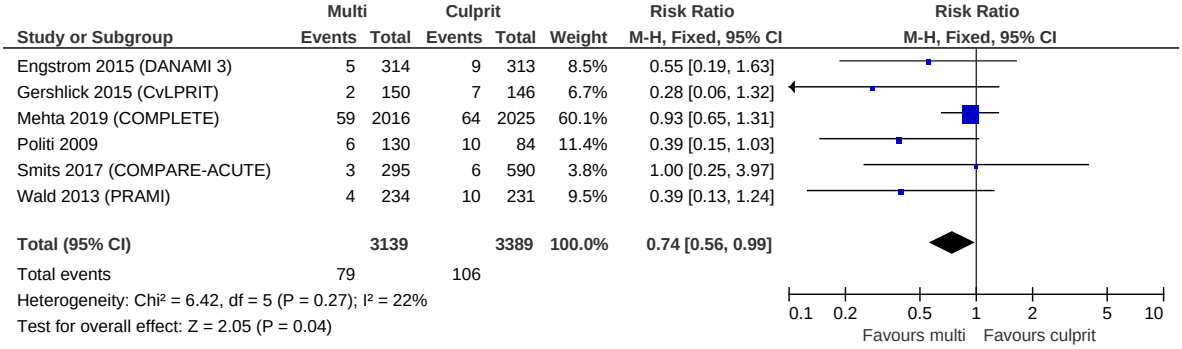


Figure 3: All-cause mortality (6 months – 3 years)



Politi 2009: 65 participants had staged PCI and 65 participants had PCI during index procedure

Figure 4: Cardiovascular mortality (6 months – 3 years)

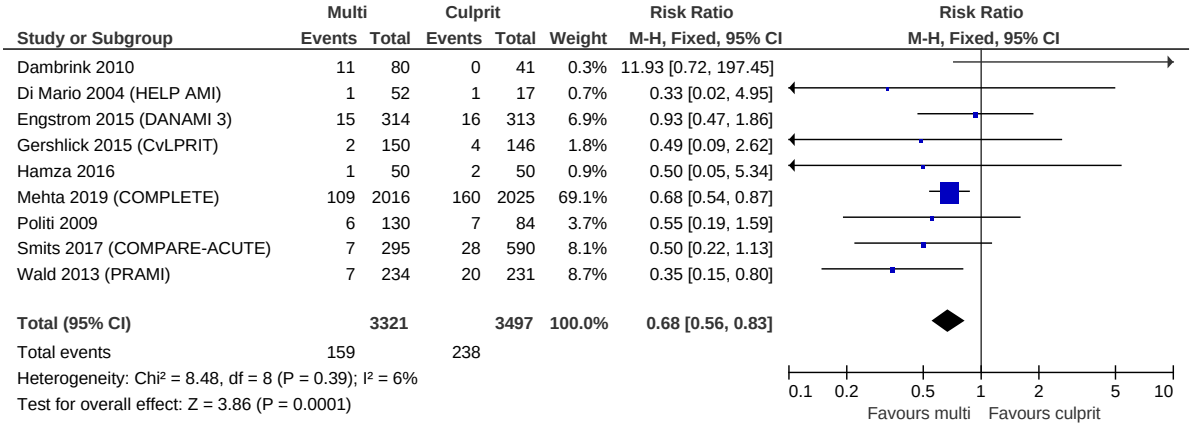


Politi 2009: 65 participants had staged PCI and 65 participants had PCI during index procedure

Figure 5: All (fatal and non-fatal) myocardial infarction (30 days)

Type of MI (fatal or non-fatal) not specified

Figure 6: All (fatal and non-fatal) myocardial infarction (6 months – 3 years)



Engstrom 2015 and Wald 2013: non-fatal MI; Dambrink 2010, Di Mario 2004, Gershlick 2015, Hamza 2016, Politi 2009, Smits 2017; Mehta 2019: type of MI not specified
Politi 2009: 65 participants had staged PCI and 65 participants had PCI during index procedure

Figure 7: Stroke at 1 year (6 months – 3 years)

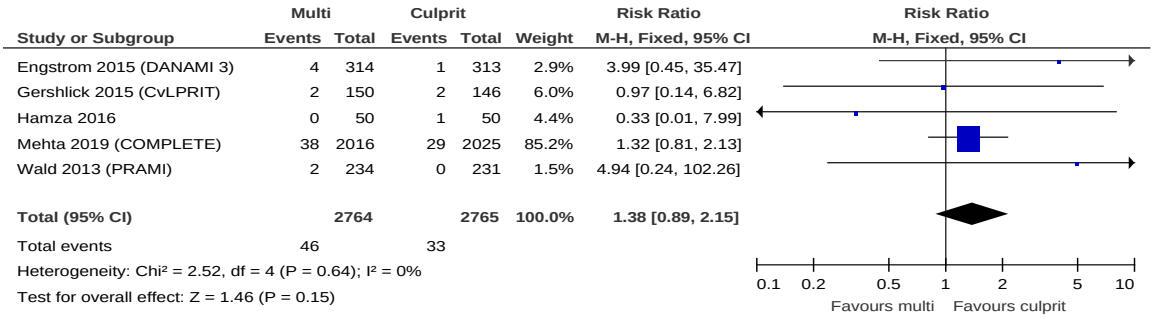


Figure 8: Contrast-induced nephropathy (6 months – 3 years)

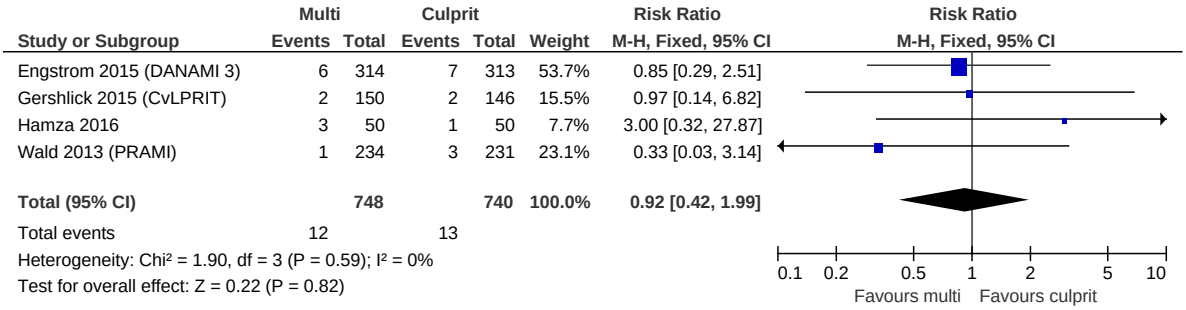
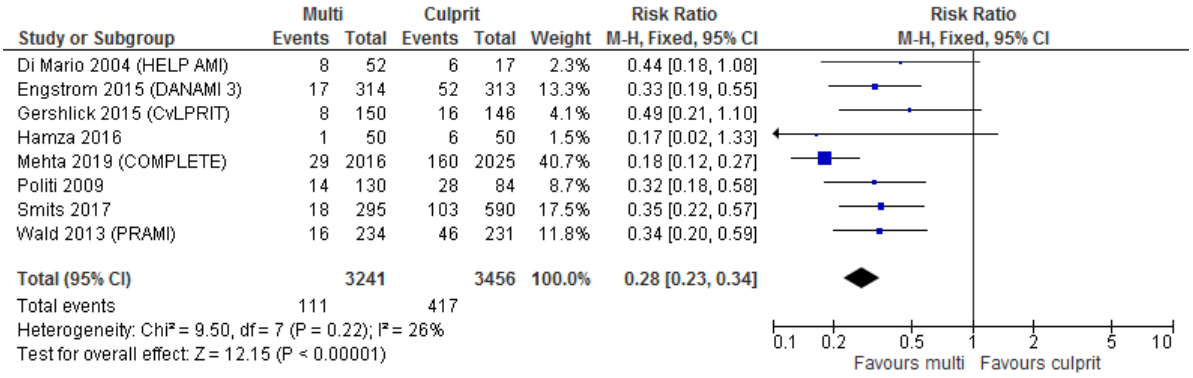


Figure 9: Unplanned revascularisation (6 months – 3 years)



Engstrom: ischemia-driven revascularision Politi 2009: 65 participants had staged PCI and 65 participants had PCI during index procedure

Figure 10: Complications related to bleeding (<30 days: 2-5 days)

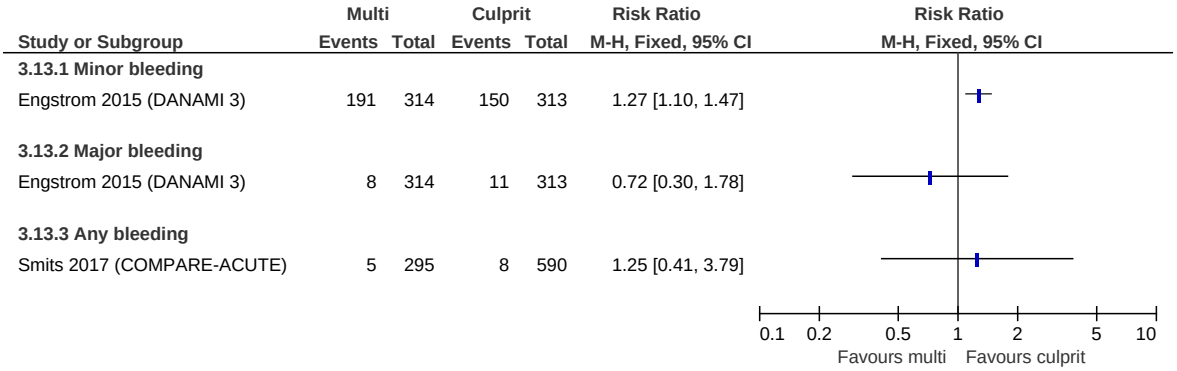


Figure 11: Complications related to bleeding – major bleeding at 1 year (6 months – 3 years)

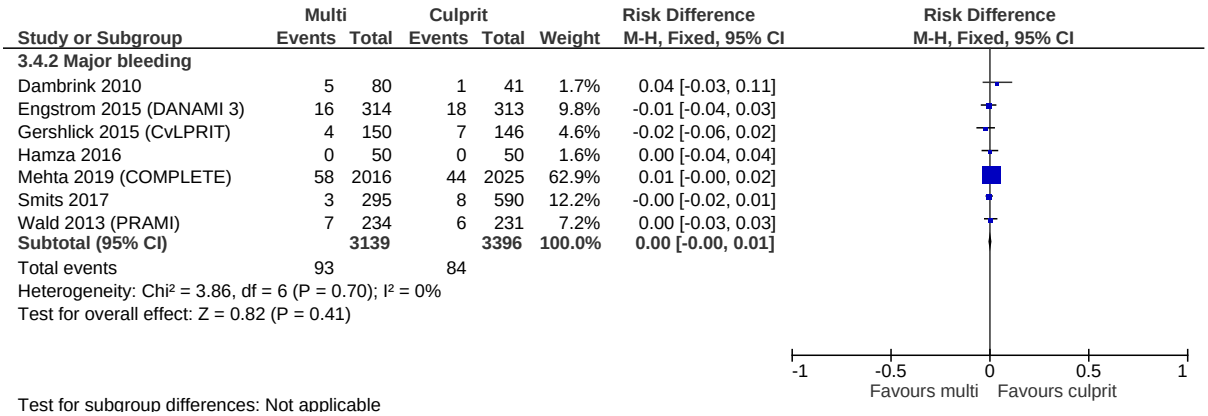
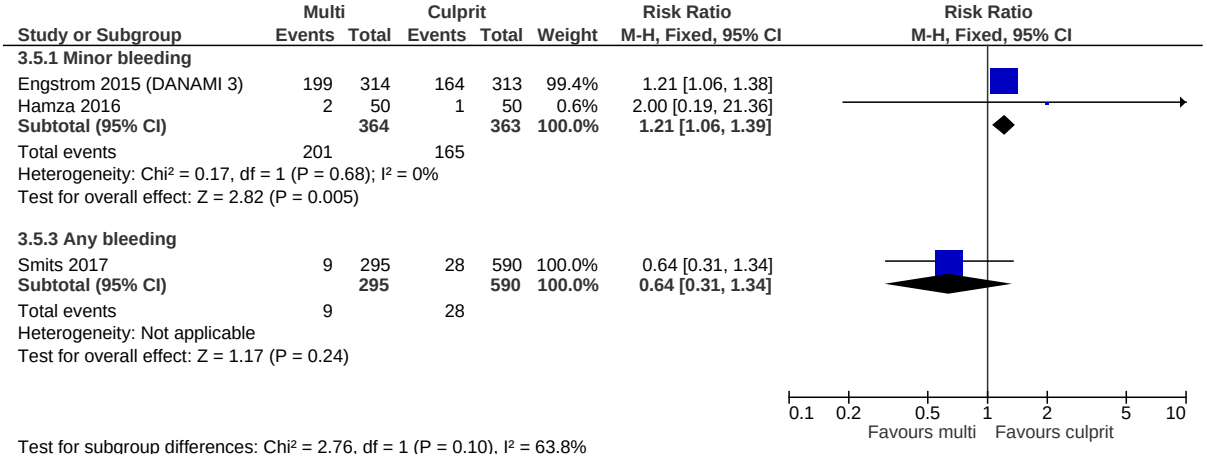


Figure 12:Complications related to bleeding – minor and unspecified bleeding at 1 year



Appendix F: GRADE tables

Table 12: Clinical evidence profile: culprit vs complete revascularisation in STEMI patients

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multi	Culprit	Relative (95% CI)	Absolute		
All-cause mortality (30 days) (follow-up 3 days/in hospital)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/366 (0.27%)	0.2%	Peto OR 0.56 (0.03 to 10.86)	1 fewer per 1000 (from 2 fewer to 20 more)	⊕OOO VERY LOW	CRITICAL
All-cause mortality (1 year) (follow-up 6 months - 2.5 years)												
9	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	145/3321 (4.4%)	5.2%	RR 0.84 (0.68 to 1.04)	8 fewer per 1000 (from 17 fewer to 2 more)	⊕OOO VERY LOW	CRITICAL
Cardiovascular mortality (1 year) (follow-up 1-2.5 years)												
6	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	79/3139 (2.5%)	3.7%	RR 0.74 (0.56 to 0.99)	10 fewer per 1000 (from 0 fewer to 16 fewer)	⊕OOO VERY LOW	CRITICAL
All myocardial infarction (30 days) (follow-up 3 days/in hospital)												

2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	2/366 (0.55%)	0.91%	see comment 4	3 fewer per 1000 (from 20 fewer to 10 more)	⊕OOO VERY LOW	CRITICAL
All myocardial infarction (1 year) (follow-up 6 months - 2.5 years)												
9	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	159/3321 (4.8%)	5.1%	RR 0.68 (0.56 to 0.83)	16 fewer per 1000 (from 9 fewer to 22 fewer)	⊕OOO VERY LOW	CRITICAL
Stroke (1 year) (follow-up 6-27 months)												
5	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	46/2764 (1.7%)	1.4%	RR 1.38 (0.89 to 2.15)	5 more per 1000 (from 2 fewer to 16 more)	⊕OOO VERY LOW	IMPORTANT
Complications related to bleeding (30 days) - Minor bleeding (follow-up median 5 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	191/314 (60.8%)	47.9%	RR 1.27 (1.1 to 1.47)	129 more per 1000 (from 48 more to 225 more)	⊕⊕OO LOW	IMPORTANT
Complications related to bleeding (30 days) - Major bleeding (follow-up median 5 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	8/314 (2.5%)	3.5%	RR 0.72 (0.3 to 1.78)	10 fewer per 1000 (from 24 fewer to 27 more)	⊕OOO VERY LOW	IMPORTANT
Complications related to bleeding (30 days) – any bleeding												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/295 (1.7%)	1.4%	RR 1.25 (0.41 to 3.79)	3 more per 1000 (from 8 fewer to 39 more)	⊕OOO VERY LOW	IMPORTANT
Contrast induced nephropathy (follow-up 6-27 months)												
4	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	12/748 (1.6%)	1.7%	RR 0.92 (0.42 to 1.99)	1 fewer per 1000 (from 10 fewer to 17 more)	⊕OOO VERY LOW	IMPORTANT
Unplanned revascularisation (1 year) (follow-up 6 months - 2.5 years)												
8	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	111/3241 (3.4%)	12.1%	RR 0.28 (0.23 to 0.34)	87 fewer per 1000 (from 80 fewer to 93 fewer)	⊕⊕OO LOW	CRITICAL
Complications related to bleeding (1 year) - Minor bleeding (follow-up 6-27 months)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	201/364 (55.2%)	27.2%	RR 1.21 (1.06 to 1.39)	57 more per 1000 (from 16 more to 106 more)	⊕OOO VERY LOW	
Complications related to bleeding (1 year) - Major bleeding (follow-up 6 months - 3 years)												
7	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[5]	none	93/3139 (3%)	2.5%	see comment 4	3 more per 1000 (from 0 fewer to 10 more)	⊕OOO VERY LOW	CRITICAL
Complications related to bleeding (1 year) - Any bleeding (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	9/295 (3.1%)	4.8%	RR 0.64 (0.31 to 1.34)	17 fewer per 1000 (from 33 fewer to 16 more)	⊕OOO VERY LOW	IMPORTANT

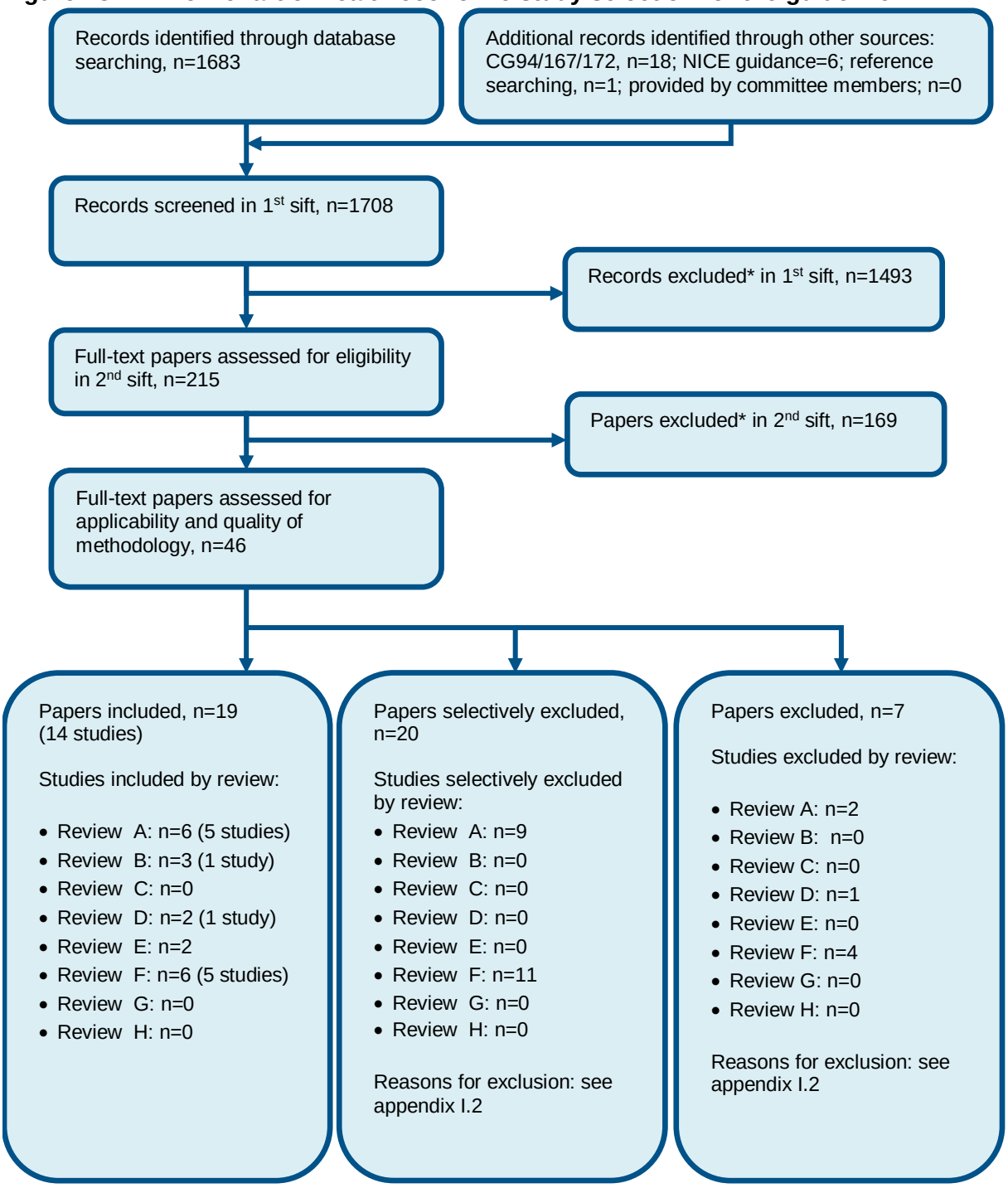
[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded for indirectness due to length of follow up
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

[4] No relative effect due to 0 events. Risk difference calculated in Review Manager

[5] Imprecision was assessed by calculating the optimal information size and graded as follows: <80% - very serious imprecision, 80-90%- serious imprecision, >90%– no imprecision

Appendix G: Health economic evidence selection

Figure 13: Flow chart of health economic study selection for the guideline



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

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

Appendix H: Health economic evidence tables

Study	Barton 2017[10]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Within trial analysis (RCT) **Approach to analysis:** Analysis of individual level data from the CvLPRIT RCT for all-cause mortality, recurrent MI, heart failure, repeat revascularisation, EQ-5D and resource use using bivariate regression. Multiple imputation was undertaken to impute missing data. Unit costs were applied. **Perspective:** UK NHS **Follow-up:** 1 year	**Population:** Patients with multi-vessel disease undergoing primary PCI for STEMI **Patient characteristics:** N= 296 Culprit vessel revascularisation: Mean age: 65.3 Male: 76.7% Multi-vessel revascularisation: Mean age: 64.6 Male: 85.3% **Intervention 1:** Culprit vessel PCI **Intervention 2:** Multi-vessel PCI (undertaken either at the	**Total costs for basecase analysis involving multiple imputation (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2−1): -£215.96 (95% CI: NR; p=0.212) **Cost breakdown:** Initial procedure costs: Intervention 1: £4,668.21[(b)] Intervention 2: £4,890.12[(b)] **Currency & cost year:** 2012/13 UK pounds **Cost components incorporated:** Culprit and multi-vessel PCI index admission procedure cost (procedure time, consumables, equipment and hospital length of stay), hospital readmissions for	**QALYs (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2−1): 0.011 (95% CI: -0.019 – 0.041; p=NR) **MACE (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2−1): -0.170 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** Intervention 2 dominant 95% CI:NR Probability Intervention 2 cost effective (£20K/30K threshold): 72%/NR Intervention 2 was also dominant for MACEs. **Analysis of uncertainty:** Two scenarios were explored, one excluding patients that did not receive the intervention they were allocated to. Intervention 2 remained dominant in this scenario. A second scenario analysis (complete case) was conducted where only patients that had data available for all costs and outcomes were included. This resulted in additional costs in intervention 2 as two patients in the culprit only arm had very high costs (>£50,000) and were excluded from this analysis. Intervention 2 resulted in an ICER of £21,495.69 with a probability of it being cost-effective at 20K threshold of 45.3%.

Treatment effect duration:[(a)] 1 year **Discounting:** Costs: n/a; Outcomes: n/a	time of Primary PCI or during that index admission).	revascularisation and follow-up staff costs.		
Data sources				
Health outcomes: Baseline event rates for the culprit vessel revascularisation intervention and relative treatment effects with the multi-vessel revascularisation intervention were obtained from the CvLPRIT trial. **Quality-of-life weights:** EQ-5D-3L (assumed as not stated), UK population valuation tariff. Quality of life varied by intervention received. **Cost sources:** NHS reference costs, PSSRU and a survey administered to participating centres.				
Comments				
Source of funding: National Institute for Health Research (NIHR). CvLPRIT study was funded by British Heart Foundation. **Limitations:** UK resource use from 2011-2013 and costs from 2012-2013 may not reflect current UK context. Use of bivalirudin higher in the trial than compared to current context and use of DAPT is different with current prasugrel usage lower and current ticagrelor usage higher than reported in the study (see Table 5 for details). Analysis based on a single study (CvLPRIT RCT) and so does not reflect full body of available evidence for this area. Time horizon of 1 year may not fully capture differences in costs and outcomes however as the intervention is dominant this might not make a difference.				
Overall applicability:[(c)] Partially applicable **Overall quality:**[(d)] Potentially serious limitations				

Abbreviations: 95% CI = 95% confidence interval; CUA = cost–utility analysis; DAPT = dual-antiplatelet therapy; EQ-5D-3L = Euroqol 5 dimensions 3 levels (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER = incremental cost-effectiveness ratio; MACE = major adverse cardiac events; MI = myocardial infarction; NR = not reported; PCI = percutaneous coronary intervention; QALYs = quality-adjusted life years; STEMI = ST-elevation myocardial infarction

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

(b) This is based on the complete case analysis and was not reported for the basecase analysis with multiple imputations; however authors report that cost savings were due to reduced downstream admissions for the multi-vessel arm.

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Di Mario 2004[22]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CCA (various health outcomes)	**Population:** Patients admitted to hospital with ischemic chest pain and/or STEMI with arteriography	**Total costs (mean per patient):** Intvn 1: £16,183 Intvn 2: £14,771 Incremental (2-1): -£1,412	**12 month outcomes:** From clinical review (1 vs 2) - same paper • All-cause mortality (30 days): Peto OR 3.77 (CI: 0.04,	Not applicable **Analysis of uncertainty:** No sensitivity analysis performed

Study design: Within-trial analysis (RCT: HELP-AMI study) **Approach to analysis:** Analysis of individual-level data for health outcomes. Initial procedure costs: exact costing methodology unclear, probably individual-level costs, unit cost source unclear. Downstream costs: trial event rates with standard unit costs used. **Perspective:** Italy health service **Time horizon:** 12 months **Treatment effect duration:**[(a)] 12 months **Discounting:** Costs: n/a; Outcomes: n/a	showing lesions in multiple coronary arteries **Patient characteristics:** n = 69 Mean age = 63.9 Male = 87.3 (See clinical evidence table for further details) **Intervention 1:** Culprit vessel revascularisation with primary PCI (using heparin-coated stents) n = 17 Diabetes = 41.2% **Intervention 2:** Multi-vessel revascularisation with primary PCI (using heparin-coated stents) n = 52 Diabetes = 11.5%	(CI = NR; p = 0.323) **Cost breakdown:** Initial procedure costs: Intvn 1: £9,141 Intvn 2: £9,659 Incremental (2-1): £518 (CI = NR; p = 0.263) Downstream costs: Intvn 1: £7,042 Intvn 2: £5,112 Incremental (2-1): -£1,930 (CI = NR; p = 0.185) **Currency & cost year:** 2004 euros (presented here as 2004 UK pounds[(b)]) **Cost components incorporated:** Initial procedure: all materials, stay in hospital including intensive care and cardiology wards. Downstream costs: additional revascularisation procedures (PCI or CABG)	356.19); ARD 19 per 1000 • All-cause mortality (1 year): RR 1.02 (CI: 0.13, 52.78); ARD 19 per 1000 • All (fatal, non-fatal) MI (1 year): RR 0.33 (CI: 0.02, 4.95); ARD -40 per 1000 • Unplanned revascularisation (1 year): RR 0.44 (CI: 0.18, 1.08) ARD -355 per 1000	
Data sources				

Health outcomes: Within-trial analysis. **Quality-of-life weights:** N/A. **Cost sources:** Time in hospital and materials used for initial procedures from within RCT patient-level analysis, source of unit costs not reported. Downstream event numbers for later revascularisation procedures from within RCT, costs based on Disease Related Group price (primary/complex angioplasty) for Lombardy region of Italy.

Comments

Source of funding: NR; one author was from Cordis Italia who manufactured the heparin-coated stents used in the trial. **Limitations:** Italian resource use and unit costs from pre-2004 (exact years not stated) may not reflect current UK context. Intervention used heparin-coated stents which are not routinely used in current practice. Contradictory descriptions of study population – not clear whether all patients had STEMI. Study arms had unbalanced proportions of patients with diabetes (culprit-vessel arm = 41.2%; multi-vessel arm = 11.5%). Measure of effect is not in line with NICE reference case methods as does not use QALYs (CCA instead of CUA). Time horizon of 1 year may not fully capture differences in costs and health outcomes. Analysis based on a single study (HELP-AMI) and so does not reflect full body of available evidence for this area. Unclear if all relevant costs are included, and some unit cost sources are unclear. No sensitivity analysis undertaken. Funding not reported but one author worked for Cordis. **Other:** None.

Overall applicability:[c] Partially applicable **Overall quality:**[d] Very serious limitations

Abbreviations: ARD= absolute risk difference; CABG= coronary artery bypass graft; CCA= cost–consequences analysis; 95% CI= 95% confidence interval; NR= not reported; PCI= percutaneous coronary intervention; QALYs= quality-adjusted life years; STEMI= ST-elevation myocardial infarction

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

(b) Converted using 2004 purchasing power parities[70]

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 13: Studies excluded from the clinical review

Study	Exclusion reason
Agarwal 2017[1]	Systematic review: methods are not adequate/unclear
Aggarwal 2012[2]	Systematic review: methods are not adequate/unclear
Anantha Narayanan 2016[3]	Systematic review: methods are not adequate/unclear
Bagai 2013[4]	Systematic review: methods are not adequate/unclear
Bainey 2014[5]	Systematic review: methods are not adequate/unclear
Bainey 2016[6]	Systematic review: methods are not adequate/unclear
Bajaj 2015[7]	Systematic review is not relevant to review question or unclear PICO
Bajraktari 2018[8]	Systematic review is not relevant to review question or unclear PICO
Bangalore 2018[9]	Systematic review: methods are not adequate/unclear
Bertaina 2018[11]	Systematic review: methods are not adequate/unclear
Bravo 2017[12]	Not included as a whole SR. Includes papers that do not satisfy our inclusion criteria.
Cavender 2009[13]	Incorrect study design
Chen 2014[14]	Commentary
Corpus 2004[15]	Incorrect study design
Correia 2018[16]	Incorrect study design
Dahal 2014[18]	Systematic review: methods are not adequate/unclear
De Waha 2018[20]	Systematic review: methods are not adequate/unclear
Di Pasquale 2016[23]	Systematic review: methods are not adequate/unclear. Narrative review.
Dziewierz 2010[24]	Incorrect study design

Eggebrecht 2018[25]	Not in English
Elgendy 2017[26]	Systematic review: methods are not adequate/unclear
Estevez 2014[28]	Abstract
Fagel 2019[29]	Incorrect population
Fan 2017[30]	Systematic review: methods are not adequate/unclear
Garcia 2019[31]	Meta-analysis – references checked
Ghani 2012[33]	Incorrect interventions
Guo 2018[34]	Systematic review: methods are not adequate/unclear
Hannan 2010[36]	Incorrect study design
Hassanin 2015[37]	Incorrect study design
Hlinomaz 2015[38]	Abstract. Not in English.
Hu 2018[40]	Incorrect study design
Ijsselmuiden 2004[41]	Not guideline condition. Mixed population of patients with multi-vessel disease but no mention of the clinical diagnosis i.e. not clear if STEMI patients
Jackson 2018[42]	Incorrect study design
Jang 2015[43]	Systematic review: methods are not adequate/unclear. NSTEMI
Jo 2011[44]	Incorrect study design
Khalid 2018[47]	Systematic review: methods are not adequate/unclear
Khan 2019[48]	Systematic review: methods are not adequate/unclear
Kong 2006[49]	Incorrect study design
Kornowski 2011[50]	Incorrect study design
Kyhl 2019[51]	No outcomes of interest
Lamelas 2019[52]	Systematic review – references checked
Lee 2012[53]	Incorrect study design
Li 2017[54]	Systematic review: methods are not adequate/unclear
Lu 2018[55]	Systematic review: methods are not adequate/unclear

Maamoun 2011[57]	Incorrect study design
Manoharan 2017[60]	Incorrect study design
Mariani 2016[61]	Systematic review: methods are not adequate/unclear
Meliga 2011[64]	Incorrect study design
Neupane 2019[66]	Systematic review – references checked
Nguyen 2017[67]	Systematic review: methods are not adequate/unclear
Ochala 2004[69]	No information on baseline characteristics, numbers randomised, event rates. Authors mention that all causes of death, AMI, urgent revascularization (including TVR), major and minor bleeding complications, worsening ofthe CCS class, unstable angina, cardiovascular hospitalization but none reported in the article
Rathod 2018[74]	Incorrect study design. Not review population
Song 2019[77]	Systematic review – references checked
Tarasov 2017[78]	Not in English
Thiele 2016[80]	In patients with cardiogenic shock
Thiele 2018[79]	In patients with cardiogenic shock
Toma 2010[81]	Incorrect study design
Vaidya 2018[82]	Systematic review: methods are not adequate/unclear
Wang 2019[84]	Meta-analysis – references checked
Xu 2019[85]	Meta-analysis – references checked
Zhang 2015[86]	Not in English

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 14: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	