3-year scoping report

Topic: Acute coronary syndrome: SIGN 148 (2016)

Date of search**:** 11 March 2019 conducted by Carolyn Sleith, Evidence and Information Scientist
Report prepared by: Jenny Harbour, Health Services Researcher and Moray Nairn, Programme Manager

Key concepts: acute coronary syndrome, myocardial infarction, unstable angina

Background
The purpose of this scoping is to identify any information that may be relevant to the key questions or recommendations of the guideline on acute coronary syndrome (SIGN 148).

A rapid high-level search of the literature was conducted using a predefined list of resources. The search focused on secondary sources of evidence (health technology assessments, evidence-based guidelines, systematic reviews and meta-analyses) and was limited to evidence published, in English language, since 2013.

The results of the evidence review in section 2 are based mainly on information contained within the executive summaries or abstracts of the evidence identified. A comprehensive assessment and critical analysis of the evidence was not carried out.
The results of the review were discussed by Dr Moray Nairn, Programme Manager, SIGN, and Professor David Newby, Chair of the guideline development group for SIGN 148: acute coronary syndrome, to identify the priorities for review listed in section 1. The review and proposed updates were circulated to the original guideline development group for comment (see section 3).

Conclusion

New evidence was identified for the following sections of the current SIGN 148 guideline: 3.2, 4.4.2, 5.2.1, 5.5, 8.1.2 and 8.2.1. Two sections should be considered for updating based on this new evidence. Firstly, section 4.4.2 on choice of dual antiplatelet agent used in combination with aspirin in patients with ACS. An important RCT published on this topic on 1 September 2019 which showed significantly lower incidence of death, myocardial infarction, or stroke among those who received prasugrel than among those who received ticagrelor. SIGN 148 recommends ticagrelor as first-line antiplatelet for most patients, therefore a more careful identification of the full body of evidence to support a recommendation on antiplatelet choice may be warranted. Secondly, section 5.5 on multivessel versus culprit-only revascularisation where there is currently no

recommendation in SIGN 148 due to a lack of good quality evidence on this topic. It should be noted that there is likely to be significant overlap between the large body of meta-analyses on this topic that is not apparent from the abstracts. Many of the meta-analyses include observational data only, and the primary evidence may not be more conclusive than that contained in SIGN 148. An important RCT published on this topic on 1 September 2019 showing patients with multivessel coronary artery disease that had received culprit lesion PCI and were subsequently randomised to complete revascularisation suffered lower rates of cardiovascular death, MI or repeat revascularisation than those receiving no additional revascularisation.

Outcome

The recommendation to the Guideline Programme Advisory Group is some recommendations may change in the light of the new evidence and selected elements of the guideline should be considered for review.

Decision

The Guideline Programme Advisory Group agreed on 25 September 2019 that a revision of SIGN 148 is warranted and the following areas should be prioritised for update:

- What is the clinical and cost effectiveness of prasugrel or ticagrelor compared to clopidogrel in patients with acute coronary syndrome?
- What is the clinical and cost effectiveness of multivessel compared to culprit-only primary percutaneous coronary intervention in patients with ST segment elevation ACS and multivessel coronary disease?

Section 1: Proposed action from the scoping summary

Guideline section	Details of update	Suggested priority (Possible, Desirable or Essential)
Section 4.4.2 (Combination aspirin and $P2Y_{12}$-receptor antagonist therapy)	One systematic review and meta-analysis of RCTs and observational data showed superior results for prasugrel (based on pooled observational data) compared with ticagrelor. Another meta-analysis of RCTs showed no difference in outcomes between prasugrel and ticagrelor. A large RCT published on 1 September 2019 reported significantly lower incidence of death, myocardial infarction, or stroke among those who received prasugrel than among those who received ticagrelor (see section 2.4).	Desirable
Section 5.5 (multivessel compared to culprit-only primary PCI)	Many meta-analyses of RCTs and observational studies show that multivessel PCI may have advantages over culprit-vessel PCI for patients with STEMI and multivessel coronary disease. There is some inconsistency in the results of these meta-analyses with some studies showing no significant difference between revascularisation methods for certain outcomes. The large volume of meta-analyses may mask a much smaller volume of primary studies, which suffer from imperfect patient selection criteria. An important RCT (COMPLETE) published results favouring complete revascularisation over culprit-only revascularisation for multivessel disease on 1 September 2019 (see section 2.4).	Desirable
Section 9.4 (revascularisation in patients with cardiogenic shock)	Several meta-analyses of observational studies or unknown study types suggest culprit-vessel PCI may be better than complete revascularisation for patients with cardiogenic shock.	Possible

Section 2: Summary of evidence by key questions

2.1 Evidence linked to existing SIGN key questions (KQ)

KQ1: What is the clinical and cost effectiveness of serial measuring plasma troponin concentration using a high-sensitivity assay within four hours of presentation compared with serial troponin measurement over 10–12 hours for the exclusion of acute myocardial infarction?

Reference and study type	Information likely to be relevant	Impact on guideline
Systematic review (observational studies). Kimenai DM, et al. Sex-specific versus overall clinical decision limits for cardiac troponin I and T for the diagnosis of acute myocardial infarction: a systematic review. Clin Chem. 2018;64(7):1034-43.	Systematic review of 28 studies comparing sex-specific clinical decision limits with overall clinical decision limits for high-sensitivity cardiac troponin I and T. Reference populations designed to establish 99th percentiles of high-sensitivity cardiac troponin I and T, published between January 2009 and October 2017, were included. Sex-specific and overall 99th percentile values were compared with overall clinical decision ranges of 23–30 ng/l for high-sensitivity cardiac troponin I and 13–25 ng/l for high-sensitivity cardiac troponin T. Of 16 hs-cTnI and 18 hs-cTnT studies, 14 (87.5%) and 11 (61.1%) studies reported lower female-specific hs-cTn cutoffs than overall clinical decision ranges, respectively. The majority of included studies (87.5% of high-sensitivity cardiac troponin I and 61.1% of high-sensitivity troponin T studies) reported lower female-specific high-sensitivity cardiac troponin I and T cutoffs compared with overall clinical decision ranges.	Section 3.2 SIGN recommendation: Sex-specific thresholds of cardiac troponin should be used for the diagnosis of myocardial infarction in men and women. <u>No impact on guideline</u>
Individual patient data meta-analysis (observational studies) Chapman AR, et al. Association of high-sensitivity cardiac troponin I concentration with cardiac outcomes in patients with suspected acute coronary syndrome.	Individual patient data meta-analysis evaluating the use of a cardiac troponin I threshold of 5 ng/L at presentation as a risk stratification tool in patients with suspected acute coronary syndrome. A multi-source search up to 2017 identified 19 cohorts studies (n=22,457); two could only be accessed as aggregate data. In 11,012 patients cardiac troponin I concentrations were less than 5 ng/L at presentation. Sixty myocardial infarction events were missed in these patients, resulting in a negative predictive value of 99.5% (95% CI 99.3% to 99.6%). There were no cardiac deaths at 30 days and 7 cardiac deaths at 12 months follow-up, giving a negative predictive value of 99.9% (95% CI 99.7% to 99.9%) for cardiac death.	Section 3.2 SIGN recommendation: In patients with suspected acute coronary syndrome, measurement of cardiac troponin at presentation and at three hours after presentation with a high-sensitivity assay should be considered as an alternative to serial measurement over 10–12

Reference and study type	Information likely to be relevant	Impact on guideline
JAMA. 2017;318(19):1913-24.		hours with a standard troponin assay to rule out myocardial infarction. No impact on guideline
Systematic review (observational studies). Pickering JW, et al. Rapid rule-out of acute myocardial infarction with a single high-sensitivity cardiac troponin T measurement below the limit of detection: a collaborative meta-analysis. Ann Intern Med. 2017;166(10):715-24.	Meta-analysis of 11 cohort studies (n=9,241) evaluating the ability of a single high-sensitivity cardiac troponin T concentration below the limit of detection (<0.005 microg/L) and a non-ischaemic ECG reading to rule out acute myocardial infarction (MI) in adults presenting with chest pain. Fourteen (0.5%) patients classified as low risk went on to have an acute MI. Pooled estimated sensitivity of the risk classification for acute MI was 98.7% (95% CI 96.6% to 99.5%). The pooled estimated sensitivity for predicting 30-day major adverse cardiac events was 98.0% (95% CI 94.7% to 99.3%).	Section 3.2 SIGN recommendation: In patients with suspected acute coronary syndrome, measurement of cardiac troponin at presentation and at three hours after presentation with a high-sensitivity assay should be considered as an alternative to serial measurement over 10–12 hours with a standard troponin assay to rule out myocardial infarction. Focus on diagnostic performance of low concentrations of high-sensitivity troponin. No impact on guideline
Non-systematic review (observational studies). Carlton E, et al. Evaluation of high-sensitivity cardiac	Pooled analysis of five prospective cohort studies (n=3,155) with blinded outcome assessment evaluating the diagnostic performance of low concentrations of high-sensitivity cardiac troponin I in patients with suspected cardiac chest pain and no ischaemia evident on electrocardiogram (ECG). The lower limit of detection (1.2 ng/L) as well as cut-off concentrations rounded to the nearest integer for a high-sensitivity troponin I assay were	Section 3.2 SIGN recommendation: In patients with suspected acute coronary syndrome, measurement of cardiac troponin at presentation and at

Reference and study type	Information likely to be relevant	Impact on guideline
troponin I levels in patients with suspected acute coronary syndrome. JAMA Cardiol. 2016;1(4):405-12.	used in the analysis. The 1.2 ng/L limit of detection gave a sensitivity of 99.0% (95% CI 96.8% to 99.7%) and a negative predictive value of 99.5% (95% CI 98.4% to 99.9%). Higher cut-off values had sensitivities less than 98%. Diagnostic performance was maintained in analyses where patients were stratified by age, sex, risk factors, coronary artery disease and early presentation. The authors concluded that high-sensitivity troponin I concentration had high sensitivity for acute myocardial infarction in the emergency care setting. Rounded cut-off values above the limit of detection may not be sufficiently sensitive for clinical use.	three hours after presentation with a high-sensitivity assay should be considered as an alternative to serial measurement over 10–12 hours with a standard troponin assay to rule out myocardial infarction. Focus on diagnostic performance of low concentrations of high-sensitivity troponin. No impact on guideline

KQ2: What is the clinical and cost effectiveness of prasugrel or ticagrelor compared to clopidogrel in patients with acute coronary syndrome?

Reference and study type	Information likely to be relevant	Impact on guideline
Systematic review with meta-analysis (RCTs and observational studies) Khan MS, et al. Prasugrel vs. ticagrelor for acute coronary syndrome patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis.	Systematic review with meta-analysis comparing prasugrel with ticagrelor in patients with acute coronary syndrome undergoing PCI. Six RCTs and 8 observational studies were included in the analysis (n=40,188). No statistically significant differences were reported for short-term (≤3 months) all-cause mortality in comparisons of prasugrel and ticagrelor. Pooled data from the observational studies indicated significantly lower long-term (≥12 months) all-cause mortality (OR 0.63, 95% CI 0.43 to 0.92, p=0.02) and short-term stent thrombosis (OR 0.46, 95% CI 0.28 to 0.75, p=0.002) for prasugrel compared with ticagrelor.	Section 4.4.2 SIGN recommendations: In the presence of ischaemic electrocardiographic changes or elevation of cardiac troponin, patients with an acute coronary syndrome should be treated immediately with both aspirin (300 mg loading dose) and ticagrelor (180 mg loading dose).

Reference and study type	Information likely to be relevant	Impact on guideline
Am J Cardiovasc Drugs. 2019;04:04.		For patients with acute coronary syndrome undergoing percutaneous coronary intervention aspirin and prasugrel (60 mg loading dose) may be considered. This reinforces the recommendation in favour of prasugrel for patients undergoing PCI however provides a head to head comparison with ticagrelor.
Meta-analysis (RCTs and observational studies) Dai W, et al. Effect of preoperative loading dose ticagrelor and clopidogrel on no-reflow phenomenon during intervention in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: a systematic review and meta-analysis. Drug Design Develop Ther. 2018;12:2039-49.	Meta-analysis evaluating use of preoperative loading doses ticagrelor (180 mg) and clopidogrel (600 mg) in patients with STEMI undergoing primary percutaneous coronary intervention (PCI). Fourteen RCTs and one observational study were included in the analysis (n=4,162). Compared with clopidogrel, preoperative loading dose ticagrelor significantly reduced the incidence of no-reflow during primary PCI (OR 0.25, 95% CI 0.15 to 0.39, p<0.0001) and major adverse cardiovascular events within 30 days (OR 0.58, 95% CI 0.41 to 0.82, p=0.002). Significant improvements in TIMI flow after PCI were also found for ticagrelor compared with clopidogrel: OR 1.85, 95% CI 1.40 to 2.45, p<0.0001. No statistically significant differences were found for post-PCI bleeding events.	Section 4.4.2 SIGN recommendations: In the presence of ischaemic electrocardiographic changes or elevation of cardiac troponin, patients with an acute coronary syndrome should be treated immediately with both aspirin (300 mg loading dose) and ticagrelor (180 mg loading dose). This outcome not included in key question. No impact on guideline

Reference and study type	Information likely to be relevant	Impact on guideline
Meta-analysis Bundhun PK, et al. Head to head comparison of prasugrel versus ticagrelor in patients with acute coronary syndrome: a systematic review and meta-analysis of randomized trials. BMC Pharmacol Toxicol. 2017;18(1):80.	Meta-analysis of studies directly comparing prasugrel with ticagrelor in patients with acute coronary syndrome. Few details are given in the abstract about the review methodology. The primary endpoint was adverse cardiovascular events. Four studies of unknown design were included in the analysis (n=563). There were no statistically significant differences between prasugrel and ticagrelor for mortality, recurrent myocardial infarction, major adverse cardiac events, stroke, stent thrombosis, or TIMI defined minor and minimal bleeding.	Section 4.4.2 SIGN recommendations: In the presence of ischaemic electrocardiographic changes or elevation of cardiac troponin, patients with an acute coronary syndrome should be treated immediately with both aspirin (300 mg loading dose) and ticagrelor (180 mg loading dose). For patients with acute coronary syndrome undergoing percutaneous coronary intervention aspirin and prasugrel (60 mg loading dose) may be considered. <u>No impact on guideline</u>
Meta-analysis (RCTs and observational studies) Nairooz R, et al. Meta-analysis of clopidogrel pretreatment in acute coronary syndrome patients undergoing invasive strategy. Int J Cardiol. 2017;229:82-9.	Meta-analysis comparing clopidogrel pre-treatment with clopidogrel administration in the cardiac catheterisation laboratory at the time of PCI in invasively-managed patients with acute coronary syndrome. Sixteen studies (n=61,517) were included in the analysis but it is not clear from the abstract what type of study these were. Clopidogrel pre-treatment was associated with significantly lower major adverse cardiac events (OR 0.77, 95% CI 0.68 to 0.86, p<0.0001) and all-cause mortality (OR 0.70, 95% CI 0.58 to 0.85, p=0.0003) at 30 days follow-up compared with clopidogrel at time of PCI. Mortality at longest follow-up was significantly lower in the pre-treatment group: OR 0.78, 95% CI 0.62 to 0.97, p=0.03. There were no significant differences in major bleeding events. Sensitivity and subgroup analyses in randomised versus observational studies and STEMI versus NSTEMI patients, were similar to the main results.	Section 4.4.2 SIGN recommendation: Patients with acute coronary syndrome should be considered for aspirin (300 mg loading dose) and clopidogrel (300 mg loading dose) where the risks (bleeding) outweigh the benefits (reduction in recurrent atherothrombotic events) of ticagrelor or prasugrel.

Reference and study type	Information likely to be relevant	Impact on guideline
		Loading dose v no loading dose was not considered in guideline.

KQ 2: What is the clinical and cost effectiveness of prasugrel or ticagrelor compared to clopidogrel in patients with acute coronary syndrome? **(Economic evidence)**

Reference and study type	Information likely to be relevant	Impact on guideline
Jiang M, You JH. Cost-effectiveness analysis of personalized antiplatelet therapy in patients with acute coronary syndrome. Pharmacogenomics. 2016;17(7):701-13.	Economic analysis using a decision-analytic model to simulate four strategies for antiplatelet therapy in patients with acute coronary syndrome undergoing PCI: universal clopidogrel 75 mg daily, universal prasugrel or ticagrelor, pharmacogenetic-guided therapy, and platelet reactivity testing-guided therapy. The pharmacogenetic-guided therapy strategy was the preferred option with the lowest cost (US$75,208/£57,468) and highest QALY gains (7.6). Base-case results were robust in sensitivity analyses.	Section 4.4.2 Studies comparing prasugrel to clopidogrel,and ticagrelor to clopidogrel have shown that ticagrelor (for the prevention of atherothrombotic events in adult patients with acute coronary syndrome) and prasugrel (for the prevention of atherothrombotic events in patients with ACS undergoing primary or delayed PCI) are cost-effective treatment options compared with clopidogrel. Pharmacogenetic-guided therapy was not included as an intervention in the guideline.
Janzon M, *et al.* Health economic analysis of ticagrelor in patients with acute coronary syndromes intended for	***Note:*** *only included because it provides more recent cost-effectiveness analysis from UK healthcare system perspective.* Economic evaluation exploring the cost effectiveness of ticagrelor compared with clopidogrel in patients with acute coronary syndrome scheduled for non-	Section 4.4.2 SIGN recommendation: In the presence of ischaemic electrocardiographic changes or elevation of cardiac troponin,

Reference and study type	Information likely to be relevant	Impact on guideline
non-invasive therapy. Heart. 2015;101(2):119-25.	invasive management. Patient data were included from the PLATO study and the cost-effectiveness analysis was performed from the perspective of healthcare systems in Sweden, the UK, Germany, and Brazil. The model used in the analysis was developed elsewhere and is not described in the abstract of the paper. Healthcare costs, event rates and health-related quality of life were estimated over a 12-month period. Long-term costs and outcomes were estimated from the PLATO data and published literature. In the UK analysis ticagrelor was associated with lifetime QALY gains of 0.16 and increased healthcare costs of €551 (£476) compared with clopidogrel. This gave a cost per QALY for ticagrelor in the UK of €3,395 (£2,934). There was a high probability that the cost per QALY for ticagrelor would be below conventional threshold values of cost effectiveness in the UK.	patients with an acute coronary syndrome should be treated immediately with both aspirin (300 mg loading dose) and ticagrelor (180 mg loading dose). No impact on guideline

KQ 6: What is the clinical and cost effectiveness of multivessel compared to culprit-only primary percutaneous coronary intervention in patients with ST segment elevation myocardial infarction and multivessel coronary disease?

Due to the volume of meta-analyses on this topic, studies were restricted to analyses that included >1 RCT. Note that meta-analyses may include similar RCTs.

a) Patients with ACS and multivessel disease

Reference and study type	Information likely to be relevant	Impact on guideline
Meta-analysis (RCTs) Bravo CA, et al. Complete versus culprit-only revascularisation in ST elevation myocardial infarction with multi-vessel disease. Cochrane	Cochrane systematic review (9 RCTs, n=2,633) comparing early complete revascularisation with culprit vessel only PCI in patients with STEMI and multi-vessel coronary disease. The primary outcomes were long-term (≥12 months) all-cause mortality, cardiovascular mortality, non-fatal MI and adverse events. There were no statistically significant differences between complete and culprit-only PCI for long-term all-cause mortality or combined adverse events. Complete revascularisation was associated with lower long-term cardiovascular mortality (RR 0.50, 95% CI 0.32 to 0.79), long-term non-fatal	Section 5.5 No SIGN Recommendation: These findings support and extend the evidence in the SIGN guideline, however meta-analyses fail to determine conclusively whether MV PCI

Reference and study type	Information likely to be relevant	Impact on guideline
Database of Systematic Reviews 2017.	MI (RR 0.62, 95% CI 0.44 to 0.89) and long-term revascularisation (RR 0.47, 95% CI 0.39 to 0.57). Trial sequential analysis indicated that more RCTs are needed to reach conclusive results on all-cause mortality, long-term cardiovascular mortality and long-term non-fatal MI. The quality of the evidence was judged to be very low for all primary and the majority of the secondary outcomes mainly due to risk of bias, imprecision, and indirectness.	are superior to culprit-vessel PCI, due to inconsistent results. *Complete revascularisation better:* Long-term CV mortality Long-term non-fatal MI Long-term revascularisation *Culprit revascularisation better:* None *No difference:* All-cause mortality Adverse events
Meta-analysis (RCTs) Bajraktari G, et al. Complete revascularisation for patients with ST-segment elevation myocardial infarction and multivessel coronary artery disease: a meta-analysis of randomized trials. Coronary Artery Disease. 2018;29(3):204-15.	Meta-analysis of 10 RCTs (n=3,291) comparing complete revascularisation with culprit artery only revascularisation during primary PCI in patients with STEMI and multi-vessel coronary disease. Complete revascularisation was associated with significant reductions in risk of major adverse cardiac events (RR 0.57, 95% CI 0.43 to 0.76, p<0.0001), cardiac mortality (RR 0.52, 95% CI 0.31 to 0.87, p=0.014), and repeat revascularisation (RR 0.50, 95% CI 0.30 to 0.84, p=0.009) compared with culprit artery only revascularisation. No significant differences were reported for risk of all-cause mortality, recurrent non-fatal MI, stroke, or major bleeding.	Section 5.5 No SIGN Recommendation: These findings support and extend the evidence in the SIGN guideline, however meta-analyses fail to determine conclusively whether MV PCI are superior to culprit-vessel PCI, due to inconsistent results. *Complete revascularisation better:* CV mortality Repeat revascularisation Adverse events

Reference and study type	Information likely to be relevant	Impact on guideline
		Culprit revascularisation better: None *No difference:* All-cause mortality Recurrent non-fatal MI Stroke Major bleeding
Meta-analysis (RCTs) Bangalore S, et al. Meta-analysis of culprit-only versus multivessel percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction and multivessel coronary disease. Am J Cardiol. 2018;121(5):529-36.	Pairwise meta-analysis and mixed treatment comparison of 11 trials (n=3,150) comparing routine multi-vessel PCI with culprit-only PCI in patients with STEMI and multi-vessel coronary disease. Multi-vessel PCI was either a single procedure or a staged procedure. The primary efficacy outcome was a composite of mortality and recurrent MI. In pairwise meta-analysis single procedure multi-vessel PCI was associated with a significant reduction in risk of death or recurrent MI compared with culprit-only PCI (RR 0.52, 95% CI 0.37 to 0.73, p<0.001). Results from the mixed treatment comparison are not reported in the study abstract.	Section 5.5 No SIGN Recommendation: These findings support and extend the evidence in the SIGN guideline, however meta-analyses fail to determine conclusively whether MV PCI are superior to culprit-vessel PCI, due to inconsistent results. *Complete revascularisation better:* Death or recurrent MI *Culprit revascularisation better:* None *No difference:* None

Reference and study type	Information likely to be relevant	Impact on guideline
Meta-analysis (RCTs) Fan G, et al. Optimal reperfusion strategy in patients with acute STEMI and multivessel disease-an updated meta-analysis. Herz. 2018;27:27.	Meta-analysis comparing culprit-only revascularisation with complete revascularisation in patients with acute STEMI and multi-vessel coronary disease. Multi-source search identified 8 RCTs for inclusion (n=2,870). Complete revascularisation was associated with statistically significant reductions in risk of major adverse cardiac events (OR 2.44, 95% CI 1.96 to 3.03, p<0.001), mortality (OR 1.76, 95% CI 1.25 to 2.47, p=0.001), recurrent MI (OR 1.62, 95% CI 1.12 to 2.35, p=0.01) and repeat revascularisation (OR 3.20, 95% CI 2.41 to 4.24, p<0.001) compared with culprit-only revascularisation. There were no statistically significant differences between groups for individual safety outcomes, including contrast-induced nephropathy, stroke, and bleeding.	Section 5.5 No SIGN Recommendation: These findings support and extend the evidence in the SIGN guideline, however meta-analyses fail to determine conclusively whether MV PCI are superior to culprit-vessel PCI, due to inconsistent results. *Complete revascularisation better:* Mortality Repeat revascularisation Recurrent MI Adverse events *Culprit revascularisation better:* None *No difference:* Individual safety outcomes (nephropathy, stroke, bleeding)
Meta-analysis (RCTs) Pasceri V, et al. Complete revascularisation during primary percutaneous coronary intervention reduces death and myocardial infarction in	Meta-analysis of 11 RCTs (n=3,561) comparing complete revascularisation with culprit-only revascularisation in patients with STEMI and multi-vessel coronary disease. Patients with cardiogenic shock were excluded. Complete revascularisation was associated with significant reductions in risk of a composite of death or MI: RR 0.76, 95% CI 0.58 to 0.99, p=0.04. In 6 studies, immediate (during primary PCI) complete revascularisation was associated with significant reductions in risk of total mortality (RR 0.62, 95% CI 0.39 to 0.97, p=0.03) and MI (RR 0.40, 95% CI 0.25 to 0.66). No significant	Section 5.5 No SIGN Recommendation: These findings support and extend the evidence in the SIGN guideline, however meta-analyses fail to determine conclusively whether MV PCI

Reference and study type	Information likely to be relevant	Impact on guideline
patients with multivessel disease: meta-analysis and meta-regression of randomized trials. JACC Cardiovasc Interven. 2018;11(9):833-43.	differences were reported for these outcomes in 5 studies on comparing culprit-only with staged complete revascularisation.	are superior to culprit-vessel PCI, due to inconsistent results. *Complete revascularisation better:* Death or recurrent MI Total mortality (for immediate revascularisation) MI (for immediate revascularisation) *Culprit revascularisation better:* None *No difference:* Total mortality (for staged revascularisation) MI (for staged revascularisation)
Meta-analysis (RCTs) Vaidya SR, et al. Culprit versus multivessel coronary intervention in ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. Coronary Artery Dis. 2018;29(2):151-60.	Meta-analysis of 9 RCTs (n=2,991) comparing complete multi-vessel PCI with infarct-related artery only revascularisation in patients with STEMI. Complete multi-vessel PCI was associated with significantly lower risk of MACE (RR 0.54, 95% CI 0.41 to 0.71, p<0.00001), cardiovascular mortality (RR 0.48, 95% CI 0.28 to 0.80, p=0.005) and repeat revascularisation (RR 0.38, 95% CI 0.38, 95% CI 0.30 to 0.47, p<0.00001) compared with infarct-related artery only PCI. There were no statistically significant differences in contrast-induced nephropathy, major bleeding, all-cause mortality or non-fatal MI. **Likely an update to the previous meta-analysis by this author (see below):*	Section 5.5 No SIGN Recommendation: These findings support and extend the evidence in the SIGN guideline, however meta-analyses fail to determine conclusively whether MV PCI are superior to culprit-vessel PCI, due to inconsistent results.

Reference and study type	Information likely to be relevant	Impact on guideline
	Vaidya SR, et al. Infarct related artery only versus complete revascularisation in ST-segment elevation myocardial infarction and multi vessel disease: a meta-analysis. Cardiovas Diagn Ther. 2017;7(1):16-26.	*Complete revascularisation better:* MACE CV mortality Repeat revascularisation *Culprit revascularisation better:* None *No difference:* All-cause mortality Non-fatal MI Nephropathy, Major bleeding
Meta-analysis (RCTs) Vaidya SR, et al. Infarct related artery only versus complete revascularisation in ST-segment elevation myocardial infarction and multi vessel disease: a meta-analysis. Cardiovas Diagn Ther. 2017;7(1):16-26.	Meta-analysis of 6 RCTs (n=1,792) comparing complete revascularisation with infarct artery only revascularisation in patients with STEMI and multi-vessel coronary disease. There were statistically significant reductions in risk of MACE (RR 0.51, 95% CI 0.41 to 0.64, p<0.00001), repeat revascularisation (RR 0.41, 95% CI 0.31 to 0.54, p<0.00001), cardiovascular mortality (RR 0.42, 95% CI 0.24 to 0.74, p=0.003) and non-fatal MI (RR 0.64, 95% CI 0.34 to 1.20, p=0.16) in the complete revascularisation group compared with the infarct artery only group.	Section 5.5 No SIGN Recommendation: <u>These findings support and extend the evidence in the SIGN guideline, however meta-analyses fail to determine conclusively whether MV PCI are superior to culprit-vessel PCI, due to inconsistent results.</u> *Complete revascularisation better:* MACE CV mortality Repeat revascularisation

Reference and study type	Information likely to be relevant	Impact on guideline
		Culprit revascularisation better: None *No difference:* All-cause mortality Non-fatal MI Nephropathy, Major bleeding
Meta-analysis (RCTs) Elgendy I, et al. Complete or culprit-only revascularisation for patients with multivessel coronary artery disease undergoing percutaneous coronary intervention: a pairwise and network meta-analysis of randomized trials. JACC Cardiovascular Interventions, 2017;10(4):315-24.	Pairwise and mixed treatment comparison comparing multi-vessel complete revascularisaton during primary PCI with culprit-only PCI in patients with STEMI and multi-vessel coronary artery disease. No information is provided in the abstract about the literature search to identify relevant studies. Ten trials (n=2,285) were included in the analysis. In the pairwise meta-analysis, complete/multi-vessel revascularisation was associated with a significantly lower risk of major adverse cardiac events: RR 0.44, 95% CI 0.30 to 0.66. No statistically significant differences were found for all-cause mortality risk or spontaneous re-infarction risk. Mixed treatment comparison indicated the significant reduction in risk of major cardiac events was retained irrespective of timing of revascularisation.	Section 5.5 No SIGN Recommendation: These findings support and extend the evidence in the SIGN guideline, however meta-analyses fail to determine conclusively whether MV PCI are superior to culprit-vessel PCI, due to inconsistent results. *Complete revascularisation better:* MACE *Culprit revascularisation better:* None *No difference:* All-cause mortality Non-fatal MI

Reference and study type	Information likely to be relevant	Impact on guideline
Meta-analysis (RCTs) Fan ZG, et al. The optimal strategy of percutaneous coronary intervention for ST-elevation myocardial infarction patients with multivessel disease: an updated meta-analysis of 9 randomized controlled trials. Minerva Cardioangiologica. 2017;65(2):148-56.	Meta-analysis of nine RCTs (n unknown) to determine the optimal strategy for PCI in patients with STEMI and multi-vessel coronary disease. Comparisons in the meta-analysis include preventive PCI versus culprit-only PCI and complete multi-vessel PCI during the primary procedure versus staged PCI. The primary endpoint was major adverse cardiac events (MACE). In comparisons of preventive PCI and culprit-only PCI there were statistically significant reductions in MACE (OR 0.41, 95% CI 0.31 to 0.51, p<0.001), mortality (OR 0.41, 95% CI 0.27 to 0.62, p<0.001), re-infarction (OR 0.54, 95% CI 0.32 to 0.91, p=0.021) and repeat revascularisation (OR 0.37, 95% CI 0.26 to 0.51, p<0.001) in the preventive PCI group compared with the culprit-only group. Mortality was significantly reduced in the staged PCI strategy compared with complete multi-vessel PCI during the primary procedure (findings not reported in abstract).	Section 5.5 No SIGN Recommendation: These findings support and extend the evidence in the SIGN guideline, however meta-analyses fail to determine conclusively whether MV PCI are superior to culprit-vessel PCI, due to inconsistent results. *Complete revascularisation better:* MACE Long-term mortality Reinfarction Repeat revascularisation *Culprit revascularisation better:* None *No difference:* None Also staged revascularisation > index revascularisation Guideline does not distinguish between staged and index complete revascularisation approaches. This comparison could be considered.

Reference and study type	Information likely to be relevant	Impact on guideline
Meta-analysis (RCTs) Agarwal N, et al. Staged versus index procedure complete revascularisation in ST-elevation myocardial infarction: a meta-analysis. J Intervent Cardiol. 2017;30(5):397-404.	Meta-analysis of 6 RCTs (n=1,126) comparing multi-vessel intervention as a staged procedure with multi-vessel intervention during the index procedure in patients with STEMI and multi-vessel coronary artery disease. At a mean follow-up of 13 months, the composite outcome of MI or death occurred significantly less often in the staged multi-vessel revascularisation compared with index procedure multi-vessel revascularisation: RR 1.66, 95%CI 1.09 to 2.52, p=0.02. Staged multi-vessel revascularisation was associated with significant reductions in all-cause mortality (RR 2.55, 95%CI 1.42 to 4.58, p<0.01), cardiovascular mortality (RR 2.8, 95%CI 1.33 to 5.86, p=0.01), and short-term (<30 days) mortality (RR 3.54, 95%CI 1.51 to 8.29, p<0.01) compared with index procedure multi-vessel revascularisation. There were no significant differences in major adverse cardiac events, repeat MI, or repeat revascularisation.	Section 5.5 No SIGN Recommendation: These findings support and extend the evidence in the SIGN guideline, however meta-analyses fail to determine conclusively whether MV PCI are superior to culprit-vessel PCI, due to inconsistent results. *Staged revascularisation better:* MI or death All-cause mortality CV mortality *Index revascularisation better:* None *No difference:* MACE Reinfarction Repeat revascularisation
Meta-analysis (RCTs and CCTs) Li Z, et al. Staged versus one-time complete revascularisation with percutaneous coronary intervention in STEMI	Systematic review and meta-analysis of 4 RCTS and 6 non-randomised controlled trials comparing staged PCI with complete PCI in patients with STEMI and multi-vessel coronary disease. Long-term major adverse cardiovascular events and their components (mortality, re-infarction, revascularisation) were the primary endpoint. Long-term mortality was significantly reduced in staged PCI compared with multi-vessel complete PCI (OR 0.44, 95% CI 0.29 to 0.66, p<0.0001), as was short-term mortality (OR 0.23, 95% CI 0.10 to 0.51, p=0.0003). Long- and short-term were not defined	Section 5.5 No SIGN Recommendation: These findings support and extend the evidence in the SIGN guideline, however meta-analyses fail to determine conclusively whether MV PCI

Reference and study type	Information likely to be relevant	Impact on guideline
patients with multivessel disease: a systematic review and meta-analysis. PLoS ONE. 2017;12(1):e0169406.	in the abstract. There were no statistically significant differences in overall MACE, re-infarction rates or revascularisation.	are superior to culprit-vessel PCI, due to inconsistent results. *Staged revascularisation better:* Long-term mortality Short-term mortality *Index revascularisation better:* None *No difference:* MACE Reinfarction Repeat revascularisation
Meta-analysis (RCTs) Nguyen AV, et al. Optimal percutaneous coronary intervention in patients with ST-elevation myocardial infarction and multivessel disease: an updated, large-scale systematic review and meta-analysis. Int J Cardiol. 2017;244:67-76.	Systematic review and meta-analysis of 13 RCTs (n=2,830) comparing culprit-only revascularisation with immediate complete revascularisation and staged complete revascularisation in patients with STEMI and multi-vessel coronary disease undergoing PCI. Very little detail is given about methods in the abstract. Culprit-only revascularisation was associated with significant increased risk of MACE (adjusted RR 1.67, 95% CI 1.27 to 2.19) and repeat revascularisation (adjusted RR 2.12, 95% CI 1.67 to 2.69) compared with complete revascularisation. Culprit-only revascularisation was associated with significantly increased risk of MACE (adjusted RR 1.99, 1.53 to 2.6), cardiovascular mortality (adjusted RR 2.06, 95% CI 1.07 to 3.96), MI (adjusted RR 1.72, 95% CI 1.04 to 2.86) and repeat revascularisation/repeat PCI compared with immediate complete revascularisation. The only statistically significant difference for comparisons between culprit-only revascularisation and staged complete revascularization were for repeat revascularization and repeat PCI.	Section 5.5 No SIGN Recommendation: These findings support and extend the evidence in the SIGN guideline, however meta-analyses fail to determine conclusively whether MV PCI are superior to culprit-vessel PCI, due to inconsistent results. *Complete revascularisation better:* MACE CV mortality Repeat revascularisation

Reference and study type	Information likely to be relevant	Impact on guideline
		Culprit revascularisation better: None *No difference:* Non-cardiovascular mortality, Stroke, Nephropathy, Rehospitalization, Stent thrombosis Bleeding Also staged revascularisation v index revascularisation (NS)
Meta-analysis (RCTs) Wang CH, et al. Complete revascularisation versus culprit-only revascularisation in ST-segment elevation myocardial infarction and multivessel disease patients undergoing primary percutaneous coronary intervention: a meta-analysis and trial sequential analysis. Int J Cardiol. 2017;228:844-52.	Meta-analysis of 8 RCTs (n=2,060) comparing complete revascularisation with culprit-only revascularisation during primary PCI in patients with STEMI and multi-vessel coronary disease. Complete revascularisation was associated with significantly lower risk of MACE (RR 0.60, 95% CI 0.50 to 0.72) and repeat revascularisation (RR 0.49, 95% CI 0.33 to 0.73) compared with culprit-only revascularisation. In subgroup analyses, immediate complete revascularisation was associated with significant reductions in risk of MACE (RR 0.44, 95% CI 0.32 to 0.60), all-cause death and/or MI (RR 0.55, 95% CI 0.36 to 0.85), non-fatal MI (RR 0.35, 95% CI 0.17 to 0.71), and repeat revascularisation (RR 0.35, 95% CI 0.24 to 0.52) compared with culprit-only revascularisation. Staged complete revascularisation was associated with significant reductions in risk of MACE compared with culprit-only revascularisation: RR 0.71, 95% CI 0.56 to 0.89. Trial sequential analysis indicated firm evidence for MACE and revascularisation in the overall population and immediate complete revascularisation groups.	Section 5.5 No SIGN Recommendation: <u>These findings support and extend the evidence in the SIGN guideline, however meta-analyses fail to determine conclusively whether MV PCI are superior to culprit-vessel PCI, due to inconsistent results.</u> *Complete revascularisation better:* MACE All-cause mortality or MI Non-fatal MI Repeat revascularisation

Reference and study type	Information likely to be relevant	Impact on guideline
		Culprit revascularisation better: None *No difference:* Stroke, Nephropathy, Bleeding
Meta-analysis (RCTs) Anantha Narayanan M, et al. What is the optimal approach to a non-culprit stenosis after ST-elevation myocardial infarction - conservative therapy or upfront revascularisation? An updated meta-analysis of randomized trials. Int J Cardiol. 2016;216:18-24.	Meta-analysis comparing complete revascularisation with culprit vessel only revascularisation during PCI after STEMI in patients with multi-vessel coronary disease. Seven trials (n=2,004) were identified in a multi-source search from inception to 2016. Complete revascularisation was associated with significantly lower rates of major adverse cardiac events (RR 0.58, 95% CI 0.43 to 0.78, p<0.001), cardiac deaths (RR 0.42, 95% CI 0.24 to 0.74, p=0.003), and repeat revascularisation (RR 0.36, 95% CI 0.27 to 0.48, p<0.001) compared with culprit vessel only revascularisation. No statistically significant differences were reported for all-cause mortality, recurrent MI, stroke, or major bleeding.	Section 5.5 No SIGN Recommendation: These findings support and extend the evidence in the SIGN guideline, however meta-analyses fail to determine conclusively whether MV PCI are superior to culprit-vessel PCI, due to inconsistent results. *Complete revascularisation better:* MACE CV mortality Repeat revascularisation *Culprit revascularisation better:* None *No difference:* All-cause mortality, Stroke, Recurrent MI, Bleeding

Reference and study type	Information likely to be relevant	Impact on guideline
Mukete B, et al. Multivessel revascularisation does not increase contrast-induced acute kidney injury incidence in acute myocardial infarction: a meta-analysis. Am J Cardiovasc Drugs. 2016;16(6):419-26.	Meta-analysis of four trials (n=1,537) assessing incidence of contrast-induced acute kidney injury following complete revascularisation compared with infarct-related artery revascularisation in patients with STEMI. Significantly more contrast was used in the complete revascularisation patients (p=0.006). There was a significantly increased incidence of cardiovascular death (2.0% vs. 4.7%, p=0.01) and ischaemia-driven revascularisation (6.2% vs. 18.3%, p<0.01) in the infarct-related artery revascularisation patients. No statistically significant differences were detected in the incidence of contrast-induced acute kidney injury, major bleeding, or stroke.	Section 5.5 No SIGN Recommendation: These findings support and extend the evidence in the SIGN guideline, however meta-analyses fail to determine conclusively whether MV PCI are superior to culprit-vessel PCI, due to inconsistent results. *Complete revascularisation better:* CV mortality Repeat revascularisation *Culprit revascularisation better:* None *No difference:* Nephropathy Stroke, Bleeding
Meta-analysis (RCTs) Shah R, et al. Meta-analysis comparing complete revascularisation versus infarct-related only strategies for patients with ST-segment elevation	Pairwise meta-analysis and mixed treatment comparison of 9 RCTs (n=2,176) comparing infarct-related artery only revascularisation, complete revascularisation during index procedure and staged complete revascularisation in patients with STEMI. In the mixed treatment comparison, complete revascularisation during the index procedure was associated with a decreased risk of major adverse cardiac events (OR 0.36, 95% CI 0.25 to 0.54), recurrent MI (OR 0.50, 95% CI 0.24 to 0.91), revascularisation (OR 0.24, 95% CI 0.15 to 0.38) and cardiovascular mortality (OR 0.44, 95% CI 0.20 to 0.87) compared with infarct-related artery only revascularisation.	Section 5.5 No SIGN Recommendation: These findings support and extend the evidence in the SIGN guideline, however meta-analyses fail to determine conclusively whether MV PCI

Reference and study type	Information likely to be relevant	Impact on guideline
myocardial infarction and multivessel coronary artery disease. Am J Cardiol. 2016;118(10):1466-72.	Rates of MACE, recurrent MI and cardiovascular mortality were also lower in staged complete revascularisation compared with infarct-related artery only revascularisation. In direct pairwise meta-analysis the risk of MI was 66% lower with complete revascularisation during the index procedure compared with infarct-related artery only revascularisation. **The mixed treatment comparison should have reported Credible Intervals rather than Confidence Intervals.*	are superior to culprit-vessel PCI, due to inconsistent results. *Complete revascularisation better:* MACE CV mortality Repeat revascularisation *Culprit revascularisation better:* None *No difference:* All-cause mortality
Meta-analysis (RCTs) Villablanca PA, et al. Culprit-lesion only versus complete multivessel percutaneous intervention in ST-elevation myocardial infarction: a systematic review and meta-analysis of randomized trials. International J Cardiol. 2016;220:251-9.	Meta-analysis of 7 RCTs (n=2,006) comparing multi-vessel PCI with culprit-only PCI in patients with STEMI and multi-vessel coronary artery disease. Multi-vessel PCI was associated with significant reductions in risk of MACE (OR 0.62, 95% CI 0.43 to 0.90), cardiovascular mortality (OR 0.46, 95% CI 0.27 to 0.80) and repeat revascularisation (OR 0.39, 95% CI 0.30 to 0.51) compared with culprit-only revascularisation in patients undergoing primary PCI. No significant differences were detected for recurrent MI, all-cause mortality, non-cardiovascular mortality, all bleeding events, contrast-induced nephropathy or stroke. The number needed to treat in order to prevent one cardiovascular death was estimated as 47, to prevent a repeat revascularisation as 11, and to prevent one MACE was 16 patients.	Section 5.5 No SIGN Recommendation: These findings support and extend the evidence in the SIGN guideline, however meta-analyses fail to determine conclusively whether MV PCI are superior to culprit-vessel PCI, due to inconsistent results. *Complete revascularisation better:* MACE CV mortality Repeat revascularisation

Reference and study type	Information likely to be relevant	Impact on guideline
		Culprit revascularisation better: None *No difference:* All-cause mortality Recurrent MI Nephropathy Stroke Bleeding
Meta-analysis (RCTs) Kowalewski M, et al. Complete revascularisation in ST-elevation myocardial infarction and multivessel disease: meta-analysis of randomised controlled trials. Heart. 2015;101(16):1309-17.	Meta-analysis of seven RCTs (n=1,303) comparing complete multi-vessel PCI with culprit-only revascularisation or staged revascularisation in patients with STEMI and multi-vessel coronary disease. No details is given in the abstract about the methods used. The primary endpoint used was a composite of major adverse cardiac events (MACE) including death, recurrent MI and repeat revascularisation. Complete multi-vessel PCI was associated with reduced odds of MACE compared with non-complete (culprit-only or staged) PCI: OR 0.59, 95% CI 0.36 to 0.97, p=0.04. This was driven mainly by reductions in risk of recurrent MI (OR 0.45, 95% CI 0.27 to 0.85, p=0.01) and repeat revascularisation (OR 0.51, 95% CI 0.31 to 0.84, p=0.008).	Section 5.5 No SIGN Recommendation: <u>These findings support and extend the evidence in the SIGN guideline, however meta-analyses fail to determine conclusively whether MV PCI are superior to culprit-vessel PCI, due to inconsistent results.</u> *Complete revascularisation better:* MACE Recurrent MI Repeat revascularisation *Culprit revascularisation better:* None *No difference:* All-cause mortality CV mortality

Reference and study type	Information likely to be relevant	Impact on guideline
Meta-analysis (RCTs and observational studies) Moretti C, et al. Management of multivessel coronary disease in STEMI patients: a systematic review and meta-analysis. Int J Cardiology. 2015;179:552-7.	Systematic review with meta-analysis comparing culprit-only with complete revascularisation in patients with STEMI and multi-vessel coronary disease. Nine studies (n=4,686) – mixture of RCTs and observational –were included. Patients with cardiogenic shock were excluded. The primary endpoint was major adverse cardiac events (MACE) at one year follow-up; this included death, MI and revascularisation. There were no statistically significant differences in MACE or components of MACE, with the exception of a significant reduction in repeat revascularization (OR 0.62, 95% CI 0.39 to 0.98), in patients undergoing culprit-only PCI compared with complete PCI performed during the primary PCI. Six studies (n=5,855), of which only one was an RCT, compared culprit-only with complete PCI during the index hospitalization: there were no statistically significant differences in MACE but a significant reduction in repeat revascularisation (OR 0.60, 95% CI 0.40 to 0.90).	Section 5.5 No SIGN Recommendation: <u>These findings do not support evidence in the SIGN guideline.</u> *Complete revascularisation better:* Repeat revascularisation *Culprit revascularisation better:* None *No difference:* MACE Mortality MI
Meta-analysis (RCTs) Sarathy K, et al. Target-vessel versus multivessel revascularisation in ST-elevation myocardial infarction: a meta-analysis of randomised trials. Heart Lung Circ. 2015;24(4):327-34.	Meta-analysis of 4 RCTs (n=775) comparing culprit-only revascularization with multi-vessel revascularization in patients with STEMI and multi-vessel coronary disease. Compared with culprit-only revascularisation, multi-vessel revascularisation was associated with significantly lower incidence of non-fatal MI (OR 0.38, 95% CI 0.19 to 0.76), refractory angina (OR 0.40, 95% CI 0.24 to 0.74), repeat revascularisation (OR 0.34, 95% CI 0.20 to 0.66), a composite of death from cardiac causes or refractory angina or non-fatal MI (OR 0.34, 95% CI 0.22 to 0.51), and a composite of death from cardiac causes or non-fatal MI (OR 0.42, 95% CI 0.25 to 0.72).	Section 5.5 No SIGN Recommendation: <u>These findings support and extend the evidence in the SIGN guideline, however meta-analyses fail to determine conclusively whether MV PCI are superior to culprit-vessel PCI, due to inconsistent results.</u> *Complete revascularisation better:* Non-fatal MI

Reference and study type	Information likely to be relevant	Impact on guideline
		Refractory angina CV mortality or angina or MI Repeat revascularisation *Culprit revascularisation better:* None *No difference:* None
Meta-analysis (RCTs and observational studies) Song YJ, et al. Preventive versus culprit-only percutaneous coronary intervention in ST-elevation myocardial infarction patients with multivessel disease: a meta-analysis. J Intervent Cardiol. 2015;28(1):1-13.	Meta-analysis comparing complete (preventive) revascularisation with culprit-only revascularisation in patients with STEMI and multi-vessel coronary artery disease undergoing PCI. Both RCTs (7 studies) and observational studies (23 studies) were included (total n=44,256). Preventive PCI was associated with a significant reduction in repeat revascularisation (OR 0.71, 95% CI 0.51 to 0.99) compared with culprit-only PCI. No significant differences were reported for all-cause mortality, MI, or MACE. When data were stratified by revascularisation strategy, culprit-only PCI was associated with a significant survival benefit over multi-vessel PCI during the index procedure. Staged PCI was associated with a significantly lower incidence of all-cause mortality compared with culprit-only revascularisation or multi-vessel PCI during the index procedure.	Section 5.5 No SIGN Recommendation: <u>These findings do not fully support evidence in the SIGN guideline though provide evidence of superiority of staged v index complete revascularisation.</u> *Complete revascularisation better:* Repeat revascularisation *Culprit revascularisation better:* None *No difference:* All-cause mortality MI MACE

Reference and study type	Information likely to be relevant	Impact on guideline
		Also, staged revascularisation>index revascularisation for all-cause mortality
Meta-analysis (RCTs) Spencer FA, et al. Culprit vessel versus immediate complete revascularisation in patients with ST-segment myocardial infarction-a systematic review. Am Heart J. 2015;170(6):1133-9.	Systematic review and meta-analysis of five RCTs (n=1,606*) comparing multi-vessel revascularisation with culprit-only PCI in patients with STEMI and multi-vessel coronary artery disease. The primary outcomes of interest were recurrent MI, recurrent revascularisation, and mortality. Multi-vessel revascularisation was associated with significantly decreased risk of repeat revascularisation (RR 0.36, 95% CI 0.27 to 0.49) and recurrent non-fatal MI (RR 0.58, 95% CI 0.36 to 0.93). No statistically significant differences in mortality or adverse events were detected. **Authors state they performed a 'complete case' meta-analysis and report that 1,568 patients had complete data, so this may not be the actual number of patients in the analysis.*	Section 5.5 No SIGN Recommendation: <u>These findings support and extend the evidence in the SIGN guideline, however meta-analyses fail to determine conclusively whether MV PCI are superior to culprit-vessel PCI, due to inconsistent results.</u> *Complete revascularisation better:* Recurrent non-fatal MI Repeat revascularisation *Culprit revascularisation better:* None *No difference:* Mortality Adverse events

b) patients with acute MI/STEMI and cardiogenic shock

Reference and study type	Information likely to be relevant	Impact on guideline
Meta-analysis (RCTs and observational studies) Khan M, et al. Meta-analysis comparing culprit vessel only versus multivessel percutaneous coronary intervention in patients with acute myocardial infarction and cardiogenic shock. Am J Cardiol. 2019;123(2):218-26.	Meta-analysis comparing multi-vessel PCI with culprit vessel only intervention in acute MI patients with multi-vessel coronary disease and cardiogenic stroke. Thirteen studies of unspecified design (n=7,906) were included in the analysis; it is implied in the abstract that these were mainly observational studies. There were no statistically significant differences in risk of short-term mortality, long-term mortality, re-infarction, revascularisation, bleeding or stroke outcomes. There was a statistically significant increase in risk of renal failure in the multi-vessel revascularisation group compared with culprit-only vessel intervention (RR 1.35, 95% CI 1.10 to 1.66, p=0.004).	Section 9.4 SIGN recommendation: Patients presenting with cardiogenic shock due to left ventricular failure within six hours of acute myocardial infarction should be considered for immediate coronary revascularisation. <u>These findings extend the evidence in the SIGN guideline. Consider whether a recommendation on format of PCI may be considered?</u> *Complete revascularisation better:* None *Culprit revascularisation better:* Renal failure *No difference:* Short-term mortality, Long-term mortality, Reinfarction, Revascularisation, Bleeding Stroke

Reference and study type	Information likely to be relevant	Impact on guideline
Meta-analysis (observational studies) de Waha S, et al. Multivessel versus culprit lesion only percutaneous coronary intervention in cardiogenic shock complicating acute myocardial infarction: a systematic review and meta-analysis. Eur Heart J Acute Cardiovasc Care. 2018;7(1):28-37.	Systematic review and meta-analysis comparing immediate multi-vessel PCI with culprit-only PCI (possibly staged) in patients with cardiogenic shock complicating acute MI. The ten included studies (n=6,051) were all observational cohort studies. The primary outcome was mortality at hospital discharge or 30-days after hospital admission. Short-term mortality was significantly lower in culprit-only PCI compared with multi-vessel PCI: RR 1.26, 95% CI 1.12 to 1.41, p=0.001. No statistically significant differences were reported for MI, stroke, acute renal failure, bleeding or long-term mortality.	Section 9.4 SIGN recommendation: Patients presenting with cardiogenic shock due to left ventricular failure within six hours of acute myocardial infarction should be considered for immediate coronary revascularisation. <u>These findings extend the evidence in the SIGN guideline. Consider whether a recommendation on format of PCI may be considered?</u> *Complete revascularisation better:* None *Culprit revascularisation better:* Short-term mortality *No difference:* Long-term mortality, Reinfarction, Bleeding, Renal failure, Stroke
Meta-analysis (unknown study type)	Systematic review and meta-analysis comparing culprit-only PCI with multi-vessel PCI in patients with acute MI and cardiogenic shock. The primary endpoint was in-hospital/30-day mortality. No information is given on the	Section 9.4 SIGN recommendation: Patients presenting with

Reference and study type	Information likely to be relevant	Impact on guideline
Khalid M, et al. Culprit vessel only versus multivessel percutaneous coronary intervention in acute myocardial infarction with cardiogenic shock: a systematic review and meta-analysis. Cardiovasc Revascular Med. 2018;21:21.	number or type of studies included in the analysis. Culprit-vessel revascularisation PCI was associated with significantly lower short-term mortality (OR 0.73, CI 0.61 to 0.87) and severe renal failure requiring renal replacement therapy (OR 0.76, 95% CI 0.59 to 0.98) compared with multivessel PCI. No significant differences were found for long-term mortality, stroke, bleeding, and recurrent MI.	cardiogenic shock due to left ventricular failure within six hours of acute myocardial infarction should be considered for immediate coronary revascularisation. <u>These findings extend the evidence in the SIGN guideline. Consider whether a recommendation on format of PCI may be considered?</u> *Complete revascularisation better:* None *Culprit revascularisation better:* Short-term mortality, Renal failure *No difference:* Long-term mortality, Reinfarction, Bleeding, Stroke
Meta-analysis (unknown study type) Rahman H, et al. Revascularisation strategies in cardiogenic	Systematic review and meta-analysis comparing culprit-only revascularisation with immediate multi-vessel revascularisation in patients with acute MI, multi-vessel coronary disease and cardiogenic shock. Thirteen studies of unspecified design were included in the analysis (n=7,311). Short-term outcomes were assessed in-hospital or at ≤30 days, long-term outcomes were ≥6 months. Culprit-only revascularisation was associated with significant	Section 9.4 SIGN recommendation: Patients presenting with cardiogenic shock due to left ventricular failure within six hours of acute myocardial

Reference and study type	Information likely to be relevant	Impact on guideline
shock complicating acute myocardial infarction: a systematic review and meta-analysis. Cardiovasc Revasc Med. 2018;19(6):647-54.	reductions in risk of short-term all-cause mortality (RR 0.87, 95% CI 0.77 to 0.97, p=0.01) and renal failure (RR 0.75, 95% CI 0.61 to 0.94, p=0.01) compared with immediate complete revascularisation. There were no significant differences in short-term re-infarction, major bleeding or stroke. Similarly there were no significant differences in long-term all-cause mortality or re-infarction.	infarction should be considered for immediate coronary revascularisation. <u>These findings extend the evidence in the SIGN guideline. Consider whether a recommendation on format of PCI may be considered?</u> *Complete revascularisation better:* None *Culprit revascularisation better:* Short-term mortality, Renal failure *No difference:* Long-term mortality, Reinfarction, Bleeding, Stroke
Meta-analysis (observational studies) Kolte D, et al. Culprit vessel-only versus multivessel percutaneous coronary intervention in patients with cardiogenic shock complicating ST-segment-elevation	Meta-analysis of 11 non-randomised studies (n=5,850) comparing immediate or single-stage multi-vessel PCI with culprit vessel only PCI in patients with STEMI, multi-vessel coronary disease and cardiogenic stroke. The primary endpoint was in-hospital or 30-day (short-term) mortality. No statistically significant differences were found in short-term mortality, long-term mortality, cardiovascular death, re-infarction, repeat revascularisation, in-hospital stroke, renal failure or major bleeding.	Section 9.4 SIGN recommendation: Patients presenting with cardiogenic shock due to left ventricular failure within six hours of acute myocardial infarction should be considered for immediate coronary revascularisation.

Reference and study type	Information likely to be relevant	Impact on guideline
myocardial infarction: a collaborative meta-analysis. Circulation Cardiovasc Intervent. 2017;10(11).		<u>These findings extend the evidence in the SIGN guideline, however show no difference in outcome between multivessel or culprit vessel PCI.</u> *Complete revascularisation better:* None *Culprit revascularisation better:* None *No difference:* Long-term mortality, Short-term mortality, CV mortality, Renal failure Reinfarction, Repeat revascularisation Bleeding, Stroke

KQ 6: What is the clinical and cost effectiveness of multi-vessel compared to culprit-only primary percutaneous coronary intervention in patients with ST segment elevation myocardial infarction and multivessel coronary disease?
(Economic evidence)

Reference and study type	Information likely to be relevant	Impact on guideline
Barton GR, *et al.* Economic evaluation of complete	Economic analysis based on a multi-centre RCT (n=296) comparing complete revascularisation at index hospitalisation with culprit vessel only revascularisation in patients with STEMI and multi-vessel coronary disease	Section 5.5 No SIGN recommendation

revascularisation for patients with multivessel disease undergoing primary percutaneous coronary intervention. Value Health. 2017;20(6):745-51.	undergoing primary PCI. Costs for the primary PCI procedure, length of hospital stay and readmissions estimated for the analysis. Mean incremental overall hospital costs for complete revascularisation were estimated to be -£215.96 (95% CI -£1390.20 to £958.29) compared with culprit-only revascularisation. Complete revascularisation was also associated with a per-patient mean reduction in major adverse cardiac events of 0.17 (95% CI 0.04 to 0.30) and a QALY gain of 0.01 (95% CI -0.02 to 0.04). At a willingness-to-pay threshold of £20,000 the probability of complete revascularisation being cost-effective was 72.0%.	Complete revascularisation (at index) is cost effective compared with culprit vessel revascularisation

KQ 9: What is the optimal duration (clinical and cost-effectiveness) of dual antiplatelet therapy in patients with acute coronary syndrome?

Reference and study type	Information likely to be relevant	Impact on guideline
Meta-analysis (RCTs) Misumida N, et al. Efficacy and safety of short-term dual antiplatelet therapy (<=6 months) after percutaneous coronary intervention for acute coronary syndrome: a systematic review and meta-analysis of randomized controlled trials. Clin Cardiol. 2018;41(11):1455-62.	Systematic review and meta-analysis of 10 RCTs (n=12,696) comparing short-term (≤6 months) with long-term (≥12 months) dual antiplatelet therapy in patients with ACS undergoing PCI. Included studies used dual antiplatelet therapy for 3-6 months in the short-term group and 12-24 months in the long-term group. There were no statistically significant differences between groups in MI, stent thrombosis, major bleeding events, all-cause mortality, cardiac death, or net adverse cardiac and cerebrovascular events.	Section 8.1.2 SIGN recommendation: Patients with acute coronary syndrome should receive dual antiplatelet therapy for six months. Longer durations may be used where the risks of atherothrombotic events outweigh the risk of bleeding. Shorter durations may be used where the risks of bleeding outweigh the risk of atherothrombotic events. No impact on guideline
Meta-analysis (RCTs)	Meta-analysis of three RCTs (n=3,391) comparing antiplatelet de-escalation with continuation in patients with ACS treated with PCI. No information is given in the abstract about how studies were identified or other methods. A	Section 8.1.2 No SIGN recommendation on de-escalation

Reference and study type	Information likely to be relevant	Impact on guideline
Kheiri B, et al. De-escalation of antiplatelet therapy in patients with acute coronary syndrome undergoing percutaneous coronary intervention: a meta-analysis of randomized clinical trials. J Cardiovasc Pharmacol Therap. 2018:1074248418809098.	composite of bleeding and thrombotic events was significantly reduced in the group switching to clopidogrel (de-escalation) compared with the continuation group: RR 0.64, 95% CI 0.43 to 0.97, p=0.03. No statistically significant differences were reported for major adverse cardiovascular events, all bleeding, or BARC ≥3 bleeding.	

KQ 9: What is the optimal duration (clinical and cost-effectiveness) of dual antiplatelet therapy in patients with acute coronary syndrome? **(Economic evidence)**

Reference and study type	Information likely to be relevant	Impact on guideline
Jiang M, You JHS. Cost-effectiveness analysis of 30-month vs 12-month dual antiplatelet therapy with clopidogrel and aspirin after drug-eluting stents in patients with acute coronary syndrome. Clin Cardiol. 2017;40(10):789-96.	Economic evaluation using a lifetime decision-analytic model to simulate two antiplatelet strategies in event-free ACS patients who had completed 12 months dual antiplatelet therapy following drug eluting stent implantation: aspirin monotherapy versus continuation of dual antiplatelet therapy (clopidogrel plus aspirin) for an additional 18 months. Clinical event rates, direct medical costs and QALYs gained were calculated from a US healthcare provider perspective. In the base case, continued dual antiplatelet therapy was associated with higher QALYs (8.18 vs. 8.16) and lower costs (USD$42,982/£32,788 vs. US$44,063/£33,612). In probabilistic sensitivity analyses, continued dual antiplatelet therapy was the preferred strategy in 74.75% of simulations at a willingness-to-pay threshold of US$50,000 (£38,128) per QALY. Cost effectiveness of dual antiplatelet therapy for 30 months was highly subject to changes in the odds of non-fatal stroke and death.	Section 8.1.2 No SIGN recommendation for extended DAPT

KQ 10: What is the clinical and cost effectiveness of rivaroxaban or apixaban or dabigatrin in addition to dual antiplatelet therapy in patients with acute coronary syndrome?

Reference and study type	Information likely to be relevant	Impact on guideline
NICE TA335: rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome (2015)	Guidance from TA335 (extracted verbatim): 1.1. Rivaroxaban is recommended as an option within its marketing authorisation, in combination with aspirin plus clopidogrel or aspirin alone, for preventing atherothrombotic events in people who have had an acute coronary syndrome with elevated cardiac biomarkers. 1.2. Clinicians should carefully assess the person's risk of bleeding before treatment with rivaroxaban is started. The decision to start treatment should be made after an informed discussion between the clinician and the patient about the benefits and risks of rivaroxaban in combination with aspirin plus clopidogrel or with aspirin alone, compared with aspirin plus clopidogrel or aspirin alone. 1.3. A decision on continuation of treatment should be taken no later than 12 months after starting treatment. Clinicians should regularly reassess the relative benefits and risks of continuing treatment with rivaroxaban and discuss them with the patient.	Section 8.2.1 SIGN Recommendation: Patients with acute coronary syndrome should not be offered rivaroxaban, apixaban or dabigatran in addition to dual antiplatelet therapy. Guideline already notes small clinical benefit but large bleeding risk. No impact on guideline
Chiarito M, et al. Direct oral anticoagulants in addition to antiplatelet therapy for secondary prevention after acute coronary syndromes: a systematic review and meta-analysis. JAMA Cardiol. 2018;3(3):234-41.	Systematic review and meta-analysis of six RCTs (n=29,667) comparing direct oral anticoagulant (DOAC) therapy in addition to antiplatelet therapy after ACS, stratified by baseline clinical presentation. The primary efficacy endpoint was a composite of cardiovascular death, MI and stroke. The primary safety endpoint was major bleeding. The primary efficacy endpoint risk was significantly lower in patients treated with a DOAC plus antiplatelet therapy compared with antiplatelet therapy alone: OR 0.85, 95% CI 0.77 to 0.93, p<0.001. However, this beneficial effect was only observed in patients with STEMI (OR 0.76, 95% CI 0.66 to 0.88, p<0.001). No significant treatment effect was observed in patients with NSTE-ACS. DOAC therapy in addition to antiplatelet therapy was associated with a higher risk of major bleeding (OR	Section 8.2.1 SIGN Recommendation: Patients with acute coronary syndrome should not be offered rivaroxaban, apixaban or dabigatran in addition to dual antiplatelet therapy. Guideline already notes small clinical benefit but large

	3.17, 95% CI 2.27 to 4.42, p<0.001) compared with antiplatelet therapy alone in patients with STEMI and patients with NSTE-ACS.	bleeding risk. No impact on guideline

KQ 10: What is the clinical and cost effectiveness of rivaroxaban or apixaban or dabigatrin in addition to dual antiplatelet therapy in patients with acute coronary syndrome?
(Economic evidence)

Reference and study type	Information likely to be relevant	Impact on guideline
Begum N, *et al.* Cost-effectiveness analysis of rivaroxaban in the secondary prevention of acute coronary syndromes in Sweden. Cardiol Therapy. 2015;4(2):131-53.	Economic evaluation assessing the cost effectiveness of rivaroxaban combined with standard antiplatelet therapy compared with standard antiplatelet therapy alone for secondary prevention of ACS. The analysis took a Swedish societal perspective and used clinical data from the global ATLAS ACS 2-TIMI 51 trial. Rivaroxaban was associated with improvements in survival and QALYs in the base case, yielding an incremental cost per QALY of 71,246 Swedish Krona/SEK (€8,045/£6,942). In probabilistic sensitivity analyses rivaroxaban was cost effective in >99.9% of cases at a willingness-to-pay threshold of SEK 500,000 (€56,458/£48,720).	Section 8.2.1 SIGN Recommendation: Patients with acute coronary syndrome should not be offered rivaroxaban, apixaban or dabigatran in addition to dual antiplatelet therapy. If the recommendation in this section will not change, then this will not have impact on the guideline. If rivaroxaban is recommended, this finding could be considered to demonstrate that it is a cost-effective option for secondary prevention of cardiovascular events in ACS patients receiving single or dual antiplatelet therapy.

2.2 New evidence for sections in SIGN 148 not associated with a key question

4.5.3 DIRECT THROMBIN INHIBITORS		
Reference and study type	**Information likely to be relevant**	**Impact on guideline**
Meta-analysis (RCTs) Fahrni G, et al. Prolonged high-dose bivalirudin infusion reduces major bleeding without increasing stent thrombosis in patients undergoing primary percutaneous coronary intervention: novel insights from an updated meta-analysis. J Am Heart Assoc. 2016;5(7):22.	Meta-analysis of 6 RCTs (n=17,294) comparing bivalirudin (with or without prolonged infusion) with conventional antithrombotic therapy in STEMI patients undergoing primary PCI. Pre-specified outcomes were major bleeding, acute stent thrombosis, 30-day all-cause mortality and 30-day cardiac mortality. Bivalirudin was associated with significant reductions in risk of major bleeding (OR 0.65, 95% CI 0.48 to 0.88, p=0.006), all-cause mortality (OR 0.81, 95% CI 0.67 to 0.98, p=0.03) and cardiac mortality (OR 0.69, 95% CI 0.55 to 0.87, p=0.001) compared with heparin (± glycoprotein IIb/IIIa inhibitors). Bivalirudin was also associated with an increased risk of acute stent thrombosis compared with heparin: OR 2.75, 95% CI 1.46 to 5.18, p=0.002. *There were other meta-analyses on this topic which all concluded that bivalirudin did not significantly affect mortality in patients with ACS.	Section 4.5.3 No SIGN recommendation
5. 1 CHOICE OF REPERFUSION THERAPY		
Meta-analysis (RCTs) Yang HT, *et al.* Invasive reperfusion after 12 hours of the symptom onset remains beneficial in patients with ST-segment elevation myocardial infarction: evidence from a meta-analysis of published data. Cardiol J. 2018;03:03.	Meta-analysis comparing late reperfusion (≥12 hours) with standard drug therapy in patients with acute MI. Eighteen studies (n=14,677) of unknown design were included in the analysis. Compared with medical therapy, late PCI was associated with statistically significant decreases in all-cause mortality (RR 0.60, 95% CI 0.44 to 0.83, p=0.002), MACE (RR 0.67, 95% CI 0.50 to 0.89, p<0.001), and heart failure (RR 0.76, 95% CI 0.60 to 0.97, p=0.03). Subgroup analyses indicated that these benefits were for PCI after 12 hours but not from 2-60 days after onset of symptoms.	Section 5.1 SIGN recommendation: Patients with an ST-segment-elevation acute coronary syndrome should be treated immediately with primary percutaneous coronary intervention. <u>The guideline does not compare late PCI with medical therapies.</u>
8.7 MINERALOCORTICOID RECEPTOR ANTAGONISTS		

Meta-analysis (RCTs) Dahal K, et al. Aldosterone antagonist therapy and mortality in patients with ST-segment elevation myocardial infarction without heart failure: a systematic review and meta-analysis. JAMA Intern Med. 2018;178(7):913-20.	Systematic review and meta-analysis of 10 RCTs (n=4,147) evaluating the use of aldosterone antagonists in patients with STEMI and LVEF >40% or without congestive heart failure. Aldosterone treatment of patients with STEMI without heart failure was associated with a significantly lower risk of mortality (OR 0.62, 95% CI 0.42 to 0.91, p=0.01), a significant increase in LVEF (MD 1.58%, 95% CI 0.18% to 2.97%, p=0.03) and a small increase in serum potassium levels (MD 0.07 mEq/L, 95% CI 0.01 to 0.13 mEq/L, p=0.02) compared with controls. No significant differences were found for risk of MI, new congestive heart failure, ventricular arrhythmia, or serum creatinine levels.	Section 8.7 SIGN recommendation: Patients with myocardial infarction complicated by left ventricular dysfunction (ejection fraction <40%) in the presence of either clinical features of heart failure or diabetes mellitus should be commenced on long-term eplerenone therapy. This is a different indication for MCRA drugs than the one included in the guideline and could be considered?

2.3 Evidence for potentially relevant topics which are not included in SIGN 148

ADENOSINE AS AN ADJUNCT TO REVASCULARISATION

Reference and study type	Information likely to be relevant	Impact on guideline
Meta-analysis (RCTs) Bulluck H, et al. Clinical benefit of adenosine as an adjunct to reperfusion in ST-elevation myocardial infarction patients: an updated meta-analysis of randomized controlled trials. Int J Cardiol. 2016;202:228-37.	Meta-analysis of 12 RCTs (n=4,273) evaluating the use of intracoronary or intravenous adenosine therapy as an adjunct to reperfusion in STEMI patients. The primary clinical endpoints were all-cause mortality, non-fatal MI and heart failure. Risk of heart failure (RR 0.44, 95% CI 0.25 to 0.78, p=0.005) and coronary no-reflow (RR for TIMI flow <3 post-reperfusion 0.68, 95% CI 0.47 to 0.99, p=0.04) were significantly reduced in patients administered intracoronary adenosine. No statistically significant effects were reported for patients receiving intravenous adenosine. There was no significant difference in non-fatal MI or all-cause mortality in patients treated with either intracoronary or intravenous adenosine.	Not a clinical priority *(David Newby)*

Reference and study type	Information likely to be relevant	Impact on guideline
Meta-analysis (RCTs) Gao Q, et al. Efficacy of adenosine in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention: a PRISMA-compliant meta-analysis. Medicine. 2015;94(32):e1279.	Meta-analysis of 15 RCTs (n=1,736) evaluating the efficacy of adjunctive adenosine therapy compared with placebo in patients with acute MI undergoing primary PCI. Compared with placebo, adenosine was associated with a lower risk of heart failure (RR 0.65, 95% CI 0.43 to 0.97, p=0.03) and coronary no-reflow (RR for TIMI flow grade <3 post intervention 0.62, 95% CI 0.45 to 0.85. p=0.003). Sub-group analyses indicated that adenosine improved LVEF in patients treated intravenously and patients given regular dose intracoronary therapy compared with placebo.	Not a clinical priority *(David Newby)*

CELL THERAPIES (including stem cell therapy)

Reference and study type	Information likely to be relevant	Impact on guideline
Meta-analysis (RCTs) Wang C, et al. Impact of bone marrow mononuclear cells therapy on left ventricular function in patients with ST-elevated myocardial infarction: a meta-analysis. Medicine. 2018;97(16):e0359.	Meta-analysis assessing the efficacy of bone marrow mononuclear cell therapy in patients with STEMI. In 24 trials (n=1,536) cell therapy was associated with a significant reduction in infarct size (MD -2.32, 95% CI -4.03 to -0.62, p=0.007) and improved myocardial perfusion (MD -3.04, 95% CI -3.94 to -2.15, p<0.001) compared with controls.	Use of stem cell therapies for cardiac regeneration are complex procedures restricted to specialist settings and probably not appropriate for inclusion in the SIGN guideline at this stage. *(David Newby)*
Meta-analysis (RCTs) Zhang J, et al. Bone marrow mononuclear cells transfer for patients after	Meta-analysis of 22 RCTs (n=1,360) assessing the efficacy of intracoronary bone marrow mononuclear cells in patients with STEMI who had undergone successful PCI. Sub-group analyses assessed optimal timing and dose of cell therapy. Pooled statistics showed a significant improvement in LVEF in the bone marrow mononuclear cell therapy group compared with controls: MD	See above

Reference and study type	Information likely to be relevant	Impact on guideline
ST-elevated myocardial infarction: a meta-analysis of randomized control trials. Yonsei Med J. 2018;59(5):611-23.	2.58, 95% CI 1.32 to 3.84, p<0.001. LVEDV (MD -3.73, 95% CI -6.94 to -0.52, p=0.02) and LVESV (MD -4.67, 95% CI -7.07 to -2.28, p<0.001) were also significantly improved in the bone marrow cell group compared with controls. In sensitivity and subgroup analyses the reduction in LVEDV was lost, although the improvements in LVEF and LVESV remained.	
Meta-analysis (RCTs) Jeyaraman M, *et al.* Autologous bone marrow stem cell therapy in patients with ST-elevation myocardial infarction: a systematic review and meta-analysis. Can J Cardiol. 2017;33(12):1611-23.	Systematic review and meta-analysis of 42 RCTs (n=3,365) assessing efficacy and safety of intracoronary administration of bone marrow stem cell therapy in patients with STEMI after PCI. The primary outcome was all-cause mortality. There was no statistically significant reduction in mortality or adverse event rates. Trial sequential analysis suggested a low probability that future studies would change the conclusions of the analysis.	See above
Meta-analysis (RCTs) Wang Z, et al. Rational transplant timing and dose of mesenchymal stromal cells in patients with acute myocardial infarction: a meta-analysis of randomized controlled trials. Stem Cell Res Ther. 2017;8(1):21.	Meta-analysis of eight RCTs (n=449) to determine the optimal mesenchymal stromal cell transplant time and cell dose in patients with acute MI. Patients receiving a stromal cell infusion within 1 week had significantly increased LVEF compared with controls (MD 3.22%, 95% CI 1.31% to 5.14%, p<0.05); this difference was not significant in patients receiving an infusion more than 1 week after acute MI. LVEF was also significantly improved in the cell therapy group compared to controls when patients received a dose of less than 10^7 cells: MD 2.25%, 95% CI 0.56% to 3.93%, p<0.05. Patients treated within 1 week with a cell dose $<10^7$ had a significant improvement in LVEF of MD 3.32% (95% CI 1.14% to 5.50%, p=0.003).	See above
Xu JY, et al. Effects of timing on intracoronary autologous bone marrow-derived cell transplantation in acute	Meta-analysis of 34 RCTs (n=2,307) with a minimum of 3 months follow-up investigating optimal timing of bone marrow derived cell therapy in acute MI patients undergoing emergency PCI. Bone marrow cell transplantation within 3-7 days after PCI resulted in a significant increase in LVEF compared with controls: WMD 3.32%, 85% CI 1.91% to 4.74%, p<0.00001. There was no	See above

Reference and study type	Information likely to be relevant	Impact on guideline
myocardial infarction: a meta-analysis of randomized controlled trials. Stem Cell Res Ther. 2017;8(1):231.	significant effects in patients treated within 24 hours or more than 7 days after PCI. Subgroup analyses suggested that bone marrow cell therapy was more effective in patients with baseline LVEF ≤50% (WMD -5.25, 95% CI -9.30 to -1.20, p=0.01) or who received a dose of 10^7-10^8 cells (WMD -12.99, 95% CI -19.07 to -6.91, p<0.0001). *This paper may be a second publication of the same meta-analysis from 2016 (Xu JY, et al. Stem cell transplantation dose in patients with acute myocardial infarction: a meta-analysis. Chronic Dis Translat Med. 2016;2(2):92-101).	
Lee SH, et al. Discrepancy between short-term and long-term effects of bone marrow-derived cell therapy in acute myocardial infarction: a systematic review and meta-analysis. Stem Cell Res Ther. 2016;7(1):153.	Systematic review and meta-analysis of 43 studies (n=2,635) evaluating short-term and long-term effectiveness of bone marrow derived cell therapy in patients with acute MI. The study design of included studies is unclear from the abstract. A modest improvement in LVEF was reported at 6 months follow-up but it is unclear if this was statistically significant and there were no significant differences in LVEF at longer follow-up times. No safety issues were reported during follow-up. At 5 years follow-up all-cause mortality was significantly lower in the cell therapy group.	See above
Li R, Li XM, Chen JR. Clinical efficacy and safety of autologous stem cell transplantation for patients with ST-segment elevation myocardial infarction. Therapeut Clin Risk Manag. 2016;12:1171-89.	Systematic review and meta-analysis of 28 RCTs (n=1,938) evaluating efficacy and safety of autologous stem cell therapy in patients with STEMI. Minimal details were provided in the abstract about methods used to identify and assess studies. There was a statistically significant improvement in LVEF at 12 months follow-up in the treatment group (3.15%, 95% CI 1.01% to 5.29%, p<0.01). Statistically significant differences in LVEF were also reported at 3-4 months and six months (p≤0.05). Infarct size was significantly smaller in the treatment group compared with controls at 12 months follow-up (p<0.01). No significant differences were found for adverse reactions.	See above
Liu B, et al. Impact of timing following acute	Network meta-analysis comparing different timings of bone marrow stem cell therapy following acute MI. The literature search 31 studies (n=2,035) where	See above

Reference and study type	Information likely to be relevant	Impact on guideline
myocardial infarction on efficacy and safety of bone marrow stem cells therapy: a network meta-analysis. Stem Cells Int. 2016;2016:1031794.	patients received treatment at 1-3 days, 4-7 days, 8-14 days, 15-30 days or placebo/control. Multiple treatment comparison indicated that the group receiving treatment within 4-7 days may have significantly increased LVEF compared to controls at 6 months follow-up (mean of mean difference 3.05, 95% credible interval (CrI) 0.92 to 5.25) and 12 months follow-up (mean of mean differences 4.18, 95% CrI 2.30 to 5.84). Patients in this group also had significant reductions in major adverse cardiac events compared with controls (OR 0.34, 95% CrI 0.13 to 0.96).	
Xu JY, et al. Stem cell transplantation dose in patients with acute myocardial infarction: a meta-analysis. Chronic Dis Translat Med. 2016;2(2):92-101.	Meta-analysis evaluating whether stem cell transplantation improved global LVEF in patients with acute MI and the optimal dose and timing of transplantation. Four subgroups were identified based on stem cell dose (≤1 × 10^7 cells, ≤1 × 10^8 cells, ≤1 × 10^9 cells, and ≤1 × 10^{10} cells) and follow-up time (<6 months, 6-12 months, and ≥12 months). Approximately 40 RCTs* (n=1,927) were included in the analysis. Change in global LVEF was significantly greater in the stem cell transplant group compared with controls: MD 3.31%, 95% CI 2.35% to 4.26%, p<0.01. Sub-group analyses showed that significant differences in mean LVEF were only reported in subgroups treated with ≤10^8 (MD 2.60%, 95% CI 0.95% to 4.25%, p=0.002) or ≤10^9 (MD 3.25%, 95% CI 2.31% to 4.20%, p<0.01) cells. *Abstract states 34 studies found, which included 40 RCTs. Potentially included systematic reviews or meta-analyses?	See above
Cong XQ, et al. Short-term effect of autologous bone marrow stem cells to treat acute myocardial infarction: a meta-analysis of randomized controlled clinical trials. J Cardiovasc Translat Res. 2015;8(4):221-31.	Meta-analysis of 17 RCTs (n unknown) evaluating the short-term efficacy and safety of bone marrow stem cell therapy via an intracoronary route in patients with STEMI. No systematic review methods are reported in the abstract. At 3-6 months follow-up intracoronary bone marrow stem cell therapy was associated with significant improvements in LVEF (2.74%, 95 % CI 2.09 to 3.39, p<0.00001), left ventricular end-systolic volume and wall motion score index. At 12 months follow-up LVEF (5.1%, 95% CI 4.16 to 6.03, p<0.00001), LVEDV, LVESV and wall motion score index were all significantly improved in the bone marrow stem cell group.	See above

Reference and study type	Information likely to be relevant	Impact on guideline
Gyongyosi M, et al. Meta-analysis of cell-based cardiac studies (ACCRUE) in patients with acute myocardial infarction based on individual patient data. Circulation Res. 2015;116(8):1346-60.	Individual patient data meta-analysis assessing the safety and efficacy of intracoronary cell therapy compared with controls after acute MI. Data were extracted for patients in 12 RCTs (n=1,252). The primary endpoint was freedom from combined major adverse cardiac and cerebrovascular events. No statistically significant results were reported for major adverse cardiac and cerebrovascular events, death, or for death/acute MI/stroke. No significant differences in left ventricular function were identified.	See above

ENDOVASCULAR COOLING AND THERAPEUTIC HYPOTHERMIA

Reference and study type	Information likely to be relevant	Impact on guideline
Dae M, et al. Effects of endovascular cooling on infarct size in ST-segment elevation myocardial infarction: a patient-level pooled analysis from randomized trials. J Interventional Cardiol. 2018;31(3):269-76.	A patient-level pooled analysis of 6 RCTs (n=629) on endovascular cooling during primary PCI in patients with STEMI. No information is provided in the abstract on how the RCTs were identified. Patients with an anterior infarct hypothermia <35 degrees C following endovascular cooling had a statistically significant absolute reduction in infarct size of 6.5%, p=0.03 (relative reduction 30%) compared with controls. There was no significant difference in infarct size for patients with anterior infarct and ≥35 degrees C temperature or patients with inferior infarct.	Small numbers – no patient-related outcomes reported.
Villablanca PA, et al. Therapeutic hypothermia in ST elevation myocardial infarction: a systematic review and meta-analysis of randomised control	Systematic review and meta-analysis of 6 RCTs (n=819) assessing the efficacy and safety of therapeutic hypothermia in patients with STEMI. No information was provided in the abstract about methods used. The primary endpoint was major adverse cardiac events (MACE). No significant benefits of therapeutic hypothermia were reported for MACE, all-cause mortality, recurrent MI, heart failure/pulmonary oedema, infarct size, all bleeding,	No benefits reported.

Reference and study type	Information likely to be relevant	Impact on guideline
trials. Heart. 2016;102(9):712-9.	ventricular arrhythmias or bradycardias. A statistically significant difference was observed for therapeutic hypothermia use in patients with anterior wall MI (standard difference of the mean -0.23, 95% CI -0.45 to -0.02).	

GLP-1 RECEPTOR AGONISTS

Reference and study type	Information likely to be relevant	Impact on guideline
Huang M, et al. Protective effect of glucagon-like peptide-1 agents on reperfusion injury for acute myocardial infarction: a meta-analysis of randomized controlled trials. Ann Med. 2017;49(7):552-61.	Meta-analysis of six RCTs (n=800) comparing using glucagon-like peptide-1 (GLP-1) receptor agonists in acute MI patients to prevent reperfusion injury during PCI with placebo. GLP-1 agents were associated with significant improvements in LVEF (WMD GLP-12.46%, 95% CI 0.23% to 4.70%), reduced infarct size (WMD -5.29g, 95% CI -10.39g to -0.19g), and area at risk (WMD -0.08%, 95% CI -0.12% to -0.04%) compared with placebo. There were no statistically significant differences in incidence of cardiovascular events. There was a statistically significant increase in the risk of gastrointestinal adverse events in patients treated with GLP-1 (RR 5.50, 95% CI 2.85 to 10.60).	No evidence of benefit in hard cardiovascular outcomes, but evidence of harms.

ISCHAEMIC CONDITIONING

Reference and study type	Information likely to be relevant	Impact on guideline
Liu H, et al. Remote ischemic conditioning improves myocardial parameters and clinical	Systematic review and meta-analysis of 10 RCTs (n=1,006) evaluating the effects of remote ischaemic conditioning on myocardial parameters and clinical outcomes in patients with STEMI undergoing primary PCI. Remote ischaemic conditioning resulted in significantly lower risk of all-cause mortality	Not clinical priority. Evidence accumulating but not yet conclusive (see section 2.4)

Reference and study type	Information likely to be relevant	Impact on guideline
outcomes during primary percutaneous coronary intervention: a meta-analysis of randomized controlled trials. Oncotarget. 2018;9(9):8653-64.	(OR 0.27, 95% CI 0.12 to 0.62, p=0.002) and major adverse cardiovascular or cerebrovascular events (OR 0.45, 95% CI 0.27 to 0.75, p=0.002). Remote ischaemic conditioning was also associated with significant reductions in myocardial enzyme levels (standardized mean difference -0.86, 95% CI -1.44 to -0.28, p=0.004) and increased incidence of ST-segment resolution (OR 1.74, 95% CI 1.09 to 2.77).	
Man C, et al. Meta-analysis of remote ischemic conditioning in patients with acute myocardial infarction. Sci Reports. 2017;7:43529.	Meta-analysis of 13 RCTs (n unknown) to evaluate the benefits of remote ischaemic conditioning in patients with acute MI. Remote ischaemic conditioning was associated with significantly reduced all-cause mortality (RR 0.33, 95% CI 0.17 to 0.64, p=0.001). Significant changes favouring remote ischaemic conditioning were also recorded for creatine kinase-myocardiac band, troponin T and ST-segment resolution. Subgroup analyses suggested the effects of remote ischaemic conditioning may vary depending on the limb used, duration of therapy, and clinical setting.	Not clinical priority. Evidence accumulating but not yet conclusive (see section 2.4)
McLeod SL, et al. Remote ischemic preconditioning to reduce reperfusion injury during acute ST-segment-elevation myocardial infarction: a systematic review and meta-analysis. J Am Heart Assoc. 2017;6(5):17.	Systematic review and meta-analysis of 9 RCTs (n=1,220) comparing PCI with and without remote ischaemic conditioning to determine the impact of remote ischaemic conditioning prior to catheterisation on myocardial salvage index, infarct size and major adverse cardiovascular events in patients with STEMI. Major cardiovascular events were significantly lower in the PCI plus remote ischaemic conditioning group compared with PCI without remote ischaemic conditioning: RR 0.57, 95% CI 0.40 to 0.82. The myocardial salvage index was significantly higher and infarct size significantly reduced in the PCI plus remote ischaemic monitoring group.	Not clinical priority. Evidence accumulating but not yet conclusive (see section 2.4)

INVASIVE MANAGEMENT *V* CONSERVATIVE STRATEGIES IN ELDERLY ACS PATIENTS

Reference and study type	Information likely to be relevant	Impact on guideline
Ma W, et al. Early invasive versus initially conservative strategy in elderly patients older than 75 years with non-ST-elevation acute coronary syndrome: a meta-analysis. Heart Lung Circ. 2018;27(5):611-20.	Meta-analysis comparing an invasive strategy with a conservative strategy in the management of elderly patients (>75 years) with NSTEMI. Four RCTs and nine observational studies were included in the analysis (n=832,007). Compared with the conservative strategy, the early invasive approach significantly reduced the risk of death at 6 months to 5 years follow-up: RR 0.65, 95% CI 0.59 to 0.73, p<0.001. This benefit was mainly derived from results of observational studies (RR 0.63, 95% CI 0.57 to 0.70, p<0.001). Patients treated with the invasive strategy had a higher risk of any in-hospital bleeding compared with patients treated with the conservative strategy: RR 2.51, 95% CI 1.53 to 4.11, p<0.001. No significant differences were observed for major in-hospital bleeding.	The evidence for this subject is accumulating but, at present, is insufficient to draw firm conclusions as it is mostly based on observational studies. RCTs are in progress which will further inform the topic however these are not due to report in the next 12 months (see section 2.4)
Saraswat A, et al. An invasive vs a conservative approach in elderly patients with non-ST-segment elevation myocardial infarction: systematic review and meta-analysis. Canadian J Cardiol. 2018;34(3):274-80.	Systematic review and meta-analysis comparing an invasive and conservative strategy of NSTEMI management in elderly patients (≥75 years). Minimal details are provided in the abstract about the methods used in the analysis. Three RCTs and 6 observational studies were included in the analysis (n=19,698). The invasive management strategy was associated with significantly lower 12-month mortality (OR 0.45, 95% CI 0.34 to 0.59 p<0.00001), 30-day mortality (OR 0.50, 95% CI 0.33 to 0.75, p=0.0009), and stroke events (OR 0.42, 95% CI 0.28 to 0.61, p<0.00001). Major bleeding was significantly higher in the invasive management group (OR 1.63, 95% CI 1.05 to 2.54, p=0.03). When analyses were restricted to RCTs there were lower re-infarction rates in the invasive management group at 12 months follow-up.	The evidence for this subject is accumulating but, at present, is insufficient to draw firm conclusions as it is mostly based on observational studies. RCTs are in progress which will further inform the topic however these are not due to report in the next 12 months (see section 2.4).

2.4 Additional evidence submitted for consideration by Professor David Newby

Reference and study type	Information likely to be relevant	Impact on guideline
Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes (ISAR-REACT 5) Schüpke S, Neumann F-J, Menichelli M, Mayer K, Bernlochner I, Wöhrle J, et al. N Eng J Med 2019 https://www.nejm.org/doi/full/10.1056/NEJMoa1908973	Among patients who presented with ACS with or without ST-segment elevation, the incidence of death, myocardial infarction, or stroke after 1 year was significantly lower among those who received prasugrel than among those who received ticagrelor (hazard ratio, 1.36; 95% CI, 1.09 to 1.70; p=0.006), and the incidence of major bleeding was not significantly different between the two groups	Potentially major. This result contradicts the recommendation in SIGN 148.
Complete vs Culprit-only Revascularization to Treat Multi-vessel Disease After Early PCI for STEMI (COMPLETE) Mehta SR, Wood DA, Storey RF, Mehran R, Bainey KR, Nguyen H, et al. N Eng J Med 2019 https://www.nejm.org/doi/full/10.1056/NEJMoa1907775	Among patients with STEMI and multivessel coronary artery disease, complete revascularisation was superior to culprit-lesion-only PCI in reducing the risk of cardiovascular death or myocardial infarction (hazard ratio, 0.74; 95% CI 0.60 to 0.91; p=0.004), as well as the risk of cardiovascular death, myocardial infarction, or ischemia-driven revascularisation (HR 0.51, 95% CI 0.43 to 0.61;p<0.001). Published 1 September 2019	Potentially major. This trial supports complete revascularisation over culprit-lesion revascularisation
Effect of Remote Ischaemic Conditioning on Clinical Outcomes in STEMI Patients Undergoing PPCI (CONDI2/ERIC-PPCI) https://clinicaltrials.gov/ct2/show/NCT02342522	The CONDI2/ERIC-PPCI trial is an RCT investigating whether remote ischemic conditioning can reduce cardiac death and hospitalisation for heart failure at 12 months in 5,400 patients presenting with a ST-elevation myocardial infarction (STEMI) and treated by percutaneous coronary intervention (PPCI). Completion date: December 2019	Preliminary results presented at ESC 2019 showed no significant effect of ischaemic conditioning.
The British Heart Foundation SENIOR-RITA Trial (SENIOR-RITA) https://clinicaltrials.gov/ct2/show/NCT03052036	SENIOR-RITA is a multicentre prospective open-label trial randomizing patients presenting with type 1 NSTEMI aged ≥75 years between invasive and conservative treatment strategies, to compare time to cardiovascular death or non-fatal MI within one year from randomisation.	This major UK RCT will provide evidence on invasive v conservative strategies for elderly people with NSTEMI.

Reference and study type	Information likely to be relevant	Impact on guideline
	Completion date: September 2020- September 2029	
High-Sensitivity Cardiac Troponin On Presentation to Rule Out Myocardial Infarction (HiSTORIC) https://clinicaltrials.gov/ct2/show/NCT03005158	Patients with suspected acute coronary syndrome account for 10% of all presentations to the Emergency Department and up to 40% of unplanned hospital admissions. The majority of patients do not have a heart attack (myocardial infarction), and may be safely discharged from the Emergency Department. The investigators propose to evaluate whether the use of the HighSTEACS pathway in patients with suspected acute coronary syndrome reduces length of stay and allows more patients to be safely discharged from the Emergency Department. This pathways utilizes high-sensitivity cardiac troponin I testing and will rule out myocardial infarction if troponin concentrations are <5 ng/L on presentation, with further testing indicated at 3 hours only in those presenting early or with troponin concentrations between 5 ng/L and the 99th centile. Completion date: December 2021	This trial is being carried out in Edinburgh and will provide evidence for the troponin section, on publication.

Section 3: Consultation feedback

This topic exploration was reviewed by the group responsible for developing SIGN 148, who were asked to comment primarily on the comprehensiveness and accuracy of the summary of findings and whether there is sufficient new evidence to warrant a refresh of the guideline. Guideline development group membership can be found in section 13.2 of the guideline.

Reviewer	Comments
Graham Bell, Lay representative, Penicuik	KQ2 (section 4.4.2) - The work by Nairoo (2017) and Jiang (2016) seem to me to be important. KQ6 (section 5.5) - The formatting of PCI issue and the volume of work suggesting MV PCI is superior to culprit is clearly still a vexed question. I must accept the experts' view but speaking as a patient I would prefer to have the lot done. But then remember I had a triple bypass (23 years ago now!) So perhaps I would say that.
Dr John Irving Consultant Cardiologist Ninewells Hospital, Dundee	KQ2 (section 4.4.2) - Practice changing trials published in 2019 which contradict the published guidelines. Clopidogrel superior to ticagrelor in patients >70 years of age. Large head-to-head randomised trial in ACS showing prasugrel superior to ticagrelor. KQ9 (section 8.1.2) - Ongoing studies will answer this question in a few years Other – A large negative trial on ischemic conditioning (CONDI2/ERIC-PPCI) was presented at ESC 2019.
Dr David McAllister Senior Clinical Lecturer/Honorary Consultant (Public Health), Institute Of Health & Wellbeing, University of Glasgow	Nothing to suggest

Annex 1: Search results

	ACS Scoping Search Searched on 11/3/19 from 2013–2019
Resource	**Results**
Previous HIS projects on this topic	Healthcare Improvement Scotland. Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (review of technology appraisal guidance 182). 2014 [cited 2019 Mar 11]; Available from: http://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/mta_resources/appraisal_317.aspx.
UK guidelines and guidance	
SIGN	SIGN. Acute Coronary Syndrome. 2016 [cited 2019 Mar 11]; Available from: https://www.sign.ac.uk/sign-148-acute-coronary-syndrome.html.
NICE	1. NICE. Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes. 2014 [cited 2019 Mar 11]; Available from: https://www.nice.org.uk/guidance/ta317. 2. NICE. Acute coronary syndromes in adults QS68. 2014 [cited 2019 Mar 11]; Available from: https://www.nice.org.uk/guidance/qs68. 3. NICE. Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome. 2015 [cited 2019 Mar 11]; Available from: https://www.nice.org.uk/guidance/ta335. 4. NICE. Coronary revascularisation: Cangrelor. 2015 [cited 2019 Mar 11]; Available from: https://www.nice.org.uk/advice/esnm63/chapter/Key-points-from-the-evidence. 5. NICE. Chest Pain - Pathway. 2019 [cited 2019 Mar 11]; Available from: https://pathways.nice.org.uk/pathways/chest-pain. 6. NICE. Myocardial Infarction - pathway. 2019 [cited 2019 Mar 11]; Available from: https://pathways.nice.org.uk/pathways/myocardial-infarction-rehabilitation-and-preventing-further-cardiovascular-disease. 7. NICE. Hyperglycaemia in acute coronary syndromes overview - pathway. 2019 [cited 2019 Mar 11]; Available from: https://pathways.nice.org.uk/pathways/hyperglycaemia-in-acute-coronary-syndromes. 8. NICE. Myocardial infarction with ST-segment elevation overview - pathway. 2019 [cited 2019 Mar 11]; Available from: https://pathways.nice.org.uk/pathways/myocardial-infarction-with-st-segment-elevation. 9. NICE. Acute coronary syndromes - In development Due 2020. 2020 [cited 2019 Mar 11]; Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ng10085. 10. NICE. Atherothrombotic events - vorapaxar [ID616] - Suspended. TBC [cited 2019 Mar 11]; Available from: https://www.nice.org.uk/guidance/indevelopment/gid-tag493.

Guidelines International Network (GIN)	*Restricted to publication date 2015+ and English language* State of Qatar. The assessment and management of acute coronary syndrome in adults. 2016 [cited 2019 Mar 11]; Available from: https://www.moph.gov.qa/healthstrategies/Documents/Guidelines/Acute%20Coronary%20Syndrome.pdf.
TRIP Database (UK Guidelines only)	0
Secondary literature and economic evaluations	
ECRI	ECRI. Acute oxygen therapy. 2016 [cited 2019 Mar 11]; Available from: https://www.ecri.org/components/SpecialReports/Pages/24629.aspx.
Cochrane library	145 Protocols for reviews from 2013-2019 13 relevant reviews see below. 1. Andrade-Castellanos CA, Colunga-Lozano LE, Delgado-Figueroa N, Magee K. Heparin versus placebo for non-ST elevation acute coronary syndromes. Cochrane Database of Systematic Reviews. 2014(6). 2. Bennett MH, Lehm JP, Jepson N. Hyperbaric oxygen therapy for acute coronary syndrome. Cochrane Database of Systematic Reviews. 2015(7). 3. Bosch X, Marrugat J, Sanchis J. Platelet glycoprotein IIb/IIIa blockers during percutaneous coronary intervention and as the initial medical treatment of non-ST segment elevation acute coronary syndromes. Cochrane Database of Systematic Reviews. 2013(11). 4. Bravo CA, Hirji SA, Bhatt DL, Kataria R, Faxon DP, Ohman EM, *et al.* Complete versus culprit-only revascularisation in ST elevation myocardial infarction with multi-vessel disease. Cochrane Database of Systematic Reviews. 2017(5). 5. Cabello JB, Burls A, Emparanza JI, Bayliss SE, Quinn T. Oxygen therapy for acute myocardial infarction. Cochrane Database of Systematic Reviews. 2016(12). 6. Fanning JP, Nyong J, Scott IA, Aroney CN, Walters DL. Routine invasive strategies versus selective invasive strategies for unstable angina and non-ST elevation myocardial infarction in the stent era. Cochrane Database of Systematic Reviews. 2016(5). 7. Feinberg J, Nielsen EE, Greenhalgh J, Hounsome J, Sethi NJ, Safi S, *et al.* Drug-eluting stents versus bare-metal stents for acute coronary syndrome. Cochrane Database of Systematic Reviews. 2017(8). 8. Fisher SA, Zhang H, Doree C, Mathur A, Martin-Rendon E. Stem cell treatment for acute myocardial infarction. Cochrane Database of Systematic Reviews. 2015(9). 9. McCaul M, Lourens A, Kredo T. Pre-hospital versus in-hospital thrombolysis for ST-elevation myocardial infarction. Cochrane Database of Systematic Reviews. 2014(9).

	10. Schumann J, Henrich EC, Strobl H, Prondzinsky R, Weiche S, Thiele H*, et al.* Inotropic agents and vasodilator strategies for the treatment of cardiogenic shock or low cardiac output syndrome. Cochrane Database of Systematic Reviews. 2018(1). 11. Su Q, Nyi TS, Li L. Adenosine and verapamil for no-reflow during primary percutaneous coronary intervention in people with acute myocardial infarction. Cochrane Database of Systematic Reviews. 2015(5). 12. Unverzagt S, Buerke M, de Waha A, Haerting J, Pietzner D, Seyfarth M*, et al.* Intra-aortic balloon pump counterpulsation (IABP) for myocardial infarction complicated by cardiogenic shock. Cochrane Database of Systematic Reviews. 2015(3). 13. Vale N, Nordmann AJ, Schwartz GG, de Lemos J, Colivicchi F, den Hartog F*, et al.* Statins for acute coronary syndrome. Cochrane Database of Systematic Reviews. 2014(9).
HTA database	1. Melloni C, Jones WS, Washam JB, Hasselblad V, Mayer SB, Halim S*, et al.* Antiplatelet and anticoagulant treatments for unstable angina/non–ST elevation myocardial infarction2014. 2. Mitchell MD, Blinebury CM, Haber HL, Betesh J. Supplemental oxygen therapy for patients with acute myocardial infarction. Philadelphia: Center for Evidence-based Practice (CEP); 2014. 3. Nihr HSC. Ciclosporin (CicloMulsion) for reperfusion injury prevention prior to percutaneous coronary intervention for ST-segment elevation acute myocardial infarction. Birmingham: NIHR Horizon Scanning Centre (NIHR HSC); 2014. 4. Westwood M, van Asselt T, Ramaekers B, Whiting P, Thokala P, Joore M*, et al.* High-sensitivity troponin assays for the early rule-out or diagnosis of acute myocardial infarction in people with acute chest pain: a systematic review and cost-effectiveness analysis2015.
Medline	3,520 SRs on Medline in English from 2013-2019. Not sifted but in Endnote library 1,902 economics studies using filter from 2013-2019. Not sifted, but in Endnote library
Primary studies (only if insufficient secondary evidence found)	
Medline	11,349 RCTs using filter from 2013-2019 not exported.
Cochrane library	13,856 RCTs in CENTRAL (2013-2019) not exported
Ongoing secondary research	
EUnetHTA Planned & Ongoing Projects database	Nothing in POP alerts file.
PROSPERO database	97 (out of 295) relevant looking protocols. In endnote
Ongoing research (only if insufficient secondary evidence and primary studies found)	

Clinicaltrials.gov *(ongoing studies that have recently closed or are due to complete in the next 6-12 months.)*	56 relevant results. Imported into Endnote library.

Cochrane

#1	MeSH descriptor: [Myocardial Infarction] explode all trees	MeSH	10207
#2	MeSH descriptor: [Angina, Unstable] explode all trees	MeSH	1054
#3	MeSH descriptor: [Coronary Thrombosis] this term only	MeSH	410
#4	acute coronary syndrom*	Limits	5523
#5	acs	Limits	2894
#6	myocardial infarct*	Limits	23734
#7	unstable angina	Limits	3081
#8	unstable near/2 coronary	Limits	385
#9	non-ST-segment elevation	Limits	1096
#10	ST-segment elevation	Limits	4231
#11	STEMI or non-STEMI or NSTEMI or nonSTEMI	Limits	2328
#12	heart attack	Limits	2193
#13	hear near/2 infarct*	Limits	0
#14	ST-elevation	Limits	2333
#15	coronary near/2 thrombos*	Limits	615
#16	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15	Limits	14813

with Cochrane Library publication date from Nov 2013 to Mar 2019