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(Review)

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[Intervention Review]

Complete versus culprit-only revascularisation in ST elevation myocardial infarction with multi-vessel disease

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ABSTRACT

Background

Multi-vessel coronary disease in people with ST elevation myocardial infarction (STEMI) is common and is associated with worse prognosis after STEMI. Based on limited evidence, international guidelines recommend intervention on only the culprit vessel during STEMI. This, in turn, leaves other significantly stenosed coronary arteries for medical therapy or revascularisation based on inducible ischaemia on provocative testing. Newer data suggest that intervention on both the culprit and non-culprit stenotic coronary arteries (complete intervention) may yield better results compared with culprit-only intervention.

Objectives

To assess the effects of early complete revascularisation compared with culprit vessel only intervention strategy in people with STEMI and multi-vessel coronary disease.

Search methods

We searched the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, World Health Organization International Clinical Trials Registry Platform Search Portal, and ClinicalTrials.gov. The date of the last search was 4 January 2017. We applied no language restrictions. We handsearched conference proceedings to December 2016, and contacted authors and companies related to the field.

Selection criteria

We included only randomised controlled trials (RCTs), wherein complete revascularisation strategy was compared with a culprit-only percutaneous coronary intervention (PCI) for the treatment of people with STEMI and multi-vessel coronary disease.

Data collection and analysis

We assessed the methodological quality of each trial using the Cochrane 'Risk of bias' tool. We resolved the disagreements by discussion among review authors. We followed standard methodological approaches recommended by Cochrane. The primary outcomes were long-term (one year or greater after the index intervention) all-cause mortality, long-term cardiovascular mortality, long-term non-fatal myocardial infarction, and adverse events. The secondary outcomes were short-term (within the first 30 days after the index intervention) all-cause mortality, short-term cardiovascular mortality, short-term non-fatal myocardial infarction, revascularisation, health-related quality of life, and cost. We analysed data using fixed-effect models, and expressed results as risk ratios (RR) with 95% confidence intervals (CI). We used GRADE criteria to assess the quality of evidence and we conducted Trial Sequential Analysis (TSA) to control risks of random errors.

Main results

We included nine RCTs, that involved 2633 people with STEMI and multi-vessel coronary disease randomly assigned to either a complete (n = 1381) versus culprit-only (n = 1252) revascularisation strategy. The complete and the culprit-only revascularisation strategies did not differ for long-term all-cause mortality (65/1274 (5.1%) in complete group versus 72/1143 (6.3%) in culprit-only group; RR 0.80, 95% CI 0.58 to 1.11; participants = 2417; studies = 8; $I^2 = 0\%$; very low quality evidence). Compared with culprit-only intervention, the complete revascularisation strategy was associated with a lower proportion of long-term cardiovascular mortality (28/1143 (2.4%) in complete group versus 51/1086 (4.7%) in culprit-only group; RR 0.50, 95% CI 0.32 to 0.79; participants = 2229; studies = 6; $I^2 = 0\%$; very low quality evidence) and long-term non-fatal myocardial infarction (47/1095 (4.3%) in complete group versus 70/1004 (7.0%) in culprit-only group; RR 0.62, 95% CI 0.44 to 0.89; participants = 2099; studies = 6; $I^2 = 0\%$; very low quality evidence). The complete and the culprit-only revascularisation strategies did not differ in combined adverse events (51/2096 (2.4%) in complete group versus 57/1990 (2.9%) in culprit-only group; RR 0.84, 95% CI 0.58 to 1.21; participants = 4086; $I^2 = 0\%$; very low quality evidence). Complete revascularisation was associated with lower proportion of long-term revascularisation (145/1374 (10.6%) in complete group versus 258/1242 (20.8%) in culprit-only group; RR 0.47, 95% CI 0.39 to 0.57; participants = 2616; studies = 9; $I^2 = 31\%$; very low quality evidence). TSA of long-term all-cause mortality, long-term cardiovascular mortality, and long-term non-fatal myocardial infarction showed that more RCTs are needed to reach more conclusive results on these outcomes. Regarding long-term repeat revascularisation more RCTs may not change our present result. 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.

Authors' conclusions

Compared with culprit-only intervention, the complete revascularisation strategy may be superior due to lower proportions of long-term cardiovascular mortality, long-term revascularisation, and long-term non-fatal myocardial infarction, but these findings are based on evidence of very low quality. TSA also supports the need for more RCTs in order to draw stronger conclusions regarding the effects of complete revascularisation on long-term all-cause mortality, long-term cardiovascular mortality, and long-term non-fatal myocardial infarction.

PLAIN LANGUAGE SUMMARY

Complete versus culprit-only revascularisation in ST elevation heart attack with multi-vessel disease

Review question

In people with narrowing of multiple coronary arteries (blood vessels that surround and supply the heart with blood), along with one completely occluded (blocked) that is causing a heart attack, whether it is better to open all arteries or only the one that is causing the heart attack.

Background

The co-existence of multiple significantly narrowed coronary vessels (called multi-vessel disease) with a completely occluded coronary artery that is causing the heart attack, is commonly seen among people having a heart attack. Current treatment of these narrowed or completely obstructed coronary arteries involves an intravascular (within a blood vessel) procedure known as percutaneous coronary intervention, which uses a balloon that is positioned and inflated at the site of the blockage thereby opening the artery and restoring normal blood flow. This is usually followed by placement of a stent (small mesh tube) to avoid the previously narrowed arteries closing again. In addition to the blocked artery, there may be other narrowed coronary arteries, but several cardiology societies recommend intervening only on the vessel(s) causing the heart attack thereby leaving the other narrowed arteries untreated unless the person continues to have symptoms.

Study characteristics

Complete versus culprit-only revascularisation in ST elevation myocardial infarction with multi-vessel disease (Review)

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We searched for clinical trials in adults who had percutaneous coronary intervention for the management of heart attack and multi-vessel disease. The evidence is current to 4 January 2017. Only four trials reported funding from government organisations or charitable institutions. The other trials did not mention the source of funding and no private companies were mentioned as sources of finance. In the included trials, both the participants and researchers were aware of what treatment the participants received which may have biased the results. One trial ended enrolment earlier than planned because the difference between treatment was significant. This may have overestimated the difference between intervention groups. For most trials, the number of participants that were included was not enough to see a potential difference between treatments.

Key results

We included nine clinical trials with 2633 people with heart attack and multi-vessel disease. Compared with participants who underwent opening of only the coronary artery that caused heart attack, people who underwent treatment on all narrowed vessels had fewer deaths from diseases of the heart and blood supply (called cardiovascular disease), required fewer treatments to open the problematic coronary arteries, and had fewer heart attacks at the end of one year or later since the treatment. Based on our analyses, although the treatment on all narrowed vessels appears to be a better treatment strategy, there still exists a need for more well-designed clinical trials to confirm that this approach is associated with fewer deaths from cardiovascular diseases or heart attack, or both.

Quality of the evidence

The evidence is of very low quality. For instance, the number of participants in the included studies was insufficient, the medical team was aware of the study group that the participants were allocated to and that may have affected our conclusions. There is a need for well-designed clinical trials with more participants to determine which treatment strategy is superior.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Complete revascularisation compared to culprit-only revascularisation in ST elevated myocardial infarction with multi-vessel disease

Complete revascularisation compared to culprit-only revascularisation in ST elevated myocardial infarction with multi-vessel disease

Patient or population: people with STEMI and MVD.

Intervention: complete revascularisation.

Comparison: culprit only.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with culprit only	Risk with complete revascularisation				
Long-term all-cause mortality (≥ 1 year after the intervention)	Study population		RR 0.80 (0.58 to 1.11)	2417 (8 RCTs)	⊕⊕⊕⊕ Very low 1,2,3,4	PRAMI study terminated early. CvLPRIT and PRAMI concerning for attrition bias. Only CvLPRIT was judged to have low risk for selection bias.
	63 per 1000	50 per 1000 (37 to 70)				
Long-term cardiovascular mortality (≥ 1 year after the intervention)	Study population		RR 0.50 (0.32 to 0.79)	2229 (6 RCTs)	⊕⊕⊕⊕ Very low 1,2,3,4	PRAMI study terminated early. CvLPRIT and PRAMI concerning for attrition bias. Only CvLPRIT was judged to have low risk for selection bias.
	47 per 1000	23 per 1000 (15 to 37)				
Long-term myocardial infarction (≥ 1 year after the intervention)	Study population		RR 0.62 (0.44 to 0.89)	2099 (6 RCTs)	⊕⊕⊕⊕ Very low 1,2,3,4	PRAMI study terminated early. CvLPRIT and PRAMI concerning for attrition bias. Only CvLPRIT was judged to have low risk for selection bias.
	70 per 1000	43 per 1000 (31 to 62)				
Overall adverse events (pooled short and long term)	Study population		OR 0.84 (0.58 to 1.21)	4086 (6 RCTs)	⊕⊕⊕⊕ Very low 1,2,3,4	PRAMI study terminated early. CvLPRIT and PRAMI concerning for attrition bias. Only CvLPRIT was judged to have low risk for selection bias. Open label to the operator may affect this outcome.
	29 per 1000	24 per 1000 (17 to 35)				
Short-term all-cause mortality (within the first 30 days after the intervention)	Study population		RR 0.65 (0.18 to 2.37)	696 (2 RCTs)	⊕⊕⊕⊕ Very low 1,2,3,4	HELP-AMI trial did not describe in detail their methodology to analyse for bias.
	15 per 1000	10 per 1000 (3 to 36)				

Long-term revascularisation (≥ 1 year after the intervention)	Study population		RR 0.47 (0.39 to 0.57)	2616 (9 RCTs)	⊕⊕⊕⊕ Very low 1,2,3	PRAMI study terminated early. CvLPRIT and PRAMI concerning for attrition bias. Only CvLPRIT was judged to have low risk for selection bias. Open label to the operator may affect this outcome.
	208 per 1000	98 per 1000 (81 to 118)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MVD:** multi-vessel disease; **RCT:** randomised controlled trial; **RR:** risk ratio; **STEMI:** ST elevated myocardial infarction.

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

¹ Downgraded due to publication (reporting) bias.

² Downgraded due to study limitations (largely risk of attrition bias and selection bias).

³ Downgraded because of indirectness: black and Hispanic people, as well as women were under-represented.

⁴ Downgraded due to imprecision.

BACKGROUND

Description of the condition

The World Health Organization (WHO) reported that in 2012 there were 17.5 million global deaths due to cardiovascular diseases, accounting for 31% of all deaths (WHO 2014); furthermore, they estimated about 20 million cardiovascular associated deaths in 2015 (WHO 2005). In contemporary practice, among the people who present to the hospital with ST elevation myocardial infarction (STEMI), between 40% and 65% have concurrent multi-vessel disease (MVD) or a combination of a completely occluded coronary artery and significant but incomplete stenosis of other coronary vessels (Dziewierz 2010; Jo 2011; Park 2014; Sorajja 2007). As the burden of cardiovascular diseases affects hospital systems worldwide, there is growing interest among healthcare providers to examine and improve the various treatment strategies involved in the management of STEMI in people with co-existing MVD.

Several studies have shown that the co-existence of culprit and non-culprit coronary artery stenotic lesions leads to worse outcomes. For instance, people with STEMI and MVD have higher one-year rates of the composite outcome of death, recurrent myocardial infarction, and need for revascularisation compared with people with single-vessel disease (Corpus 2004; Halkin 2005; Jaski 1992; Muller 1991; Sorajja 2007). The American College of Cardiology (ACC)/American Heart Association (AHA) (ACCF/AHA 2013) and by the European Society of Cardiology (ESC) (ESC 2012) discouraged the early intervention of the non-culprit; however, these recommendations were based on limited evidence. At that time, standard of care for people presenting with STEMI and MVD was to undergo sole intervention on the culprit lesion followed by intervention on other significant coronary artery stenoses involving non-culprit arteries, in a staged fashion; or a multi-vessel intervention in cases of cardiogenic shock or persistent ischaemia after primary percutaneous coronary intervention (P-PCI). However, more recent randomised controlled trials (RCT) have demonstrated that simultaneous intervention on both culprit and non-culprit lesions can be safely performed and that it may improve patient outcomes (CULPRIT 2015; DANAMI-3-PRIMULTI 2015; PRAGUE-13 2015; PRAMI 2013). This evidence subsequently resulted in an upgrade in the ACC/AHA and ESC/European Association for Cardio-Thoracic Surgery (EACTS) recommendations on the intervention of non-infarct-related arteries (IRA) stenotic lesions from possibly intervention that can produce harm or no benefit (class III recommendation) to an intervention that may be considered in selected people with MVD (class IIb recommendation level of evidence B) per ACC/AHA/Society for Cardiovascular Angiography and Interventions (SCAI) 2015 guidelines (ACCF/AHA/SCAI 2015), class IIa for staged intervention or IIb for simultaneous multi-vessel percutaneous coronary intervention (PCI) at the index procedure with a level of evidence B per ESC 2014 guidelines (ESC 2014).

Description of the intervention

The current standard of care for treatment of people with STEMI is P-PCI on the completely occluded artery within 90 minutes from first medical contact (ACCF/AHA 2013; ESC 2012; ESC 2014; NICE 2013). Upon presentation to the hospital, a person with STEMI is taken to the catheterisation laboratory where angiography of the coronary arteries is performed in an attempt to identify the culprit lesion, that is, the narrowed atherosclerotic lesion of the

coronary vessel responsible for the ischaemic changes seen on the electrocardiogram. The culprit lesion is treated with P-PCI comprising of balloon angioplasty followed by the insertion of a stent.

In addition to the culprit vessel, it is possible for a person to have other significantly stenosed coronary arteries. These non-culprit stenoses may not be responsible for the person's STEMI on presentation, but may eventually lead to acute or chronic ischaemic heart disease (Corpus 2004; Halkin 2005; Jaski 1992; Sorajja 2007). In people with non-culprit artery disease amenable to PCI, three different treatment strategies can be adopted: 1. P-PCI on the culprit artery along with medical management, with revascularisation of the non-culprit lesions only in the setting of recurrent symptoms, infarction, or significant inducible ischaemia on provocative testing; 2. complete revascularisation including the culprit and non-culprit arteries during the same procedure; and 3. staged intervention on the non-culprit arteries later during the same hospitalisation or shortly after discharge.

How the intervention might work

STEMI is a consequence of a sudden complete occlusion of a coronary artery, leading to infarction or myocardial cell death. P-PCI is currently the preferred treatment option for a completely occluded coronary artery in the setting of STEMI. This procedure restores the blood supply to a previously ischaemic region, thereby reducing cell death and preserving as much viable myocardium as possible. An early invasive approach for the partially occluded non-culprit lesion(s), in the setting of MVD, might help in simultaneously restoring and improving blood supply to the remaining myocardium that is at potential risk for future ischaemic events.

There is cumulative evidence that STEMI is a pro-inflammatory process that might play a role in the instability of the atherosclerotic plaques and subsequent higher risk of cardiac events surrounding the STEMI (Arroyo-Espiguero 2004; Kubo 2010). Therefore, complete revascularisation could potentially prevent subsequent cardiac events by treating any unstable inflamed atherosclerotic plaques and thus preventing complete obstruction (subsequent STEMI), transient obstruction/embolisation (non-STEMI), or progression over time to ischaemia and symptoms of angina (unstable angina or refractory angina). Intervention on the non-culprit lesions might impose a higher risk of vascular complications including periprocedural infarction, renal impairment due to the contrast load, and additional risk of bleeding when performed as a staged procedure. In addition, PCI with stent implantation always carries the risk of later stent thrombosis.

Why it is important to do this review

A timely P-PCI with revascularisation of the culprit vessel remains the mainstay of treatment for people presenting with STEMI across different continents. However, management of significantly stenotic lesions of the non-culprit vessel has been an area of constant debate and the recommendations differ among the various published guidelines worldwide. In the US, for instance, the 2013 ACC/AHA guidelines discouraged routine simultaneous P-PCI of non-culprit lesions with the culprit vessel in haemodynamically stable people because of concerns of worse outcomes (class III (harm)/level of evidence B) (ACCF/AHA 2013), and ESC encouraged intervention of the culprit vessel only (ESC 2012). With those

guidelines, simultaneous intervention of culprit and non-culprit vessels was recommended only in certain contexts such as in cardiogenic shock or when there was persistence of symptoms of cardiac ischaemia despite intervention on the culprit lesion (class I/level of evidence C [ACC/AHA 2013](#)) (class IIa/level of evidence B [ESC 2012](#)). Based on more recent evidence provided by RCTs suggesting better outcomes with complete revascularisation in people with STEMI and MVD ([CvLPRIT 2015](#); [DANAMI-3-PRIMULTI 2015](#); [PRAGUE-13 2015](#); [PRAMI 2013](#)), the ACC/AHA and ESC guidelines updated their guidelines. The [ACC/AHA/SCAI 2015](#) and [ESC 2014](#) guidelines now state that simultaneous intervention on significantly stenotic non-culprit lesions can be considered in selected people with STEMI and MVD, thus upgrading their recommendations to class IIb. The fact that the strength of the recommendation is still IIb suggests that more robust evidence is needed to make stronger recommendations in this regard. In contrast, the National Institute for Health and Care Excellence (NICE) guidelines do not make any recommendations regarding intervention on non-culprit coronary arteries due to lack of evidence ([NICE 2013](#)).

This lack of strong recommendations in regards to intervention on both culprit and non-culprit arteries during STEMI emphasises the need for good-quality evidence followed by systematic analysis, to support more specific recommendations. Such information, when available, can be of great help to healthcare providers allowing them to allocate resources more efficiently thereby improving outcomes related to this common condition amidst concerns over healthcare expenditure and varying insurance reimbursements.

OBJECTIVES

To assess the effects of early complete revascularisation compared with culprit vessel only intervention strategy in people with STEMI and MVD.

METHODS

Criteria for considering studies for this review

Types of studies

We included only RCTs comparing complete revascularisation versus culprit-only PCI strategy in people with STEMI and MVD. We included studies reported as full-text, those published as abstract, and unpublished data.

Types of participants

We included adults aged 18 years and above, who underwent P-PCI for the management of STEMI, with concurrent non-culprit significant lesions (as defined by the authors of the trial), identified at the time of the index procedure.

Types of interventions

We included studies that looked at a population of people presenting with STEMI and who were initially treated with a P-PCI and coronary angiography to assess the extent of coronary vessel obstruction in the various branches of the coronary tree. Further, in these people, the culprit and the non-culprit arteries were identified based on correlation with participants' changes on electrocardiograms. Following initial treatment of the culprit lesion, participants in these RCTs were randomised to receive either

complete or culprit vessel only intervention. A comparison was then made between these two strategies, defined as:

1. Complete revascularisation strategy: involving additional revascularisation of the clinically significant stenotic non-culprit lesion(s) (at least 50% obstruction but less than 100%) at the index procedure or in a second intervention. This was carried out in all eligible participants, except if contraindicated;
2. Culprit vessel-only intervention: involving no additional invasive approach but rather medical management of all eligible participants, even with evidence of non-culprit artery disease diagnosed at the time of P-PCI. Exceptions were made if the participant had clinical symptoms that warranted further testing and intervention (e.g. new-onset chest pain, dynamic changes on electrocardiogram, or a positive stress test).

Types of outcome measures

Primary outcomes

1. Long-term all-cause mortality: defined as death from any cause at one year or greater after the intervention.
2. Long-term cardiovascular mortality: defined as death from cardiovascular cause at one year or greater after the intervention.
3. Long-term non-fatal myocardial infarction: spontaneous myocardial infarction measured at one year or greater after the intervention.
4. Adverse events: acute kidney injury, stroke, and bleeding (defined as GUSTO (Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries) severe or moderate and TIMI (Thrombolysis in Myocardial Infarction) major or minor) at 30 days (short-term) and one year or later (long-term) after the initial intervention.

Secondary outcomes

1. Short-term all-cause mortality: defined as death from any cause measured within the first 30 days (short-term) after the index intervention.
2. Short-term cardiovascular mortality: defined as death from cardiovascular cause within the first 30 days after the index intervention.
3. Short-term non-fatal myocardial infarction: spontaneous myocardial infarction (excluding periprocedural elevation of cardiac enzymes) and measured within the first 30 days after the index intervention.
4. Revascularisation: defined as the need for revascularisation with either coronary artery bypass graft surgery (CABG) or PCI. Measured within the first 30 days (short-term) and at one year or greater (long-term) after the intervention.
5. Health-related quality of life: measured with any validated health-related quality of life instrument at one year or greater after the intervention.
6. Cost: measured at one-year follow-up or greater.

Search methods for identification of studies

Electronic searches

On 4 January 2017, we searched the following sources from their inception and we imposed no restriction on language of publication:

1. Cochrane Central Register of Controlled Trials (CENTRAL): 2016, Issue 11 (Wiley);
2. Database of Abstracts of Reviews of Effects (DARE): Issue 2 of 4, April 2015 (Wiley);
3. Health Technology Assessment Database (HTA): Issue 4 of 4, October 2016 (Wiley);
4. Ovid MEDLINE(R) 1946 to December Week 1 2016, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 3 January 2017 and Ovid MEDLINE(R) Epub Ahead of Print 3 January 2017;
5. Embase 1974 to 4 January 2017; Embase Classic 1947 to 1973; MEDLINE 1966 to 4 January 2017 (embase.com);
6. Conference Proceedings Citation Index-Science (CPCI-S) 1990 to 4 January 2017 (Web of Science).

We applied the Cochrane sensitivity-maximizing RCT filter (Lefebvre 2011) to MEDLINE (Ovid) but did not apply it to the MEDLINE In-Process or Epub searches. For Embase, we used the multi-term Embase filter with the best balance of sensitivity and specificity (Wong 2006) translated from Ovid to embase.com syntax.

For details of terms used in search strategies please see [Appendix 1](#).

Searching other resources

In order to identify articles potentially missed through the electronic searches, we:

1. handsearched reference lists of all included studies and relevant reviews retrieved by electronic searching to identify other potentially eligible trials or ancillary publications;
2. conducted a search on 8 December 2016 for other systematic reviews and Health Technology Assessment reports in Epistemonikos (www.epistemonikos.org);
3. handsearched on 8 December 2016, conference proceedings via their websites for 2011 to 2016 (congress365.escardio.org),

ACC Annual Scientific Sessions (www.onlinejacc.org/content/meeting-abstract-supplements), AHA Annual Scientific Sessions (circ.ahajournals.org), and Transcatheter Cardiovascular Therapeutics Abstracts (www.tctmd.com);

4. contacted corresponding authors of included studies for any additional published or unpublished data;
5. attempted to contact the authors of trials when information in the study report was lacking or unclear.

We also searched the following trial registers:

1. ClinicalTrials.gov (www.clinicaltrials.gov/);
2. European (EU) Clinical Trials Register (www.clinicaltrialsregister.eu/);
3. WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch/).

Data collection and analysis

Selection of studies

Two review authors (SH and CB) independently screened titles and abstracts for inclusion of all the potential studies that the search identified and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. If there were any disagreements, a third review author arbitrated. We retrieved the full-text study reports/publication and two review authors (SH and CB) independently screened the full-text and identified studies for inclusion, and identified and recorded reasons for exclusion of the ineligible studies. We resolved any disagreements through discussion or, if required, we consulted a third review author. We identified and excluded duplicate publications and collated multiple reports of the same study so that each study, rather than each report, became a unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Figure 1) and [Characteristics of excluded studies](#) table.

Figure 1. Study flow diagram.

Data extraction and management

We used a data collection form for study characteristics and outcome data that had been piloted on at least one study in the review. One review author (CB) extracted study characteristics from included studies including:

1. methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals, and date of study;
2. participants: number, mean age, age range, gender, severity of the condition, diagnostic criteria, inclusion criteria, and exclusion criteria;
3. interventions: intervention, comparison, concomitant medications, and excluded medications;
4. outcomes: primary and secondary outcomes specified and collected, and time points reported;
5. notes: funding for trial and notable conflicts of interest of trial authors.

Two review authors (CB and SH) independently extracted outcome data from included studies. We resolved any disagreements by consensus or by involving a third review author. One review author (CB) transferred data into the Review Manager 5 (RevMan 2014). We double-checked that data were entered correctly by comparing the data presented in the systematic review with those of the study reports. A second review author (SH) spot-checked study characteristics for accuracy against the trial report.

Trial Sequential Analysis

We performed Trial Sequential Analysis (TSA) for the outcomes long-term all-cause mortality, long-term cardiovascular mortality, long-term non-fatal myocardial infarction, and long-term revascularisation. We applied TSA using free software (www.ctu.dk/tsa). TSA reduces the risk of random errors due to sparse data and repetitive testing of the accumulating data (Wetterslev 2008). We calculated the diversity-adjusted required information size, that is, number of participants needed to detect or reject a hypothesis. In our meta-analysis, the required information size for dichotomous outcomes was based on the proportion in the control group; assumption of a plausible relative risk reduction (RRR) of 20% observed in the included trials; a risk of type I error (α) of 2%; a risk of type II error (β) of 10%; and the observed diversity of the meta-analysis (Jakobsen 2014). The underlying assumption of TSA is that testing for significance may be performed each time a new trial is added to the meta-analysis. We added the trials according to the year of publication, and if more than one trial was published in a year, we added trials alphabetically according to the last name of the first author or the trial name. On the basis of the required information size, we constructed trial sequential monitoring boundaries (Thorlund 2011; Wetterslev 2008). These boundaries determine the statistical inference one may draw regarding the cumulative meta-analysis that has not reached the required information size; if the trial sequential monitoring boundary is crossed by the cumulative Z curve before the required information size is reached, firm evidence may perhaps be established and further trials may be superfluous. In contrast, if the boundary benefit or harm is not surpassed, it is most probably necessary to continue doing trials in order to detect or reject a certain intervention effect. That can be determined by assessing if the cumulative Z-curve crosses the trial sequential boundaries for futility.

Assessment of risk of bias in included studies

Two review authors (SH and CB) independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion or by involving a third review author. We assessed the risk of bias according to the following domains (Wood 2008).

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias (e.g. industry funding).

We graded each potential source of bias as high, low, or unclear and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We summarised the risk of bias judgements across different studies for each of the domains listed. Wherever the information on the risk of bias related to unpublished data or correspondence with a trialist, we noted the same in the 'Risk of bias' table.

We conducted the review according to the published protocol (Hirji 2015), and reported any deviations from it under the *Differences between protocol and review*. When considering treatment effects, we took into account the risk of bias for the studies that contributed to such an outcome.

Measures of treatment effect

We analysed dichotomous data as risk ratios (RR) with 95% confidence intervals (CI) and continuous data as mean difference (MD) or standardised mean difference (SMD) with 95% CI. SMD will be used if the outcome is measured in a variety of ways, for instances with different scales and MD will be used if the outcomes is measured with the same method. We entered data presented as a scale with a consistent direction of effect. We described skewed data reported as medians and interquartile ranges narratively.

Unit of analysis issues

All included trials were randomised at the individual participant level.

Dealing with missing data

We contacted investigators to verify key study characteristics and obtain missing numerical outcome data wherever possible (e.g. when a study was published as abstract only). Where this was not feasible, and the missing data were thought to introduce serious bias, we explored the impact of including such studies on the overall assessment of results using a sensitivity analysis.

Assessment of heterogeneity

We examined heterogeneity using the I^2 statistic, which quantifies inconsistency across studies to assess the impact of heterogeneity on the meta-analysis, with an I^2 statistic of 50% or more indicative of a considerable level of inconsistency.

If we identified substantial heterogeneity, we reported it and explored possible causes by prespecified subgroup analysis and performed the analysis using a random-effects model. In the event of substantial clinical, methodological, or statistical heterogeneity, we decided not to report study results as pooled effect estimates.

Assessment of reporting biases

We were unable to assess reporting bias as the number of included studies was insufficient for an informative funnel plot (Higgins 2011).

Data synthesis

If there was evidence for homogeneous effects across studies, we analysed the data using RR and summarised all data using a fixed-effect model (Riley 2011; Wood 2008). In addition, we performed statistical analyses according to the statistical guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

We carried out the following subgroup analyses and investigated interaction.

1. Drug-eluting stent (DES) compared to bare-metal stents (BMS).
2. Sex.
3. People with diabetes mellitus compared to people without diabetes mellitus.
4. Non-culprit and culprit intervention during the same procedure compared to in separate interventions (staged).
5. Low risk of bias articles compared to high risk of bias articles.
6. Participants in cardiogenic shock compared to participants not in cardiogenic shock.

We used the following outcomes in subgroup analyses.

1. Long-term all-cause mortality.
2. Long-term cardiovascular mortality.
3. Long-term non-fatal myocardial infarction.

We used the formal test for subgroup interactions in Review Manager 5 (RevMan 2014).

Sensitivity analysis

We performed sensitivity analyses to explore the influence of the following factors on effect sizes.

1. Restricting the analysis to published studies.
2. Restricting the analysis to trials at low risk of bias, as specified in *Assessment of risk of bias in included studies*.
3. Restricting the analysis to trials using the following filters: language of publication, source of funding (industry), and country.
4. Restricting the analysis to published trials that utilised mostly DES.

Reaching conclusions

Two review authors (CB and CG) independently assessed the quality of the evidence using the GRADE approach and the GRADE profiler (GRADEpro) 3.6 (GRADEpro GDT) to assess the quality

of evidence related to each of the key outcomes listed in the *Types of outcome measures* (Chapter 12.2, *Cochrane Handbook for Systematic Reviews of Interventions*; Higgins 2011). A summary of the evidence is included in the *Summary of findings for the main comparison*.

We based our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review.

We avoided making recommendations for practice and our implications for research were meant to suggest priorities for future research and outline any remaining uncertainties in the area.

RESULTS

Description of studies

For a detailed description of studies, see the *Characteristics of included studies*, *Characteristics of excluded studies*, and *Characteristics of ongoing studies* tables.

Results of the search

Our comprehensive literature search identified 5100 records; of these, we identified 53 full-text papers and five clinical trial register records for further examination. We excluded the other studies on the basis of their titles or abstracts, which either did not meet the inclusion criteria or were not relevant to the question under trial (see Figure 1 for the PRISMA flow chart). After screening the full-text of the selected publications, nine trials (23 publications) met the inclusion criteria. All studies were in English, except for one (Zhang 2015). Although we sought additional information from the authors of all studies, two responded to these requests and only one provided additional data (DANAMI-3-PRIMULTI 2015).

Included studies

A detailed description of the characteristics of included studies is presented in the *Characteristics of included studies* table; Table 1; Table 2; and Table 3. The following is a succinct overview.

Source of data

All included trials had published data in established journals, except for the PRAGUE-13 (PRAGUE-13 2015) and Estevez (Estevez Loureiro 2014) trials, which only had abstracts. We contacted all corresponding authors, two replied and only one (DANAMI-3-PRIMULTI 2015) provided additional data (Appendix 2).

Comparisons

All included trials compared culprit-only versus complete revascularisation in people with acute STEMI and MVD. Six trials performed the intervention on the non-culprit vessels as a staged intervention (Dambrink and Ghani 2010; DANAMI-3-PRIMULTI 2015; Estevez Loureiro 2014; Politi 2009; PRAGUE-13 2015; Zhang 2015), and three trials performed the intervention of the non-culprit vessels at the same index procedure (HELP AMI 2004; Politi 2009; PRAMI 2013). In one trial, the investigators encouraged the interventionists to perform the complete revascularisation at the same index procedure (CvLPRIT 2015); however, 35% of the procedures were staged. The Politi 2009 trial had three intervention groups: complete revascularisation during the index procedure; complete revascularisation in a staged procedure; and culprit vessel-only revascularisation.

Overview of study populations

The nine trials included 2633 participants, 1381 participants were randomised to the complete revascularisation group and 1252 to the culprit-only intervention group.

Among the four publications that reported dropout, 1449 (96%) participants finished the trial, 727 (93.4%) in the complete revascularisation group and 722 (98.8%) in the culprit-only intervention group (CvLPRIT 2015; Dambrink and Ghani 2010; DANAMI-3-PRIMULTI 2015; PRAMI 2013).

Trial design

The included trials were conducted between 2003 and 2014, and the duration of follow-up ranged from one to three years, with a mean follow-up of 2.1 years.

Four trials were multi-centre (CvLPRIT 2015; DANAMI-3-PRIMULTI 2015; PRAGUE-13 2015; PRAMI 2013), one was single centre (Dambrink and Ghani 2010), and four trials did not mention the number of centres (Estevez Loureiro 2014; HELP AMI 2004; Politi 2009; Zhang 2015). The number of centres per trial ranged between one and seven.

Two trials terminated prematurely, one because of slow enrolment (Dambrink and Ghani 2010) and the other because there was a marked benefit from the complete revascularisation strategy (PRAMI 2013).

Settings

Six of the nine trials were performed in Europe (Spain, Denmark, UK, Czech Republic, and the Netherlands), one in China (Zhang 2015), and two trials did not report where the study was carried out, although based on the authorship, it is likely that they were carried out in Italy (HELP AMI 2004; Politi 2009).

Participants

The majority of participants were men, with male percentage per group between 61% and 89%. The mean age was 63.5 years and the age mean per study ranged between 62 and 65 years. Included studies did not report the ethnicity of the participants.

With the exception of two studies (Estevez Loureiro 2014; PRAGUE-13 2015), all trials reported comorbidities. The trials that reported comorbidities included people with past medical history of diabetes mellitus, arterial hypertension, hyperlipidaemia, smoking, myocardial infarction, prior CABG, prior PCI, stroke, heart failure, and chronic kidney disease. These trials had between 5% and 41% of participants with diabetes and between 26% and 64% of participants with hypertension, which were therefore the most common comorbidities among the included participants, followed by previous myocardial infarction.

With the exception of two studies (Estevez Loureiro 2014; PRAGUE-13 2015), all trials reported comedications. In the studies that reported comedications, after the intervention participants received standard medical treatment for the duration of the follow-up. The most commonly reported drugs were aspirin and clopidogrel in seven out of nine trials; six of the nine trials reported using beta-blockers, angiotensin-converting enzyme inhibitor, angiotensin receptor blockers, glycoprotein IIb/IIIa inhibitor, and statins. Five trials reported using dual antiplatelet after PCI, where

this combination treatment was provided for at least one month (CvLPRIT 2015; Dambrink and Ghani 2010; DANAMI-3-PRIMULTI 2015; HELP AMI 2004; PRAMI 2013).

The major exclusion criteria from the included trials were cardiogenic shock in seven trials (CvLPRIT 2015; DANAMI-3-PRIMULTI 2015; HELP AMI 2004; Politi 2009; PRAGUE-13 2015; PRAMI 2013; Zhang 2015), clear indication for CABG in six trials (Dambrink and Ghani 2010; DANAMI-3-PRIMULTI 2015; HELP AMI 2004; Politi 2009; PRAGUE-13 2015; PRAMI 2013), prior CABG in five trials (CvLPRIT 2015; Dambrink and Ghani 2010; Politi 2009; PRAMI 2013; Zhang 2015), and technically impossible PCI and chronic coronary obstruction in six trials (CvLPRIT 2015; Dambrink and Ghani 2010; DANAMI-3-PRIMULTI 2015; Politi 2009; PRAMI 2013; Zhang 2015). Only one trial did not report the exclusion criteria (Estevez Loureiro 2014).

Diagnosis

All trials reported that the participants had acute STEMI and MVD diagnosed during the P-PCI. Among the studies that described the definition of MVD, they considered as such, those cases where significant stenosis was present in at least one other major epicardial artery besides the culprit vessel. Significant stenosis was defined as greater than 50% stenosis in one or two planes by visual inspection (CvLPRIT 2015; Dambrink and Ghani 2010; DANAMI-3-PRIMULTI 2015; PRAMI 2013) or greater than 70% in one plane (CvLPRIT 2015; Politi 2009; PRAGUE-13 2015). After diagnosing significant stenosis by visual inspection of the coronary angiogram, in two studies the investigators performed a fractional flow reserve (FFR) measurement to decide whether the stenosis was haemodynamically significant and required intervention. The cutoff value for FFR that defined haemodynamically significant stenosis was 0.8 or less (DANAMI-3-PRIMULTI 2015) and less than 0.75 (Dambrink and Ghani 2010).

Interventions

All 2633 participants underwent the intervention after randomisation. In two trials, all participants underwent PCI with DES placement (HELP AMI 2004; Zhang 2015), while two other trials did not describe the type of stent utilised (Estevez Loureiro 2014; PRAGUE-13 2015). For more details please refer to Table 3.

Outcomes

Six trials explicitly stated the primary and secondary outcomes in their publications; only three trials did not specify their secondary outcomes (Estevez Loureiro 2014; Politi 2009; Zhang 2015). The most commonly defined primary outcome in the publications and protocols were non-fatal myocardial infarction, all-cause mortality, revascularisation, and cardiac mortality.

Reporting of outcomes

All trials collected a median of 1.2 (range one to three) primary outcomes and a median of 3.8 (range one to eight) secondary outcomes. All included trials assessed non-fatal myocardial infarction, all except one trial assessed revascularisation (Zhang 2015), all except one trial assessed all-cause mortality (Estevez Loureiro 2014), and all except two trials assessed cardiac mortality (Dambrink and Ghani 2010; HELP AMI 2004).

Four trials reported bleeding (CvLPRIT 2015; Dambrink and Ghani 2010; DANAMI-3-PRIMULTI 2015; PRAMI 2013), and three trials

reported acute kidney injury (CvLPRIT 2015; Politi 2009; PRAMI 2013). For a summary of all assessed outcomes in each trial, see the [Characteristics of included studies](#) table.

Excluded studies

We excluded twenty-eight articles after careful evaluation of the full publication ([Figure 1](#)). The main reasons for exclusion were: wrong

study design and wrong comparator. For further details, see the [Characteristics of excluded studies](#) table.

Risk of bias in included studies

For details on risk of bias of included studies see the [Characteristics of included studies](#) table. For an overview of review authors' judgements about each risk of bias item for individual trials and across all trials see [Figure 2](#) and [Figure 3](#).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
CvLPRIT 2015	+	+	-	+	-	+	+
Dambrink and Ghani 2010	+	?	?	?	+	-	-
DANAMI-3-PRIMULTI 2015	+	?	-	+	+	+	+
Estevez Loureiro 2014	?	?	?	?	?	-	?
HELP AMI 2004	?	?	?	?	?	-	?
Politi 2009	+	?	?	?	?	-	?
PRAGUE-13 2015	?	?	?	?	?	+	+
PRAMI 2013	+	?	-	+	-	+	-
Zhang 2015	?	?	?	?	?	-	?

Allocation

Five out of the nine included trials utilised electronically generated random numbers to allocate the included participants into one of the intervention groups (CvLPRIT 2015; Dambrink and Ghani 2010; DANAMI-3-PRIMULTI 2015; Politi 2009; PRAMI 2013). Four out of the nine trials did not describe their methods of generating the allocation sequence (Estevez Loureiro 2014; HELP-AMI 2004; PRAGUE-13 2015; Zhang 2015). Only one trial detailed how the allocation concealment was ensured (CvLPRIT 2015). Therefore, only the CvLPRIT trial was at low risk of selection bias. The remaining eight trials were at high risk of selection bias.

Blinding

Because of the nature of the intervention, all studies were open label for the operators. Several trials described that they were open label for the participants (CvLPRIT 2015; DANAMI-3-PRIMULTI 2015; PRAMI 2013), and blinded for investigators and outcome assessors (CvLPRIT 2015; Dambrink and Ghani 2010; DANAMI-3-PRIMULTI 2015; PRAMI 2013). One study described that it was open label for investigators and participants (PRAGUE-13 2015), and two trials did not state if they were blinded to participants (Dambrink and Ghani 2010; Zhang 2015). With the exception of the outcome of revascularisation, there was low risk of performance and detection bias since the majority of the other assessed outcomes were objective.

Incomplete outcome data

Only four trials reported the number of withdrawals (CvLPRIT 2015; Dambrink and Ghani 2010; DANAMI-3-PRIMULTI 2015; PRAMI 2013). The number of dropouts per group were similar; however, given the low number of events, there was considerably high risk of attrition bias in two trials (CvLPRIT 2015; PRAMI 2013).

Selective reporting

Among the four studies that were registered in a clinical trial database or had a published protocol, there was a low

risk of reporting bias (CvLPRIT 2015; DANAMI-3-PRIMULTI 2015; PRAGUE-13 2015; PRAMI 2013).

Other potential sources of bias

Only four trials reported funding from national institutions or charitable institutions (CvLPRIT 2015; DANAMI-3-PRIMULTI 2015; PRAGUE-13 2015; PRAMI 2013). The other trials did not mention the source of funding and no private companies were mentioned as sources of finance.

Effects of interventions

See: **Summary of findings for the main comparison** Complete revascularisation compared to culprit-only revascularisation in ST elevated myocardial infarction with multi-vessel disease

Baseline characteristics

For details of baseline characteristics see Table 2.

Complete revascularisation strategy or culprit vessel-only intervention

Primary outcomes

Long-term all-cause mortality

Eight studies found that complete and culprit-only revascularisation strategies did not differ significantly regarding long-term all-cause mortality (65/1274 (5.1%) in complete group versus 72/1143 (6.3%) in culprit-only group; RR 0.80, 95% CI 0.58 to 1.11; participants = 2417; $I^2 = 0\%$; very low quality evidence) (Analysis 1.1) (CvLPRIT 2015; Dambrink and Ghani 2010; DANAMI-3-PRIMULTI 2015; HELP AMI 2004; Politi 2009; PRAGUE-13 2015; PRAMI 2013; Zhang 2015).

The TSA showed that more studies are needed to demonstrate that the complete revascularisation strategy is related to an at least 20% long-term all-cause mortality RRR compared to the culprit-only intervention strategy (RR 0.80, TSA-adjusted CI 0.56 to 1.10) (Figure 4).

Figure 4. Trial Sequential Analysis for complete versus culprit-only revascularisation on long-term all-cause mortality. The diversity-adjusted required information size (DARIS) was calculated based on an expected relative risk reduction (RRR) of 20% from proportion event in control (Pc) group of 6.3% with an alpha of 2% and beta of 10%.

Long-term cardiovascular mortality

Six studies found that, when compared to the culprit-only intervention strategy, complete revascularisation was associated with a lower cardiovascular mortality in the long-term or one year after the index procedure (28/1143 (2.4%) in complete group versus 51/1086 (4.7%) in culprit-only group; RR 0.50, 95% CI 0.32 to 0.79; participants = 2229; $I^2 = 0\%$; very low quality evidence) ([Analysis 1.2](#))

([CvLPRIT 2015](#); [DANAMI-3-PRIMULTI 2015](#); [Politi 2009](#); [PRAGUE-13 2015](#); [PRAMI 2013](#); [Zhang 2015](#)).

The TSA showed that more studies are needed to demonstrate that the complete revascularisation strategy is related to an at least 20% long-term cardiovascular mortality RRR compared with the culprit-only intervention strategy (RR 0.51, TSA-adjusted CI 0.08 to 3.24) ([Figure 5](#)).

Figure 5. Trial Sequential Analysis for complete versus culprit-only revascularisation on long-term cardiovascular mortality. The diversity-adjusted required information size (DARIS) was calculated based on an expected relative risk reduction (RRR) of 20% from Pc group of 4.7% with an alpha of 2% and beta of 10%.

Long-term non-fatal myocardial infarction

Six studies found that complete revascularisation strategy was superior to the culprit-only intervention in terms of long-term non-fatal myocardial infarction (47/1095 (4.3%) in complete group versus 70/1004 (7.0%) in culprit-only group; RR 0.62, 95% CI 0.44 to 0.89; participants = 2099; $I^2 = 0\%$; very low quality evidence)

(Analysis 1.3) (CvLPRIT 2015; DANAMI-3-PRIMULTI 2015; HELP AMI 2004; Politi 2009; PRAMI 2013; Zhang 2015).

The TSA showed that more studies are needed to demonstrate that the complete revascularisation strategy is related to an at least 20% long-term non-fatal myocardial infarction RRR compared to the culprit-only intervention strategy (RR 0.64, TSA-adjusted CI 0.14 to 2.82) (Figure 6).

Figure 6. Trial Sequential Analysis for complete versus culprit-only revascularisation on long-term non-fatal myocardial infarction. The diversity-adjusted required information size (DARIS) was calculated based on an expected relative risk reduction (RRR) of 20% from Pc group of 7.0% with an alpha of 2% and beta of 10%.

Adverse events

Six studies contributed to the pooled analysis of all adverse events comprising acute kidney injury, stroke, and bleeding in the short-term (within the first 30 days after the index procedure) and long-term, demonstrated that the frequency of the combined adverse event rate was similar in both groups (51/2096 (2.4%) in complete group versus 57/1990 (2.9%) in culprit-only group; RR 0.84, 95% CI 0.58 to 1.21; participants = 4086; $I^2 = 0\%$; very low quality evidence).

Acute kidney injury

Two studies found no difference in the occurrence of acute kidney injury in the short-term between complete or culprit-only revascularisation strategy (4/364 (1.1%) in complete group versus 6/315 (1.9%) in culprit-only group; RR 0.50, 95% CI 0.14 to 1.81; participants = 679; $I^2 = 0\%$; very low quality evidence) (Politi 2009; PRAMI 2013). Similarly, one trial found no difference in the occurrence of acute kidney injury in the long-term between complete or culprit-only revascularisation strategy (2/150 (1.3%) in complete group versus 2/146 (1.4%) in culprit-only group; RR 0.97, 95% CI 0.14 to 6.82; participants = 296) (Analysis 1.4) (CvLPRIT 2015).

Stroke

One trial found no difference in the occurrence of short-term stroke between complete or culprit-only revascularisation strategy (2/234 (0.9%) in complete group versus 0/231 (0%) in culprit-only group; RR 4.94, 95% CI 0.24 to 102.26; participants = 465; very low quality evidence) (PRAMI 2013). Two trials showed that complete and culprit-only revascularisation strategies were associated with similar rate of stroke in the long-term (2/256 (0.8%) in complete group versus 5/254 (2%) in culprit-only group; RR 0.45, 95% CI 0.10 to 2.01; participants = 510; $I^2 = 14\%$) (Analysis 1.5) (CvLPRIT 2015; PRAGUE-13 2015).

Bleeding

Three trials showed that there was no difference in major bleeding rate between groups in the short-term (21/628 (3.3%) in complete group versus 19/585 (3.2%) in culprit-only group; RR 1.00, 95% CI 0.53 to 1.86; participants = 1213; $I^2 = 0\%$; very low quality evidence) (Dambrink and Ghani 2010; DANAMI-3-PRIMULTI 2015; PRAMI 2013). Two trials demonstrated that the frequency of bleeding in the long-term was similar between groups (20/464 (4.3%) in complete group versus 25/459 (5.4%) in culprit-only group; RR 0.79, 95% CI 0.45 to 1.41; participants = 923; $I^2 = 0\%$) (Analysis 1.6) (CvLPRIT 2015; DANAMI-3-PRIMULTI 2015).

Secondary outcomes

Short-term all-cause mortality

Two trials showed that the complete and culprit-only revascularisation strategies did not differ significantly in terms of short-term all-cause mortality (4/366 (1.1%) in complete group versus 5/330 (1.5%) in culprit-only group; RR 0.65, 95% CI 0.18 to 2.37; participants = 696; $I^2 = 0\%$; very low quality evidence) (Analysis 2.1) (DANAMI-3-PRIMULTI 2015; HELP AMI 2004).

Short-term cardiovascular mortality

One trial showed that the complete and culprit-only revascularisation strategies did not differ significantly regarding short-term cardiovascular mortality (1/314 (0.3%) in complete group versus 3/313 (1%) in culprit-only group; RR 0.33, 95% CI 0.03 to 3.18; participants = 627; $I^2 = 0\%$) (Analysis 2.2) (DANAMI-3-PRIMULTI 2015).

Short-term non-fatal myocardial infarction

One trial showed that the complete and culprit-only revascularisation strategies did not differ significantly regarding short-term non-fatal myocardial infarction (7/314 (2.2%) in complete group versus 4/313 (1.3%) in culprit-only group; RR 1.74,

95% CI 0.52 to 5.90; participants = 627; $I^2 = 0\%$) (Analysis 2.3) (DANAMI-3-PRIMULTI 2015).

Short-term and long-term revascularisation

Two trials showed that there was no difference in terms of revascularisation between groups in the short-term (6/366 (1.6%) in complete group versus 10/330 (3%) in culprit-only group; RR 0.53, 95% CI 0.20 to 1.45; participants = 696; $I^2 = 0\%$) (DANAMI-3-PRIMULTI 2015; HELP AMI 2004). Nine trials showed that the complete revascularisation strategy was associated with significantly lower rates of revascularisation in the long-term (145/1374 (10.6%) in complete group versus 258/1242 (20.8%) in culprit-only group; RR 0.47, 95% CI 0.39 to 0.57; participants = 2616; $I^2 = 31\%$; very low quality evidence) (Analysis 2.4) (CvLPRIT 2015; Dambrink and Ghani 2010; DANAMI-3-PRIMULTI 2015; Estevez Loureiro 2014; HELP AMI 2004; Politi 2009; PRAGUE-13 2015; PRAMI 2013; Zhang 2015).

In the TSA, the cumulative Z-curve crossed the sequential monitoring boundaries for benefit. This result indicates that the complete revascularisation strategy is associated to an at least 20% long-term non-fatal myocardial infarction RRR compared with the culprit-only strategy (RR 0.49, TSA-adjusted CI 0.31 to 0.79) and further trials may not change this result (Figure 7).

Figure 7. Trial Sequential Analysis for complete versus culprit-only revascularisation on long-term revascularisation. The diversity-adjusted required information size (DARIS) was calculated based on an expected relative risk reduction (RRR) of 20% from Pc group of 20.7% with an alpha of 2% and beta of 10%.

Health-related quality of life

No studies reported long-term health-related quality of life.

Cost

Only one study reported on costs and found no difference in one-year cost between the groups (MD Euros -1948.00, 95% CI -9171.85 to 5275.85; participants = 69; $I^2 = 0\%$) ([Analysis 2.5](#)) ([HELP AMI 2004](#)).

Subgroup analyses

Drug-eluting stent compared to bare-metal stents

Two trials utilised DES only in few participants (20% of the included participants in [Dambrink and Ghani 2010](#) and 10.2% in the [Politi 2009](#) trial received DES), while the other studies mostly placed DES in their revascularisation procedures. In those participants who underwent revascularisation with DES, complete revascularisation was favoured over the culprit-only revascularisation strategy in terms of long-term cardiovascular mortality (22/913 (2.4%) in complete group versus 40/903 (4.4%) in culprit-only group; RR 0.54, 95% CI 0.33 to 0.91; participants = 1816; studies = 4; $I^2 = 0\%$) and long-term non-fatal myocardial infarction (41/965 (4.2%) in complete group versus 63/920 (6.8%) in culprit-only group; RR 0.63, 95% CI 0.43 to 0.93; participants = 1885; studies = 5; $I^2 = 0\%$). In contrast, for participants in whom revascularisation was performed with BMS, neither of the revascularisation strategies was statistically favoured in terms of long-term cardiovascular mortality (6/130 (4.6%) in complete group versus 10/84 (12%) in culprit-only group; RR 0.39, 95% CI 0.15 to 1.03; participants = 214; studies = 1) or long-term non-fatal myocardial infarction (6/130 (4.6%) in complete group versus 7/84 (8.3%) in culprit-only group; RR 0.55, 95% CI 0.19 to 1.59; participants = 214; studies = 1).

Sex

Given the poor subgroup reporting in the included trials, we were unable to perform analysis by sex.

People with diabetes mellitus compared to people without diabetes mellitus

Given the poor subgroup reporting in the included trials, we were unable to perform analysis by people with or without diabetes mellitus.

Non-culprit and culprit intervention during the same procedure compared to in separate interventions (staged)

The complete revascularisation strategy performed at the index procedure was associated with lesser long-term non-fatal myocardial infarction (12/501 (2.4%) in complete group versus 32/478 (6.7%) in culprit-only group; RR 0.37, 95% CI 0.19 to 0.71; participants = 979; studies = 4; $I^2 = 0\%$), while when the intervention on the non-culprit lesions was deferred for a second intervention or staged procedure, the complete and culprit-only revascularisation strategies had similar long-term non-fatal myocardial infarction (35/594 (5.9%) in complete group versus 45/610 (7.4%) in culprit-only group; RR 0.80, 95% CI 0.52 to 1.23; participants = 1204; studies = 3; $I^2 = 0\%$). Complete revascularisation was also associated with lesser long-term cardiovascular mortality when performed either during the index procedure (10/449 (2.2%) in complete group versus 27/461 (5.9%) in culprit-only group; RR 0.40, 95% CI 0.20 to 0.82; participants = 910; studies = 3; $I^2 = 0\%$) or in a staged manner (18/694 (2.6%) in complete group versus 34/709 (4.8%) in

culprit-only group; RR 0.56, 95% CI 0.32 to 0.98; participants = 1403; studies = 4; $I^2 = 0\%$). It is important to note that in the [CvLPRIT 2015](#) trial, which was grouped with the studies that performed complete revascularisation at the index procedure, 35% of the complete revascularisation procedures were performed in a staged manner.

Low risk of bias articles compared to high risk of bias articles

Given the poor subgroup reporting in the included trials, we were unable to perform analysis by low or high risk of bias.

Participants in cardiogenic shock compared to participants not in cardiogenic shock

Given the poor subgroup reporting in the included trials, we were unable to perform analysis by participants in or not in cardiogenic shock.

Sensitivity analyses

We performed sensitivity analyses restricting the analysis to studies that were published, were in English language only, with revascularisation guided by FFR, and the type of stent used. The overall results were unaffected by excluding the studies with those characteristics from the pooled analysis.

Assessment of reporting bias

We were unable to create a funnel plot because we did not pool more than 10 trials for the analysis of any outcome.

Ongoing trials

We identified six ongoing clinical trials that are comparing complete PCI revascularisation versus PCI of culprit-only revascularisation in people with STEMI (see [Characteristics of ongoing studies](#) table).

DISCUSSION

Summary of main results

The meta-analysis of nine RCTs showed that, compared with the culprit-only intervention, complete revascularisation in people with STEMI and MVD seems to be associated with a lower long-term cardiovascular mortality, long-term revascularisation need, and long-term non-fatal myocardial infarction.

Overall completeness and applicability of evidence

Even though this systematic review included nine fairly well-designed RCTs and there was significant consistency across the studies due to similar inclusion/exclusion criteria, similar participant populations, similar procedures, and criteria to decide about intervening on the non-culprit vessel, the overall quality of evidence was very low mostly due to serious problem of imprecision, indirectness, and study limitations.

The fact that the included studies in this pooled analysis were conducted recently and were contemporary with regards to the standards of care utilised, including DES and up-to-date medical therapy, along with the flexible inclusion and exclusion criteria, ensures high applicability of these results to current-day clinical practice. Even though the studies were performed in different parts of the world, some continents were under-represented. For instance, none of the included trials studied participants in North America, South America, or Australia. Women were also under-

represented, and although none of the trials reported the race of the studied participants, it is plausible that black and Hispanic people were not included or were under-represented. Therefore, these findings have to be applied cautiously in those under-represented populations and geographic locations.

Quality of the evidence

We utilised the GRADE assessment tool to evaluate the quality of evidence for the most relevant outcomes. In general, we judged the outcomes to have very low quality of evidence. The quality of the evidence was downgraded because of the potential risk of bias, indirectness of findings, and imprecision. Given the number of studies, we were unable to exclude publication bias and we found no evidence of plausible confounding or dose-response gradient.

One of the main limitations of the included studies was the open-label design, which potentially may increase the risk of performance or detection bias. To attenuate these biases, the investigators blinded the outcome assessors and we, in our analysis, included mostly objective outcomes such as mortality and non-fatal myocardial infarction. However, we do expect that the rate of revascularisation and acute kidney injury were possibly influenced by detection and performance bias. Five of the included trials lacked a published protocol ([Dambrink and Ghani 2010](#); [Estevez Loureiro 2014](#); [HELP AMI 2004](#); [Politi 2009](#); [Zhang 2015](#)), which was concerning for risk of reporting bias; for those studies that had a published protocol, we found no evidence of reporting bias. The only study that effectively reported the allocation concealment and random sequence generation was the [CvLPRIT 2015](#) trial, which we judged to have low risk of selection bias, while the others had high risk for selection bias.

Although the studies had few dropouts, given the small number events, we considered that the proportion of participants that left the trials might have increased the risk of attrition bias in at least two studies ([CvLPRIT 2015](#); [PRAMI 2013](#)). Moreover, the early termination of one study because of significant difference between groups ([PRAMI 2013](#)), may also have introduced bias to the results (e.g. overestimate the beneficial results from the complete revascularisation strategy).

Another explanation for the very low quality of evidence comes from the fact that women and presumably minority group such as Hispanic and black people were under-represented in the included studies, which would affect the external applicability of these findings; therefore, we considered this a serious limitation in indirectness of the evidence. Another limitation that justified downgrading the quality of the evidence for imprecision was that the included studies had a small number of events and several outcomes did not meet the optimal information size, which was confirmed with the TSA.

Potential biases in the review process

In order to ensure applicability of these results to patient care, all-cause mortality was added as another primary outcome after publication of the protocol. The definition of “type of intervention” was changed to include RCTs that performed revascularisation as a second intervention at another hospitalization, which is a common practice. Additionally an element that should be considered as a potential source of bias during the review process is that the decision on intervening the non-culprit coronary arteries was

slightly different among studies. For instance, trials included in this review used slightly different degrees of stenosis while others utilised FFR measurements. Finally, some studies performed the complete revascularisation at the same index procedure while others performed the complete revascularisation at different times.

Agreements and disagreements with other studies or reviews

Major international guidelines, including those from the [ACC/AHA 2013](#) and [ESC 2012](#), favour timely intervention on the culprit artery and tend to discourage simultaneous interventions upon non-culprit lesions in the absence of objective signs or symptoms of persistent cardiac ischaemia, due to lack of good-quality evidence and even concerns of possible harm. The results of our meta-analysis suggest that in fact complete revascularization of significantly stenotic (50-70% stenotic) non-culprit lesions, regardless of signs or symptoms of ischaemia, may improve important cardiovascular outcomes.

Our findings are clearly in conformity with the newly updated [ACC/AHA/SCAI 2015](#) and [ESC 2014](#) guidelines, which allow for consideration of simultaneous intervention on both culprit and non-culprit lesions during the same index procedure, thus suggesting possible benefits in otherwise haemodynamically stable people presenting with STEMI and MVD.

There are several meta-analyses that have previously shown that complete revascularisation and culprit-only intervention strategies have similar outcomes. For example, [Vlaar 2011](#) showed in their meta-analysis of four prospective studies that there was no difference in short (odds ratio (OR) 1.98, 95% CI 0.57 to 6.85) or long-term mortality (OR 1.45, 95% CI 0.61 to 3.46). Similarly [Bagai 2013](#), after analysing three RCTs, showed that the strategies were similar (OR 0.81, 95% CI 0.32 to 2.06).

In contrast, more recently published meta-analyses have shown that complete revascularisation strategy is superior to the culprit-only intervention strategy. [Sardar 2015](#) included five RCTs and they found that, compared to a culprit-vessel-only intervention strategy, complete revascularisation was associated with a significant reduction in revascularisation (OR 0.32, 95% CI 0.21 to 0.49), cardiovascular mortality (OR 0.44, 95% CI 0.20 to 0.94), and recurrent myocardial infarction (OR 0.35, 95% CI 0.18 to 0.69). In [Elgendy 2015](#), the pooled analysis of six RCTs showed that the complete revascularisation strategy lowered the risk of urgent revascularisation (RR 0.55, 95% CI 0.35 to 0.86), but the strategies did not differ in terms of mortality (RR 0.68, 95% CI 0.4 to 1.14) and myocardial infarction (RR 0.56, 95% CI 0.24 to 1.27). In the editorial comment by [Bhatt 2015](#), the pooled analysis of the [PRAMI 2013](#) and [CvLPRIT 2015](#) trials showed that, compared with the culprit-only intervention group, the complete revascularisation strategy was associated with a lower cardiovascular mortality, revascularisation, and myocardial infarction. Similarly, [Pandit 2014](#) demonstrated that the complete revascularisation strategy was associated with reduced cardiovascular deaths (OR 0.39, 95% CI 0.18 to 0.83), revascularisation (OR 0.28, 95% CI 0.18 to 0.44), and non-fatal myocardial infarction (OR 0.38, 95% CI 0.20 to 0.75). In [Bangalore 2015](#), the complete revascularisation strategy was associated with lower mortality (RR 0.60, 95% CI 0.38 to 0.97), cardiovascular mortality (RR 0.38, 95% CI 0.20 to 0.73), and revascularisation (RR 0.42, 95% CI 0.31 to 0.57). In [Bainey 2014](#), it was shown that complete revascularisation strategy lowered in-hospital mortality

(OR 0.24, 95% CI 0.06 to 0.91) and need for revascularisation (OR 0.31, 95% CI 0.17 to 0.57). In terms of long-term mortality, the strategies appeared to be similar (OR 0.61, 95% CI 0.28 to 1.33).

Although our present systematic review is consistent with the previously published reviews and meta-analyses, this is the largest, most comprehensive, and only systematic review that included only RCTs, showing that complete revascularisation strategy is associated with a long-term reduction in cardiovascular mortality, non-fatal myocardial infarction, and revascularisation. Furthermore, this is the only systematic review in this area that has utilised GRADE to evaluate the quality of the evidence, and to include a TSA in order to control the type I and II errors and to predict if the total number of participants included in the meta-analysis was enough to draw conclusions regarding the effects of complete revascularisation.

AUTHORS' CONCLUSIONS

Implications for practice

Given the increasing prevalence of classic cardiovascular risk factors, the prevalence of ST elevation myocardial infarction (STEMI) continues to rise globally, leading to significant mortality, morbidity, and healthcare costs. The updated version of American College of Cardiology (ACC)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions (SCAI) and European Society of Cardiology (ESC) guidelines now consider it reasonable to intervene on the non-culprit vessel, at the time of the index procedure, in people with STEMI. The evidence generated by this meta-analysis shows that the complete revascularisation may be superior but we have very little confidence in the effect estimate since the quality of evidence is very low and there is still need of further research to support or disprove that potential difference.

Implications for research

STEMI and multi-vessel disease (MVD) frequently coexist, and this combination is associated with worse outcomes. In order

to improve the care of this subgroup of people, it is crucial to understand fully the pathophysiology of the coronary artery disease progression after STEMI and the correct treatment options for the non-culprit stenotic vessels. This systematic review supports the view that complete revascularisation may be a better treatment option than the culprit-only intervention strategy; however, based on the low quality of the evidence and TSA, more studies are needed in order to draw firm conclusions regarding long-term all-cause mortality, cardiovascular mortality, and non-fatal myocardial infarction. The additional important question as to whether it is better to intervene on the non-culprit vessel at the index procedure or staged needs to be further studied in a randomised controlled trial designed for this purpose. Such trials ought to be designed according to the SPIRIT Statement (Standard Protocol Items: Recommendations for Interventional Trials) and reported according to the CONSORT Statement.

Unfortunately, we could not access data that would allow us to study specific subgroups of people, such as people with diabetes, women, or certain races, which may benefit in particular from one strategy over another. Finally, even though the findings of this systematic review suggest that the complete revascularisation strategy seems better than the current standard of care, further research is needed to confirm the benefit obtained by complete revascularisation, and to determine the optimal mode, timing, and extent of revascularisation of the non-culprit arteries in people with STEMI and MVD.

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FIT {unpublished data only}

FIT (Fast Infarction Treatment): Complete Revascularisation During Primary Percutaneous Coronary Intervention (PCI) Can be Achieved Safely With an Improved Clinical Outcome During the Indexed Hospitalisation.. Ongoing study July 2010..

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

CvLPRIT 2015

Methods	<p>RCT multi-centre.</p> <p>Randomisation ratio: 1:1.</p> <p>Number of study centres: 7 centres in the UK.</p>
Participants	<p>Inclusion criteria: suspected or confirmed acute MI, significant ST elevation or LBBB on ECG (in cases of LBBB, angiographic confirmation of culprit coronary occlusion was required), < 12 hours of symptom onset, scheduled for P-PCI for clinical reasons, provision of verbal assent followed by written informed consent, MVD, the non-culprit vessel had to be a major (> 2 mm) epicardial coronary artery or branch (> 2 mm) and be suitable for stent implantation.</p> <p>Exclusion criteria: any exclusion criteria for P-PCI; aged < 18 years; clear indication for, or contraindication to, multi-vessel P-PCI according to operator judgement; previous Q-wave MI; people with prior CABG, cardiogenic shock, ventricular septal defect, or moderate/severe mitral regurgitation; chronic kidney disease (Cr > 200 µmol/L or eGFR < 30 mL/minute/1.73 m²); suspected or confirmed thrombosis of a previously stented artery; where the only significant non-IRA lesion is a chronic total occlusion.</p> <p>Diagnostic criteria</p> <p>MVD: culprit vessel plus at least 1 non-culprit coronary artery with at least 1 lesion deemed angiographically significant.</p> <p>Significant stenosis: > 70% diameter stenosis in 1e plane or > 50% in 2 planes.</p> <p>Sample size: complete revascularisation n = 150 and culprit-only revascularisation n = 146.</p>
Interventions	<p>Complete revascularisation: complete revascularisation at the same procedure, unless operator decided, for clinical reasons, that the procedure needed to be staged, in the cases of staged intervention, it was mandated that the non-culprit lesions be treated during the index admission.</p> <p>Culprit-only revascularisation: intervention on the culprit artery unless participant needed revascularisation based on ischaemic symptoms or significant ischaemia evidenced in imaging tests.</p>
Outcomes	<p>Primary: composite of all-cause mortality, recurrent MI, heart failure, and ischaemia-driven revascularisation within 12 months after index procedure.</p> <p>Secondary: cardiovascular death, individual components of the primary endpoint, stroke, major bleeding, and contrast-induced nephropathy.</p>
Notes	<p>Protocol ID: ISRCTN70913605.</p>

Risk of bias

Complete versus culprit-only revascularisation in ST elevation myocardial infarction with multi-vessel disease (Review)

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CvLPRIT 2015 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An interactive voice-response program was utilised to randomise participants.
Allocation concealment (selection bias)	Low risk	Randomisation was performed immediately after the angiography and before the intervention of the culprit artery via a centralised 24/7 telephone randomisation service.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study was open label for the participants.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes adjudicator clinicians were blinded to the group allocation.
Incomplete outcome data (attrition bias) All outcomes	High risk	Similar dropout rate in both groups, 7.3% culprit-only vs 5.5% complete revascularisation group; however, given the small number of events, the result may be affected by attrition bias.
Selective reporting (reporting bias)	Low risk	Study reported the primary outcomes indicated in the published protocol in www.isrctn.com ISRCTN70913605.
Other bias	Low risk	Study was funded by the national funding institution British Heart Foundation and Medical Research Council (MRC)/National Institutes of Health Research (NIHR) (UK) and the funding institution was not involved in the study other than economically.

Dambrink and Ghani 2010

Methods	<p>RCT.</p> <p>Randomisation ratio: 2:1.</p> <p>Number of study centres: 1 centre in the Netherlands.</p>
Participants	<p>Inclusion criteria: MVD with successful P-PCI for STEMI.</p> <p>Exclusion criteria: urgent indication for additional revascularisation, aged > 80 years, chronic occlusion of 1 of the non-culprit artery(ies), prior CABG, left main stenosis of $\geq 50\%$, restenotic lesions in non-culprit artery(ies), chronic atrial fibrillation, limited life-expectancy, or other factors that made complete follow-up unlikely.</p> <p>Diagnostic criteria</p> <p>MVD: ≥ 1 significant stenosis in at least 2 major epicardial coronary arteries or the combination of a side branch and a main epicardial vessel provided that they supplied different territories.</p> <p>Significant stenosis: diameter $\geq 50\%$ in luminal diameter in at least 1 view. FFR < 0.75 defined ischaemic stenosis and those were intervened only, and > 90% stenosis were intervened without FFR measurement.</p> <p>Sample size: complete revascularisation n = 80 and culprit-only revascularisation n = 41.</p>
Interventions	<p>Complete revascularisation: staged intervention on significant stenotic non-culprit lesions compatible with ischaemia (FFR < 0.75) with plain angioplasty, BMS, or DES.</p>

Dambrink and Ghani 2010 (Continued)

Culprit-only revascularisation: medical management after P-PCI of culprit artery only unless ischaemic symptoms were elicited with exercise testing, dobutamine stress echocardiography, or myocardial scintigraphy, in those cases ischaemia-guided revascularisation was performed.

Outcomes	<p>Primary: EF at 6 months.</p> <p>Secondary: change in EF, wall motion score, left ventricle end-systolic and end-diastolic volume, and MACE.</p>
Notes	Early termination because of slow enrolment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed with a computer program.
Allocation concealment (selection bias)	Unclear risk	Not mentioned how allocation concealment was insured.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned in the article.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Only mentioned in the study that echocardiographic and radionuclide data were blinded to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the complete revascularisation group 1.3% dropped out, vs 2.4% in the culprit-only group.
Selective reporting (reporting bias)	High risk	Study did not have a published protocol and was not registered on any clinical trial databases.
Other bias	High risk	Study had early termination because of slow enrolment. Unclear source of funding.

DANAMI-3-PRIMULTI 2015

Methods	<p>RCT multi-centre.</p> <p>Randomisation ratio: 1:1.</p> <p>Number of study centres: 2 centres in Denmark.</p>
Participants	<p>Inclusion criteria: chest pain < 12 hours' duration and ST elevation > 0.1 mV in at least 2 contiguous leads and with diameter stenosis of > 50% in ≥ non-culprit artery(ies).</p> <p>Exclusion criteria: intolerance to contrast media, anticoagulant, antithrombotic drugs, unconsciousness or cardiogenic shock, stent thrombosis, indications for CABG, or increased bleeding risk.</p> <p>Diagnostic criteria</p> <p>MVD: significant stenosis in ≥ 1 of the non-culprit artery(ies) or their major side branches in addition to that in the culprit artery.</p>

DANAMI-3-PRIMULTI 2015 (Continued)

Significant stenosis: > 50% stenosis visually in arteries > 2 mm diameter and FFR ≤ 0.8 or > 90% stenosis visually regardless FFR measurement.

Sample size: complete revascularisation n = 314 and culprit-only revascularisation n = 313.

Interventions	<p>Complete revascularisation: PCI of culprit and in a second intervention 48 hours after P-PCI and before discharge, FFR-guided PCI in all non-culprit significant stenotic lesions and > 90% stenotic despite FFR measurement.</p> <p>Culprit-only revascularisation: Intervention on the culprit-only.</p>
Outcomes	<p>Primary: composite of all-cause mortality, non-fatal MI, and ischaemia-driven (subjective or objective) revascularisation of lesions in non-culprit artery(ies) 1 year' follow-up.</p> <p>Secondary: all-cause mortality, non-fatal MI, cardiac death, urgent or non-urgent PCI of lesions in non-culprit artery(ies).</p>
Notes	Protocol ID: NCT01960933.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed electronically via a centralised web-based system.
Allocation concealment (selection bias)	Unclear risk	Not mentioned how allocation concealment was insured.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Even though the study was open label there was an independent events committee that adjudicated all events.
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the complete revascularisation group around 0.3% dropped out, while in the culprit-only group all participants completed the study.
Selective reporting (reporting bias)	Low risk	Study reported the primary outcomes indicated in the published protocol in www.ClinicalTrial.gov NCT01960933.
Other bias	Low risk	Study was funded by national funding institution (Danish Agency of Science, Technology and Innovation and Danish Council for Strategic Research) and the funding institution was not involved in the study other than economically.

Estevez Loureiro 2014

Methods	<p>RCT.</p> <p>Randomisation ratio: 1:1.</p> <p>Number of study centres: not described in abstract.</p>
Participants	Inclusion criteria: people with STEMI and MVD.

Complete versus culprit-only revascularisation in ST elevation myocardial infarction with multi-vessel disease (Review)

Estevez Loureiro 2014 (Continued)

Exclusion criteria: not described in abstract.

Diagnostic criteria

MVD: not described in abstract.

Significant stenosis: not described in abstract.

Sample size: complete revascularisation n = 100 and culprit-only revascularisation n = 99.

Interventions	<p>Invasive: staged complete intervention after P-PCI.</p> <p>Conservative: intervention of culprit-only, unless participants had residual ischaemia based on stress echocardiogram, these participants would go for staged intervention.</p>
Outcomes	<p>Primary: composite of cardiovascular death, non-fatal MI, revascularisation of any vessel, or admission due to heart failure.</p> <p>Secondary: not described in abstract.</p>
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned in the article.
Allocation concealment (selection bias)	Unclear risk	Not mentioned in the article.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned in the article.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned in the article.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned in the article.
Selective reporting (reporting bias)	High risk	Study did not have a published protocol and was not registered on any clinical trial databases.
Other bias	Unclear risk	Unclear source of funding.

HELP AMI 2004

Methods	<p>RCT multi-centre.</p> <p>Randomisation ratio: 3:1.</p> <p>Number of study centres: not described in the article.</p>
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HELP AMI 2004 (Continued)

Participants

Inclusion criteria: ischaemic chest pain started < 12 hours before hospital admission with or without ST-segment elevation of ≥ 1 mm in ≥ 2 contiguous electrocardiographic leads (peripheral leads) or 2 mm in the precordial leads. MVD amenable to angioplasty of at least 2 lesions (culprit artery and ≥ 1 (maximum 3) lesions in a major non-culprit coronary artery(ies)).

Exclusion criteria: presence of significant lesions in vein grafts or arterial conduits or in segments previously treated with angioplasty or stent, recent thrombolysis (< 1 week), cardiogenic shock, defined as hypotension with systolic blood pressure < 90 mmHg and tachycardia > 100 beats/minute, not due to hypovolaemia or requiring inotropic support or balloon counter pulsation. Single-vessel disease, left main stenosis of $\geq 50\%$, intention to treat > 1 totally occluded major epicardial vessel, diffuse calcification or severe tortuosity in the culprit and non-culprit arteries preventing the implantation of the study stents. A sided branch > 2 mm which required being covered by the stent, unless the operator was willing and technically able to maintain patency of this side branch with either further balloon angioplasty or stent placement.

Diagnostic criteria

MVD: not defined in the article.

Significant stenosis: not defined in the article.

Sample size: complete revascularisation n = 53 and culprit-only revascularisation n = 17.

Interventions

Complete revascularisation: PCI of all, culprit and non-culprit coronary artery lesions suitable to intervention with a heparin-coated stent.

Culprit-only revascularisation: PCI of culprit artery only and intervention on non-culprit artery(ies) was performed at discretion of the investigator, based on clinical status (persistent or recurrent angina), evidence of ischaemia in non-invasive tests (perfusion scintigraphy or stress echo), angiographic severity of non-culprit lesions and clinical relevance of the affected vessels as well as organisation standards of the participating centres.

Outcomes

Primary: 12-month revascularisation.

Secondary: in-hospital revascularisation, reinfarction, and death. Procedural in-hospital and total hospital cost, 12 months' follow-up.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned in the article.
Allocation concealment (selection bias)	Unclear risk	Not mentioned in the article.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned in the article.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned in the article.
Incomplete outcome data (attrition bias)	Unclear risk	Not mentioned in the article.

HELP AMI 2004 (Continued)

All outcomes

Selective reporting (reporting bias)	High risk	Study did not have a published protocol and was not registered on any clinical trial databases.
Other bias	Unclear risk	Unclear source of funding.

Politi 2009

Methods	RCT. Number of study centres: not described.
Participants	Inclusion criteria: people with prolonged (> 30 minutes) chest pain, started < 12 hours before hospital arrival and ST elevation of ≥ 1 mm in ≥ 2 contiguous limb electrocardiographic leads or 2 mm in precordial leads. Exclusion criteria: cardiogenic shock at presentation (systolic blood pressure ≤ 90 mmHg despite drug therapy), left main coronary disease ($\geq 50\%$ diameter stenosis), previous CABG surgery, severe valvular heart disease, and unsuccessful procedures. Diagnostic criteria MVD: stenosis of ≥ 2 epicardial coronary arteries or their major branches by visual estimation. Significant stenosis: > 70% diameter. Sample size: complete revascularisation n = 130 (65 staged and 65 at index procedure complete revascularisation) and culprit-only revascularisation n = 84.
Interventions	Complete revascularisation: revascularisation of all, culprit and non-culprit significant stenosis at the index procedure or staged. Culprit-only revascularisation: intervention on the culprit vessel only.
Outcomes	Primary: MACE, cardiac or non-cardiac death, in-hospital death, re-infarction, re-hospitalisation for acute coronary syndrome, and revascularisation. Secondary: not mentioned.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed with a computer program.
Allocation concealment (selection bias)	Unclear risk	Lack of information regarding how the allocation was concealed.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned in the article.

Politi 2009 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned in the article.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts were not reported in the article.
Selective reporting (reporting bias)	High risk	Study did not have a published protocol and was not registered on any clinical trial databases.
Other bias	Unclear risk	Unclear source of funding.

PRAGUE-13 2015

Methods	<p>RCT multi-centre.</p> <p>Randomisation ratio: 1:1.</p> <p>Number of study centres: 6 centres in Czech Republic.</p>
Participants	<p>Inclusion criteria: people with STEMI, angiographically successful primary PCI of culprit artery (TIMI flow grades II or III), ≥ 1 other significant stenoses of non-culprit artery(ies) found by coronary angiography (diameter of artery ≥ 2.5 mm), enrolment ≥ 48 hours following onset of symptoms.</p> <p>Exclusion criteria: stenosis of the left main of left coronary artery $\geq 50\%$, haemodynamically significant valvular disease, people in cardiogenic shock during STEMI, haemodynamic instability, angina pectoris $>$ grade 2 CCS lasting 1 month prior to STEMI.</p> <p>Diagnostic criteria</p> <p>MVD: ≥ 1 vessel, beside of the culprit vessel, with significant stenosis.</p> <p>Significant stenosis: $> 70\%$ stenosis of non-culprit artery(ies).</p> <p>Sample size: complete revascularisation n = 106 and culprit-only revascularisation n = 108.</p>
Interventions	<p>Complete revascularisation: PCI of the culprit artery and staged intervention for the non-culprit artery(ies) between days 3 and 40 after the index procedure.</p> <p>Culprit-only revascularisation: intervention on the culprit artery only.</p>
Outcomes	<p>Primary: composite endpoint of death, non-fatal acute MI, and stroke.</p> <p>Secondary: cardiovascular death, recurrent MI, target vessel failure, progression of studied stenosis of non-culprit artery, stroke, hospitalisation for heart failure, changes in left ventricular EF, hospitalisation for unstable angina pectoris, outcomes of questionnaire regarding angina pectoris, target vessel revascularisation, non-culprit target lesion revascularisation.</p>
Notes	<p>Only abstract published.</p> <p>Protocol ID: NCT01332591.</p>
Risk of bias	
Bias	Authors' judgement Support for judgement

PRAGUE-13 2015 (Continued)

Random sequence generation (selection bias)	Unclear risk	Not mentioned in the abstract or in protocol posted on www.ClinicalTrial.gov .
Allocation concealment (selection bias)	Unclear risk	Not mentioned in the abstract or in protocol posted on www.ClinicalTrial.gov .
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label study.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Open-label study.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts not reported in the abstract.
Selective reporting (reporting bias)	Low risk	Abstract reported the primary outcomes indicated in the published protocol in www.ClinicalTrial.gov NCT01332591.
Other bias	Low risk	Study was funded by a Research Grant from the Czech Ministry of Health and by The International Clinical Research Center of St. Anne's University Hospital Brno (FNUSA-ICRC) which is funded by the European Union.

PRAMI 2013

Methods	<p>RCT multi-centre.</p> <p>Randomisation ratio: 1:1.</p> <p>Number of study centres: 5 centres in the UK.</p>
Participants	<p>Inclusion criteria: people of any age with STEMI and MVD detected at the time of angiography.</p> <p>Exclusion criteria: cardiogenic shock, unable to provide consent, previous CABG, non-infarct artery stenosis of $\geq 50\%$ in the left main stem or the ostial branch of both the left anterior descending and circumflex arteries (because these are indications for CABG), or if the only non-infarct stenosis was a chronic total occlusion (because it was felt that PCI in such circumstances was contraindicated owing to a low success rate).</p> <p>Diagnostic criteria</p> <p>MVD: presence of significant stenosis in ≥ 1 coronary artery other than the culprit vessel.</p> <p>Significant stenosis: stenosis $\geq 50\%$.</p> <p>Sample size: complete revascularisation $n = 234$ and culprit-only revascularisation $n = 231$.</p>
Interventions	<p>Complete revascularisation: intervention on all, culprit and non-culprit arteries with stenosis of $\geq 50\%$.</p> <p>Culprit-only revascularisation: PCI of culprit vessel only, except in people with refractory angina with objective evidence of ischaemia which may require staged intervention.</p>
Outcomes	<p>Primary: composite of death from cardiac causes, non-fatal MI, or refractory angina.</p>

PRAMI 2013 (Continued)

Secondary: death from non-cardiac causes and revascularisation procedure.

Notes

Study was stopped earlier because of a highly significant difference between groups, favouring the complete revascularisation group. The study was funded by Bart's and the London Trust (BLT) Charitable Foundation (UK).

Protocol ID: ISRCTN73028481.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computer-generated.
Allocation concealment (selection bias)	Unclear risk	Not mentioned how allocation concealment was insured.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study was open label for the participant.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Independent cardiologist and cardiac surgeon who were not notified about study-group assignments examined specified primary and secondary outcomes.
Incomplete outcome data (attrition bias) All outcomes	High risk	Similar dropout rate in both groups, 4.3% in the complete vs 3.5% in the culprit-only intervention group; however, given the small number of events, the results may be susceptible to attrition bias.
Selective reporting (reporting bias)	Low risk	Study reported the primary outcomes indicated in the published protocol in www.isrctn.com ISRCTN73028481.
Other bias	High risk	Early termination of the study may overestimate/underestimate certain differences.

Zhang 2015

Methods

RCT.

Randomisation ratio: 1:1.

Number of study centres: not mentioned in the study.

Participants

Inclusion criteria: people with STEMI, non-culprit artery(ies) with significant stenosis, blood vessel > 2.5 mm and suitable for PCI.

Exclusion criteria: cardiogenic shock, CABG, undetermined culprit vessel, person refused PCI, non-culprit vessel occlusion is chronic, blood vessel diameter < 2.5 mm, lesions non-suitable for PCI, non-culprit vessel stenosis > 90%.

Diagnostic criteria

MVD: non-culprit vessel significant stenosis.

Significant stenosis: between 75% and 90%.

Zhang 2015 (Continued)

Sample size: complete revascularisation n = 215 and culprit-only revascularisation n = 213.

Interventions	<p>Complete revascularisation: PCI of the culprit vessel and staged intervention for the non-culprit lesions between days 7 and 10 after the index procedure.</p> <p>Culprit-only revascularisation: PCI of culprit vessel only and intervention on non-culprit vessels was performed if participant had evidence of ischaemia (symptoms, ECG changes, or nuclear study consistent with ischaemia).</p>
Outcomes	All-cause mortality, MACE (MI and cardiac death), hospitalisation due to cardiac reasons (angina, heart failure, re-hospitalisation for PCI), total hospitalisation time, stent number and hospital cost.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned in the article the method for randomisation.
Allocation concealment (selection bias)	Unclear risk	Not mentioned in the article the method for randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned in the article.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned in the article.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned in the article.
Selective reporting (reporting bias)	High risk	Study did not have a published protocol and was not registered on any clinical trial databases.
Other bias	Unclear risk	Unclear source of funding.

BMS: bare-metal stent; CABG: coronary artery bypass graft; CCS: Canadian Cardiovascular Society; Cr: creatinine; DES: drug-eluting stent; ECG: electrocardiogram; EF: ejection fraction; eGFR: estimated glomerular filtration rate; FFR: fractional flow reserve; LBBB: left bundle branch block; MACE: major adverse cardiovascular event; MI: myocardial infarction; MVD: multi-vessel disease; n: number of participants; non-IRA: non-infarct related artery; PCI: percutaneous coronary intervention; P-PCI: primary percutaneous coronary intervention; RCT: randomised controlled trial; STEMI: ST elevated myocardial infarction; TIMI: Thrombolysis in Myocardial Infarction.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
APEX AMI 2010	Wrong study design.
Chen 2005	Wrong study design.

Study	Reason for exclusion
Corpus 2004	Wrong study design.
Hamza 2016	Wrong outcomes.
Han 2008	Wrong study design.
Hong 2001	Wrong study design.
HORIZONS-AMI 2011	Wrong study design.
Ijsselmuiden 2004	Wrong participant population.
Jin 2008	Wrong study design.
Khattab 2008	Wrong study design.
Liu 2015	Wrong study design.
Maamoun 2011	Wrong study design.
Ochala 2004	Wrong comparator.
PRIMA trial 2013	Wrong comparator.
Qarawani 2008	Wrong study design.
Samson 1990	Wrong study design.
Tajstra 2012	Wrong study design.
Tapsiz 2014	Wrong study design.
Tarasov 2013	Wrong study design.
Valenti 2013	Wrong study design.

Characteristics of ongoing studies *[ordered by study ID]*

ASSIST-CMR

Trial name or title	Revascularisation Strategies for STEMI; The CMR Endpoint Study.
Methods	Open-label RCT.
Participants	People with acute STEMI and MVD as evidenced by ≥ 1 significant ($\geq 70\%$ by visual assessment or FFR < 0.80 for 50% to 70% stenosis) stenosis in non-culprit artery(ies).
Interventions	1 time primary PCI of the culprit and non-culprit lesions vs intervention of the culprit vessel only.
Outcomes	Primary: infarct size by CMR. Secondary: MACE rate at 12 months.
Starting date	April 2014.

ASSIST-CMR (Continued)

Contact information	Shahar Lavi shahar.lavi@lhsc.on.ca.
Notes	

COCUA

Trial name or title	Complete Lesion Versus Culprit Lesion Revascularisation (COCUA).
Methods	Not described.
Participants	People with acute STEMI and MVD.
Interventions	1 time primary PCI of the culprit and non-culprit lesions vs intervention of the culprit vessel only.
Outcomes	Not described.
Starting date	July 2011.
Contact information	Seung Woon Rha swrha617@yahoo.co.kr.
Notes	www.ClinicalTrial.gov NCT01180218.

COMPARE ACUTE

Trial name or title	Comparison Between FFR Guided Revascularisation Versus Conventional Strategy in Acute STEMI Patients with MVD (CompareAcute).
Methods	Open-label RCT.
Participants	People with acute STEMI and MVD.
Interventions	FFR-guided revascularisation strategy vs culprit vessel only intervention.
Outcomes	Primary: composite endpoint of all-cause mortality, non-fatal myocardial infarction, any revascularisation, and cerebrovascular events (MACCE) at 12 months between groups. Secondary: composite endpoint of cardiac death, myocardial infarction, revascularisation, stroke and major bleeding, composite of hospitalisation for heart failure and unstable angina pectoris, all-cause mortality, stent thrombosis, bleeding, treatment costs, and each component of the primary endpoint.
Starting date	May 2011.
Contact information	Steffen Helqvist.
Notes	www.ClinicalTrial.gov NCT01399736.

COMPLETE

Trial name or title	Complete vs. Culprit-only Revascularisation to Treat Multi-vessel Disease After Primary PCI for STEMI (COMPLETE).
Methods	Open-label RCT.
Participants	People with acute STEMI and MVD.
Interventions	Staged complete revascularisation strategy vs culprit vessel only intervention.
Outcomes	Primary: composite of cardiovascular death or new myocardial infarction. Secondary: composite of cardiovascular death, new myocardial infarction, ischaemia-driven revascularisation, or hospitalisation for unstable angina or heart failure.
Starting date	December 2012.
Contact information	Shamir Mehta smehta@mcmaster.ca.
Notes	www.ClinicalTrial.gov NCT01740479.

CROSS-AMI

Trial name or title	Strategies of Revascularisation in Patients with ST-segment Elevation Myocardial Infarction (STEMI) and Multivessel Disease.
Methods	Open-label RCT.
Participants	People with acute STEMI and MVD.
Interventions	Staged complete revascularisation strategy vs culprit vessel only intervention and stress echocardiography and revascularisation if required.
Outcomes	Primary: combined event of cardiovascular death/re-myocardial infarction/revascularisation of any vessel/admission due to heart failure. Secondary: incidence of acute renal failure (contrast-induced nephropathy), cost analysis of both strategies, death, cardiovascular death, re-myocardial infarction, revascularisation of any vessel, admission due to heart failure.
Starting date	September 2010.
Contact information	Rodrigo Estevez-Loureiro, MD.
Notes	

FIT

Trial name or title	FIT (Fast Infarction Treatment): Complete Revascularisation During Primary Percutaneous Coronary Intervention (PCI) Can be Achieved Safely With an Improved Clinical Outcome During the Indexed Hospitalisation.
Methods	Double-blind RCT.
Participants	People with acute STEMI and MVD.

FIT (Continued)

Interventions	Complete revascularisation strategy vs culprit vessel only intervention.
Outcomes	Primary: death at 30 days, stent thrombosis, target vessel failure and re-acute myocardial infarction. Secondary: bleeding, TIMI frame count and vascular site access complications.
Starting date	July 2010.
Contact information	Azienda Ospedaliera San Camillo Forlanini.
Notes	

CMR: cardiac magnetic resonance; FFR: fractional flow reserve; MACE: major adverse cardiovascular event; MVD: multi-vessel disease; RCT: randomised controlled trial; STEMI: ST elevated myocardial infarction; TIMI: Thrombolysis in Myocardial Infarction.

DATA AND ANALYSES

Comparison 1. Primary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Long-term all-cause mortality	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Long-term all-cause mortality	8	2417	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.58, 1.11]
2 Long-term cardiovascular mortality	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Long-term cardiovascular mortality	6	2229	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.32, 0.79]
3 Long-term non-fatal myocardial infarction	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Long-term non-fatal myocardial infarction	6	2099	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.44, 0.89]
4 Acute kidney injury	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Short-term acute kidney injury	2	679	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.14, 1.81]
4.2 Long-term acute kidney injury	1	296	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.14, 6.82]
5 Stroke	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Short-term stroke	1	465	Risk Ratio (M-H, Fixed, 95% CI)	4.94 [0.24, 102.26]
5.2 Long-term stroke	2	510	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.10, 2.01]

Complete versus culprit-only revascularisation in ST elevation myocardial infarction with multi-vessel disease (Review)

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Bleeding	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Short-term bleeding	3	1213	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.53, 1.86]
6.2 Long-term bleeding	2	923	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.45, 1.41]

Analysis 1.1. Comparison 1 Primary outcomes, Outcome 1 Long-term all-cause mortality.

Analysis 1.2. Comparison 1 Primary outcomes, Outcome 2 Long-term cardiovascular mortality.

Analysis 1.3. Comparison 1 Primary outcomes, Outcome 3 Long-term non-fatal myocardial infarction.

Analysis 1.4. Comparison 1 Primary outcomes, Outcome 4 Acute kidney injury.

Analysis 1.5. Comparison 1 Primary outcomes, Outcome 5 Stroke.

Analysis 1.6. Comparison 1 Primary outcomes, Outcome 6 Bleeding.

Comparison 2. Secondary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Short-term all-cause mortality	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Short-term all-cause mortality	2	696	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.18, 2.37]
2 Short-term cardiovascular mortality	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Short-term cardiovascular mortality	1	627	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.18]
3 Short-term non-fatal myocardial infarction	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Short-term non-fatal myocardial infarction	1	627	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [0.52, 5.90]
4 Revascularisation	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Short-term revascularisation	2	696	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.20, 1.45]
4.2 Long-term revascularisation	9	2616	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.39, 0.57]
5 Cost $\geq$ 1 year	1	69	Mean Difference (IV, Fixed, 95% CI)	-1948.0 [-9171.85, 5275.85]

Analysis 2.1. Comparison 2 Secondary outcomes, Outcome 1 Short-term all-cause mortality.

Analysis 2.2. Comparison 2 Secondary outcomes, Outcome 2 Short-term cardiovascular mortality.

Analysis 2.3. Comparison 2 Secondary outcomes, Outcome 3 Short-term non-fatal myocardial infarction.

Analysis 2.4. Comparison 2 Secondary outcomes, Outcome 4 Revascularisation.

Analysis 2.5. Comparison 2 Secondary outcomes, Outcome 5 Cost ≥ 1 year.

ADDITIONAL TABLES

Table 1. Summary of included studies

Study	Dates	Complete revascularisation (staged vs 1 time)	Intervention criteria in non-culprit vessel	Mean follow-up (years)	Description multi-vessel disease	Country	Number of centres
CvLPRIT 2015	May 2011 to May 2013	At index procedure or before discharge. 65% of participants in invasive group had at index procedure.	> 70% diameter stenosis in 1 plane or > 50% in 2 planes.	2.5	Culprit vessel plus ≥ 1 non-infarct-related epicardial artery with ≥ 1 lesion deemed angiographically significant (> 70% stenosis in 1 plane or > 50% in 2 planes).	UK	7
Dambrink and Ghani 2010	June 2004 to February 2007.	Staged 7.5 days after P-PCI.	FFR < 0.75 and in stenosis > 90%, PCI was performed without FFR measurement. PCI was with BMS or DES.	3	≥ 1 significant stenosis (> 50% stenosis in ≥ 1 view) in ≥ 2 major epicardial coronary arteries, or the combination of a side branch and a main epicardial vessel provided that they supplied different territories.	The Netherlands	1
DANAMI-3-PRIMULTI 2015	March 2011 to February 2014	Staged 2 days after P-PCI.	FFR < 0.8 and those > 90% stenotic arteries visually.	2.2	Significant stenosis (> 50% stenosis visually in arteries > 2 mm diameter) in ≥ 1 of the non-culprit epicardial coronary arteries or their major side branches in addition to the infarct-related artery.	Denmark	2
Estevez Loureiro 2014	2010 to 2013	Staged.	Complete. Criteria not described in study.	1	NR.	Spain	NR
HELP AMI 2004	NR	Index procedure.	Not described.	1	NR.	Not described	NR
Politi 2009	January 2003 to December 2007	At index procedure or staged mean 56 days after P-PCI. 50% participants of complete revascularisation had at intervention of the non-culprit lesions at index procedure.	> 70% diameter stenosis.	2.5	> 70% diameter stenosis of ≥ 2 epicardial coronary arteries or their major branches by visual estimation.	Not described	NR

Table 1. Summary of included studies (Continued)

PRAGUE-13 2015	September 2008 to December 2014	Staged between 3 and 40 days after P-PCI.	> 70% stenosis of non-culprit coronary artery.	3	≥ 1 vessel, beside the culprit vessel, with significant stenosis (> 70% stenosis).	Czech Republic	6
PRAMI 2013	April 2008 to January 2013	At index procedure.	Stenosis ≥ 50%.	2	The presence of stenosis ≥ 50% in ≥ 1 coronary artery other than the culprit vessel.	UK	5
Zhang 2015	January 2009 to June 2012	Staged between 7 and 10 days after P-PCI.	75% to 90%.	2	Non-culprit vessel with significant stenosis (75% to 90% stenosis).	China	NR

BMS: bare-metal stent; DES: drug-eluting stent; FFR: fractional flow reserve; NR: not reported in the article; PCI: percutaneous coronary intervention; P-PCI: primary percutaneous coronary intervention.

Table 2. Baseline information

Study	Group	Sample size (n)	Participants (n (%))	Dropouts (n (%))	% Male	Mean age (years)	% HTN	% DM	% HLD	% Prior MI	% Anterior STEMI
CvLPRIT 2015	Complete	150	139 (92.7)	11 (7.3)	85.3	64.6	36	12.7	27.3	4.7	36
	Culprit-only	146	139 (95.2)	8 (5.5)	76.7	65.3	35	13.7	23.3	3.4	35.6
Dambrink and Ghani 2010	Complete	80	71 (88.8)	1 (1.3)	80	62	26.3	6.3	15	6.3	21.3
	Culprit-only	41	41 (100)	1 (2.4)	80.5	61	42.5	5	30	4.9	23.3
DANAMI-3-PRI-MULTI 2015	Complete	314	294 (93.6)	1 (0.3)	80	64	41.4	9.2	NR	5.4	33.4
	Culprit-only	313	313 (100)	0	81.5	63	46.6	13.4	NR	8.6	35.8
Estevez Loureiro 2014	Complete	100	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Culprit-only	99	NR	NR	NR	NR	NR	NR	NR	NR	NR
HELP AMI 2004	Complete	52	NR	NR	88.5	63.5	36.5	11.5	41.2	NR	52
	Culprit-only	17	NR	NR	82.4	65.3	58.8	41.2	53	NR	59

Table 2. Baseline information (Continued)

Politi 2009	Complete	130	NR	NR	78.5	64	57	16.2	NR	NR	45.4
	Culprit-only	84	NR	NR	76.2	66.5	60	23.8	NR	NR	41.7
PRAGUE-13 2015	Complete	106	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Culprit-only	108	NR	NR	NR	NR	NR	NR	NR	NR	NR
PRAMI 2013	Complete	234	223 (95.3)	10 (4.3)	75.6	62	40.2	15	NR	8.1	28.6
	Culprit-only	231	229 (99)	8 (3.5)	80.5	62	40.3	20.8	NR	7	38.5
Zhang 2015	Complete	215	NR	NR	61	62.3	64.2	36.7	35.3	NR	36.7
	Culprit-only	213	NR	NR	67.1	62	61	35.2	36.6	NR	40

DM: diabetes mellitus; HLD: hyperlipidaemia; HTN: hypertension; MI: myocardial infarction; n: number of participants; NR: not reported in the article; STEMI: ST elevated myocardial infarction.

Table 3. Procedure details

Study	Group	Symp-toms to PCI time (minute)	PCI with-out stent-ing (n (%))	DES (n (%))	BMS (n (%))	2-Vessel disease (n (%))	3-Vessel dis-ease (n (%))	Received PCI non-culprit (n (%))	DAPT	DAPT du-ration
CvLPRIT 2015	Complete	182	NR	141 (94)	NR	119 (79.3)	31 (20.7)	139 (92.7)	Yes	NR
	Culprit-only	159	NR	127 (87)	NR	110 (75.3)	36 (24.7)	0		
Dambrink and Ghani 2010	Complete	NR	6 (7.5)	18 (22.5)	56 (70)	60 (75)	20 (25)	48 (60)	Yes	1 month
	Culprit-only	NR	7 (17.1)	7 (7.1)	27 (66)	33 (80.5)	8 (19.5)	0		
DANAMI-3-PRIMULTI 2015	Complete	NR	12 (3.8)	298 (95)	0	NR	97 (31)	193 (61.5)	Yes	1 year
	Culprit-only	NR	18 (5.8)	290 (92.7)	0	NR	100 (32)	0		
Estevez Loureiro 2014	Complete	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Culprit-only	NR	NR	NR	NR	NR	NR	NR		

Table 3. Procedure details (Continued)

HELP AMI 2004	Complete	210	0	52 (100)	0	36 (69)	16 (30.8)	NR	Yes	1 month
	Culprit-only	236	0	17 (100)	0	9 (53)	8 (47)	NR		
Politi 2009	Complete	NR	NR	11 (8.5)	NR	NR	48 (37)	NR	NR	NR
	Culprit-only	NR	NR	10 (12)	NR	NR	21 (25)	NR		
PRAGUE-13 2015	Complete	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Culprit-only	NR	NR	NR	NR	NR	NR	NR		
PRAMI 2013	Complete	NR	1 (< 1)	147 (63)	86 (37)	143 (61.1)	91 (39)	223 (95.3)	Yes	1 month
	Culprit-only	NR	0	135 (58)	96 (42)	155 (67.1)	76 (33)	2 (1)		
Zhang 2015	Complete	214	0	215 (100)	0	NR	NR	NR	NR	NR
	Culprit-only	227	0	213 (100)	0	NR	NR	NR		

BMS: bare-metal stent; DAPT: dual antiplatelet therapy; DES: drug-eluting stent; n: number of participants; NR: not reported in the article; PCI: percutaneous coronary intervention.

APPENDICES

Appendix 1. Search strategies

CENTRAL, DARE, and HTA (Wiley)

- 1 MeSH descriptor: [Myocardial Infarction] explode all trees
- 2 ((myocard* or heart) near/3 infarct*):ab,ti,kw
- 3 (heart next/1 attack*):ab,ti,kw
- 4 ((stun* or hibernat*) near/3 myocard*):ab,ti,kw
- 5 'cardiogenic shock':ab,ti,kw
- 6 (st near/2 elevat* near/4 ('myocardial infarction' or 'myocardial infarctions' or mi)):ab,ti,kw
- 7 stemi:ab,ti,kw
- 8 {or #1-#7}
- 9 MeSH descriptor: [Percutaneous Coronary Intervention] explode all trees
- 10 pci:ab,ti,kw or ppci:ab,ti,kw
- 11 ('percutaneous coronary' near/6 (intervention* or revascularization*)):ab,ti,kw
- 12 ((transluminal or 'trans luminal') near/6 coronary):ab,ti,kw
- 13 angioplast*:ab,ti,kw
- 14 atherectomy*:ab,ti,kw
- 15 (balloon near/2 (coronary or dilat*)):ab,ti,kw
- 16 MeSH descriptor: [Stents] explode all trees
- 17 stent*:ab,ti,kw
- 18 {or #9-#17}
- 19 (multi* near/4 vessel):ab,ti,kw
- 20 (multivessel or 'multi-vessel'):ab,ti,kw
- 21 ('infarct related' or IRA or 'non infarct related' or 'non-IRA'):ab,ti,kw
- 22 (culprit or 'culprit-only' or 'non-culprit' or nonculprit or bystander):ab,ti,kw
- 23 {or #19-#22}
- 24 #8 and #18 and #23

Ovid MEDLINE(R) 1946 to December Week 1 2016, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 03, 2017 and Ovid MEDLINE(R) Epub Ahead of Print January 03, 2017

1. exp Myocardial Infarction/
2. ((myocard* or heart) adj3 infarct*).tw.
3. heart attack*.tw.
4. ((stun* or hibernat*) adj3 myocard*).tw.

5. cardiogenic shock.tw.
6. (ST adj2 elevat* adj4 (myocardial infarction* or MI)).tw.
7. stemi.tw.
8. or/1-7
9. exp Percutaneous Coronary Intervention/
10. (PCI or PPCI).tw.
11. (percutaneous coronary adj6 (intervention* or revascularization*)).tw.
12. ((transluminal or trans-luminal) adj6 coronary).tw.
13. angioplast*.tw.
14. atherectom*.tw.
15. (balloon adj2 (coronary or dilat*)).tw.
16. exp Stents/
17. stent*.tw.
18. or/9-17
19. (multi* adj4 vessel).tw.
20. (multivessel or multi-vessel).tw.
21. (infarct related or IRA or non infarct related or non-IRA).tw.
22. (culprit or culprit-only or non-culprit or nonculprit or bystander).tw.
23. or/19-22
24. randomized controlled trial.pt.
25. controlled clinical trial.pt.
26. randomized.ab.
27. placebo.ab.
28. drug therapy.fs.
29. randomly.ab.
30. trial.ab.
31. groups.ab.
32. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33. exp animals/ not humans.sh.
34. 32 not 33
35. 8 and 18 and 23
36. 34 and 35

EMBASE (embase.com)

#28 #26 AND #27

#27 #8 AND #18 AND #23

#26 #24 NOT #25 1122006

#25 'animal'/exp OR 'nonhuman'/exp NOT 'human'/exp

#24 random*:ab,ti OR placebo* OR (double NEXT/1 blind*):ab,ti

#23 #19 OR #20 OR #21 OR #22

#22 culprit:ab,ti OR 'culprit-only':ab,ti OR 'non-culprit':ab,ti OR nonculprit:ab,ti OR bystander:ab,ti

#21 'infarct related':ab,ti OR ira:ab,ti OR 'non infarct related':ab,ti OR 'non-ira':ab,ti

#20 multivessel:ab,ti OR 'multi-vessel':ab,ti

#19 (multi* NEAR/4 vessel):ab,ti

#18 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

#17 stent*:ab,ti

#16 'stent'/exp

#15 (balloon NEAR/2 (coronary OR dilat*)):ab,ti

#14 atherectom*:ab,ti

#13 angioplast*:ab,ti

#12 ((transluminal OR 'trans luminal') NEAR/6 coronary):ab,ti

#11 ('percutaneous coronary' NEAR/6 (intervention* OR revascularization*)):ab,ti

#10 pci:ab,ti OR ppci:ab,ti

#9 'interventional cardiovascular procedure'/exp

#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

#7 stemi:ab,ti

#6 (st NEAR/2 elevat* NEAR/4 ('myocardial infarction' OR 'myocardial infarctions' OR mi)):ab,ti

#5 'cardiogenic shock':ab,ti

#4 ((stun* OR hibernat*) NEAR/3 myocard*):ab,ti

#3 (heart NEXT/1 attack*):ab,ti

#2 ((myocard* OR heart) NEAR/3 infarct*):ab,ti

#1 'heart infarction'/exp

Conference Proceedings Citation Index- Science (CPCI-S)--1990-present (Web of Science)

21 #20 AND #15 AND #7

20 #19 OR #18 OR #17 OR #16

19 TS=(culprit or "culprit-only" or "non-culprit" or nonculprit or bystander)

18 TS=("infarct related" or IRA or "non infarct related" or "non-IRA")

17 TS=(multivessel or "multi-vessel")

16 TS=(multi* near/4 vessel)

15 #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8

14 TS=(stent*)

13 TS=(balloon near/2 (coronary or dilat*))

12 TS=(atherectomy*)

11 TS=(angioplast*)

10 TS=((transluminal or "trans luminal") near/6 coronary)

9 TS=(PCI or PPCI)

8 TS=("percutaneous coronary" near/6 (intervention* or revascularization*))

7 #6 OR #5 OR #4 OR #3 OR #2 OR #1

6 TS=(stemi)

5 TS=(st near/2 elevat* near/4 ("myocardial infarction" or "myocardial infarctions" or mi))

4 TS=("cardiogenic shock")

3 TS=((stun* or hibernat*) near/3 myocard*)

2 TS=("heart attack" OR "heart attacks")

1 TS=((myocard* or heart) near/3 infarct*)

ClinicalTrials.gov (Expert search)

multivessel OR "multi vessel" OR "infarct related" OR "non infarct related" OR culprit OR "non culprit"

World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (Standard search)

multivessel OR multi vessel OR infarct related OR non infarct related OR culprit OR non culprit

European (EU) Clinical Trials Register

multivessel OR "multi vessel" OR "infarct related" OR "non infarct related" OR culprit OR "non culprit"

Epistemonikos (<http://www.epistemonikos.org>) (Advance search)

multivessel OR "multi vessel" OR "infarct related" OR "non infarct related" OR culprit OR "non culprit"

Appendix 2. Survey of authors providing information on included trials

Characteristic	Date trial author asked for additional information	Date trial author replied	Trial author provided data
CvLPRIT 2015	26 May 2016	No reply	
Dambrink and Ghani 2010	26 May 2016	No reply	
DANAMI-3-PRIMULTI 2015	26 May 2016	27 May 2016	1 July 2016
Estevez Loureiro 2014	26 May 2016	No reply	
HELP AMI 2004	26 May 2016	No reply	

(Continued)

Politi 2009	26 May 2016	No reply	
PRAGUE-13 2015	26 May 2016	No reply	
PRAMI 2013	26 May 2016	31 May 2016	Did not provide additional data
Zhang 2015	26 May 2016	No reply	

WHAT'S NEW

Date	Event	Description
8 May 2017	Amended	Minor correction to author name, addition of Published Note for ACUTE COMPARE trial.

CONTRIBUTIONS OF AUTHORS

CB: protocol writing, trial selection, data extraction, data analysis, data interpretation, review writing, and future review updates.

SH: protocol writing, trial selection, data extraction, data analysis, data interpretation, review writing, and future review updates.

DB: data interpretation and review writing.

RK: data interpretation and review writing.

DF: data analysis, data interpretation, and review writing.

EO: data analysis, data interpretation, and review writing.

KA: data analysis, data interpretation, and review writing.

AS: data analysis, data interpretation, and review writing.

MS: data analysis, data interpretation, and review writing.

SZ: data analysis, data interpretation, and review writing.

AO: data analysis, data interpretation, and review writing.

CG: TSA expert, data analysis, data interpretation, and review writing.

HK: data interpretation and review writing.

TE: data interpretation and review writing.

DH: data interpretation and review writing.

JB: data analysis, data interpretation, and review writing.

The first and second review authors contributed equally to this review.

DECLARATIONS OF INTEREST

CB: none known.

SH: none known.

DB: Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Population Health Research Institute (including for his role on the DSMB of COMPLETE); Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Lilly, Medtronic, Pfizer, Roche, Sanofi Aventis, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical; Trustee: American College of Cardiology; Unfunded Research: FlowCo, PLx Pharma, Takeda.

RK: none known.

DF: has received compensation for travel expenses related to his membership on the board of the Alliance for a Healthier Generation and the American Heart Association. Dr Faxon has also received compensation for consulting as a member of a Data Safety Monitoring Board from Medtronic, Boston Scientific, and Biotronik. Dr Faxon has received stock options from RIVA Medical as well as honoraria from the American Heart Association for his service as an editor of Circulation. All compensation received is unrelated to this review.

EO: has received compensation for consulting from Abiomed, Astra Zeneca, Biotie, Boehringer Ingelheim, Bristol Meyers Squibb, Daiichi Sankyo, Eli Lilly & Company, Faculty Connection, Gilead Sciences, Ikaria, Ivivi, Janssen Pharmaceuticals, LipoScience, Merck, Pozen, Roche, Sanofi Aventis, Stealth Peptides, The Medicines Company, and Web MD. Dr Ohman has received institutional grants for clinical trials from Daiichi Sankyo, Eli Lilly & Company, Gilead Sciences, and Janssen Pharmaceuticals. Dr Ohman has received payment for lectures from Gilead Sciences, Janssen Pharmaceuticals, and LipoScience. All compensation received is unrelated to this review.

KA: none known.

AS: none known.

MS: none known.

SZ: has received compensation for lectures from GSK and Arbor Pharmaceuticals for topics unrelated to this review.

AO: none known.

CG: none known.

HK: none known.

TE: fees from Boston Scientific, St. Jude Medical, Astra Zeneca, and Bayer.

DH: none known.

JB: none known.

SOURCES OF SUPPORT

Internal sources

- Self supported, Other.

External sources

- Self supported, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We determined that a revision to the review title was needed based on alignment with current terminology, the protocol for this review was titled "Early invasive versus conservative strategy for non-infarct related artery lesions in ST elevation myocardial infarction with multi-vessel disease".

We have changed the order of the authors and added the following authors: Deepak L Bhatt, Asishana A Osho, Christian Gluud, Henning Kelbæk, Thomas Engstrøm, Dan Eik Høfsten; and removed Ronald E Pachon.

We did not apply any filters to the Conference Proceedings Index search because the relatively small retrieval set of the base search did not warrant applying a filter.

We did not search Current Controlled Trials MetaRegister (www.controlled-trials.com/mrct/) as it is no longer active or available on the Internet.

We believe that the important outcome long-term all-cause mortality was omitted from the protocol and it was considered that this is a crucial outcome to judge the effectiveness of one intervention over the other. We judged this outcome as relevant or more relevant compared to cardiovascular mortality and adverse events, therefore we added this as another primary outcome. Moreover, all-cause mortality is likely a less biased outcome. We have added all-cause mortality as another outcome to be evaluate under the subgroup analysis section. All-cause mortality is a crucial patient oriented outcome that is important to evaluate for potential subgroup differences.

In the protocol, we planned to include only participants who received revascularisation before discharge in the complete revascularisation group. In the review, we included participants who received revascularisation of the non-culprit vessel (at least 50% obstruction but less than 100%) at the index procedure or at a second intervention including after discharge.

We removed in-stent thrombosis and PCI-related myocardial infarction measured at 30 days and one year after the intervention from the primary outcome adverse events because it overlapped with the outcome short- and long-term myocardial infarction.

We considered the outcomes short-term cardiovascular and all-cause mortality, non-fatal myocardial infarction, and revascularisation as those that occurred within the first 30 days after the index procedure.

We added the sensitivity analysis "Restricting the analysis to published trials that utilised mostly DES" because we thought it was reasonable to attribute heterogeneity or a certain effect size because of certain specific type of stent.

In addition to the cumulative meta-analysis we conducted Trial Sequential Analysis of the ones that we judged to be the most relevant outcomes.

NOTES

It was noted that at the time of submission of this meta-analysis, the ACUTE COMPARE trial was published. In an updated version we will include that trial.

INDEX TERMS

Medical Subject Headings (MeSH)

Cause of Death; Coronary Stenosis [complications] [mortality] [*surgery]; Myocardial Revascularization [adverse effects] [*methods] [mortality]; Randomized Controlled Trials as Topic; ST Elevation Myocardial Infarction [etiology] [mortality] [*surgery]

MeSH check words

Female; Humans; Male