Complete Revascularisation Following Acute MI: A Contemporary Review

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Abstract

Acute MI (AMI) is a leading cause of mortality globally. Swift diagnosis is imperative, with timely reperfusion crucial to minimise adverse outcomes. Revascularisation strategies include culprit-vessel-only therapy, staged complete revascularisation or immediate complete revascularisation. Evidence from randomised trials strongly favours complete revascularisation in ST-elevation MI (STEMI). Data regarding immediate complete revascularisation compared to a staged approach are limited, with uncertainties regarding the advantages of physiology-guided treatment compared to angiographic assessment alone. Non-STEMI (NSTEMI) patients with multivessel disease are often complex and current guidelines offer limited recommendations for this patient group, emphasising the need for individualised treatment. Observational studies have sought to find the optimal approach, yet conflicting data prevails. Dedicated trials for this issue in NSTEMI patients are currently unavailable. To enhance the decision-making processes for patients with AMI, future trials should consider the inclusion of functional health status and health-related quality of life outcomes. The existing gaps in knowledge underscore the intricacies of managing AMI and the ongoing necessity for comprehensive research to refine treatment strategies.

Keywords

Complete revascularisation, acute myocardial infarction, percutaneous coronary intervention

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Acute MI (AMI) is the leading cause of morbidity and mortality in the developed world. Patients presenting with ST-elevation MI (STEMI) are usually experiencing transmural infarction secondary to complete culprit vessel occlusion and are treated with immediate reperfusion therapy. Patients experiencing non-ST-segment elevation MI (NSTEMI) have a more heterogeneous aetiology, but a substantial proportion will have had a plaque rupture event. Both STEMI and NSTEMI necessitate rapid diagnosis for effective intervention and improved outcomes.[1–5]

STEMI arises from acute plaque rupture, resulting in thrombotic occlusion of the coronary artery. It demands rapid reperfusion therapy to protect myocardial tissue from infarction and reduce the risk of mortality.[6,7] Primary percutaneous coronary intervention (PPCI) remains the gold standard of reperfusion, with evidence from trials such as DANAMI-2 consistently favouring PPCI over fibrinolysis.[8] About 40–50% of patients presenting with STEMI have multivessel coronary artery disease (MVD), which is associated with increased risk of recurrent MI and death.[9,10] Coronary artery bypass surgery (CABG) is commonly used for the management of MVD; however, percutaneous coronary intervention (PCI) has been increasingly used to treat patients with MVD, especially if presenting with STEMI and percutaneous revascularisation has already been undertaken.[11] CABG has a limited role in the acute phase of STEMI and its use in this setting continues to decrease.[12,13]

The primary goal of revascularisation in patients with NSTEMI is to reduce the risk of reinfarction. Identification of the culprit artery is usually based on a combination of ECG and echocardiographic changes combined with the angiographic appearances of the vessels. This may be supplemented with the use of intracoronary imaging to identify plaque rupture. It can often be challenging to accurately identify the culprit lesion. Selecting the appropriate revascularisation strategy, especially for patients with MVD, can be challenging even when the culprit is clear.[14] Recent data shows that up to 50% of patients with NSTEMI have MVD, defined as the presence of >75% luminal diameter stenosis in two or more major epicardial arteries.[15] MVD worsens clinical outcomes of NSTEMI, including increased rates of reinfarction, mortality and major adverse cardiac events (MACE).[16–18]

Arguments for and against both culprit-vessel-only revascularisation (CVO) and complete revascularisation (CR) remain for both STEMI and NSTEMI. The aim of this review is to present the evidence comparing the efficacy and safety of CR and CVO in AMI. It will also compare immediate complete revascularisation (iCR) with staged CR (sCR), as well as revascularisation based on angiographic appearance alone or using physiology to guide PCI.

Evidence for Revascularisation Methods for STEMI

Early guidelines supported the treatment of infarct-related arteries (IRA) only based on the hypothesis that single-vessel PCI had a more favourable risk:benefit ratio. Furthermore, it was believed that it was the most cost-effective option.[19] This recommendation was associated with the reduced use of contrast media, which reduces the risk of contrast-induced nephropathy (CIN), reduces radiation exposure and eliminates the risk of

peri-procedural infarction in non-culprit territories.[16,20] However, given improvements in technique and technology, the risk of these complications has been progressively minimised.[4,21] It was hypothesised that the protective effect of multivessel PCI is achieved by the complete treatment of other potentially unstable plaques (not limited to the culprit lesion), that arises as the result of the widespread inflammatory reaction that occurs with acute coronary syndromes.[5]

Small early studies failed to show a clinical benefit (based on MACE or the need for repeat revascularisation) for CR over CVO in patients with MVD, with increased procedural time and contrast use.[22–24] One study even showed an increase in adverse events. In contrast, others found a significant reduction in MACE, even after adjustment for several relevant multivariate predictors.[25] This trial compared CVO to both iCR and sCR and both reduced MACE. A reduction in MACE using a CR strategy has been consistent in recent larger trials. Table 1 shows a summary of the studies relating to CR versus CVO.[22–32]

The COMPLETE trial was the largest randomised trial for multivessel revascularisation strategy for STEMI with just over 4,000 patients.[31] CR was found to be superior to CVO revascularisation for reducing ischaemic events, ischaemia-driven revascularisation and mortality at a median follow-up of 3 years. The first co-primary endpoint was the composite of cardiovascular death or MI; this occurred in 7.8% with CR compared to 10.5% in the CVO group (HR 0.74; 95% CI [0.60–0.91]; p=0.004). The second co-primary outcome added ischaemia-driven revascularisation to the endpoint and again was strongly in favour of CR (8.9% versus 16.7%; HR 0.51; 95% CI [0.43–0.61]; p<0.001).[31] For both co-primary outcomes, the benefit of CR was consistent regardless of the intended timing of non-culprit lesion PCI. The COMPLETE trial has shown the long-term benefit of CR, with continued divergence of the survival curves in favour of CR over several years. During the early period after STEMI, events related to the index infarction and culprit-lesion PCI may account for a substantial proportion of the events that occurred in both treatment groups. Limitations of the trial include the lack of inclusion of patients with cardiogenic shock as well as patients with non-culprit lesion PCI which was performed during the same procedure as that for the index culprit-lesion PCI for STEMI. However, the COMPLETE trial provides strong support for using CR, rather than adopting a CVO strategy, with evidence of long-term benefit.

The FIRE trial investigated the efficacy of CR in STEMI and NSTEMI among older patients aged 75 years or older with MI and MVD.[32] Those who underwent physiology-guided CR had a lower risk of MACE, including ischaemia-driven revascularisation at 1 year, than those who received CVO (15.7% versus 21.0% HR 0.73; 95% CI [0.57–0.93]; p=0.01). Cardiovascular death or MI occurred in 8.9% of patients in the CR group and 13.5% of those in the CVO group (HR 0.64; 95% CI [0.47–0.88]). This is an important finding, as older patients may be more likely to undergo CVO revascularisation since the perceived benefit may be smaller. It is the authors' opinion that this trial does not detract from the need to take a holistic approach to the care of older patients and consider their frailty and co-morbidities when making complex decisions about revascularisation.

The COMPARE-ACUTE trial found a significant reduction in MACE, including repeat revascularisation at 12 months when using physiology-guided CR.[30] The significant improvement was the need for repeat revascularisation in the CR group. No significant differences were observed in death, non-fatal MI or cerebrovascular events. The primary outcome occurred in 7.8% of patients in the CR group and in 20.5% of patients in the CVO group (HR 0.35; 95% CI [0.22–0.55]; p<0.001). The CvLPRIT trial also demonstrated a significant reduction in MACE including ischaemia-driven revascularisation within 12 months in the CR arm (HR 0.45; 95% CI [0.24–0.84]; p=0.009). A trend toward benefit was seen early after CR at 30 days.[28] Similar to the findings of the COMPARE-ACUTE trial, there was no significant difference observed in terms of death, non-fatal MI or heart failure. A trend for more heart failure cases was reported in the CVO group in the CvLPRIT trial, with a greater incidence of death during 12-month follow-up.[28] Some have speculated that CR treatment may improve early myocardial stunning and myocardial salvage by increasing blood flow to watershed areas of infarction. It has also been hypothesised that hibernation that results from severe coronary artery disease (CAD) can contribute to the development of heart failure. The STITCH trial evaluated patients with CAD and left ventricular dysfunction with different imaging techniques – single-photon-emission CT, dobutamine echocardiography, or both – and showed that revascularisation of hibernating myocardium using CABG results in improved left ventricular function.[33] However, the REVIVED trial, which evaluated PCI for patients with stable coronary artery disease and severely impaired left ventricular function, did not demonstrate any improvement in symptoms, LV function or survival.[34]

Trials of CR use inconsistent endpoints to evaluate the effectiveness of the strategy. Common outcomes used include the composite of CV death, non-fatal AMI and repeat revascularisation. The PRAMI trial also included patients with refractory angina, while the COMPARE-ACUTE study included patients with cerebrovascular events.[27,30] Repeat revascularisation or even 'ischaemia-driven revascularisation' is a controversial marker of strategy failure, since patients and physicians are not blinded to the presence of unrevascularised CAD in the CVO arm, which means findings might be affected by bias and the placebo effect, particularly when the indication for revascularisation was angina. Ischaemia testing was performed more frequently in the PRAMI trial for patients in the CVO arm, either because patients had increased symptoms after AMI or perhaps because physicians were more aware of untreated lesions.[27]

Pooled meta-analyses comparing the efficacy and safety of CR and CVO strategies have been published. Pavasini et al. and Bainey et al. combined six and ten randomised controlled trials (RCTs) of STEMI, respectively.[35,36] Pavasini et al. compared CV death between the strategies and reported a significantly reduced risk in the CR group (HR 0.62; 95% CI [0.39–0.97]) after median follow-up of 2 years.[35] Additionally, the secondary endpoints of non-fatal MI (HR 0.68; 95% CI [0.55–0.84]) and revascularisation (HR 0.29; 95% CI [0.22–0.38]) were also significantly reduced.[35] This was consistent with Bainey et al., who also reported a reduction in CV death or non-fatal MI in the CR arm (7.3% versus 10.3%; OR 0.69; 95% CI [0.55–0.87]).

Recent European Society of Cardiology (ESC) guidelines for STEMI state that routine revascularisation of non-infarct-related artery lesions should be considered in STEMI patients with MVD during the index procedure or within 45 days (1A recommendation), with PCI of non-infarct-related artery lesions based on severity assessed by angiography (1B recommendation).[37–39] Furthermore, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines state that staged PCI (in hospital or after discharge) of a significantly stenosed non-culprit artery in patients presenting with STEMI is recommended in selected patients to improve outcomes (1A recommendation).[25,28,29,40] Trials comparing CR versus CVO strategy are summarised in *Table 1*.

Table 1: Randomised Controlled Trials for Complete Revascularisation versus Culprit-vessel-only Revascularisation in ST-elevation MI

Trial	Sample Size	Revascularisation Strategies	MACE/MACCE Rate	All-cause/CV Death or MI
HELP-AMI 2004[22]	69	CVO PCI versus MV staged or primary PCI	0% versus 3.8% (p=0.164) at 12 months	NA
Ghani et al. 2012[23]	121	FFR-guided PCI MV primary PCI versus conservative treatment of non-infarct lesions	35.4% versus 35% (p=0.96) at 36 months	5% versus 0% (p=0.29)
PRAGUE-13 2015[24]	214	MV primary PCI versus conservative medical treatment for non-infarct lesions	16% versus 13.9% (p>0.05) at 38 months	5.7% versus 6.5% (p>0.05)
Politi et al. 2010[25]	263	CVO PCI versus MV staged PCI versus MV staged or primary PCI	50.0% versus 20.0% versus 23.1% (p<0.001) at 30 months	The incidence of in-hospital death, repeat revascularisation and re-hospitalisation was significantly higher in the CVO PCI group (all p<0.05)
Hamza et al. 2016[26]	100	CVO PCI versus MV staged or primary PCI	24% versus 6% (p=0.01) at 6 months	Death (8% versus 2% [p=0.17]) MI (4% versus 2% [p=0.56])
PRAMI 2013[27]	465	CVO PCI versus MV primary PCI	22.9% versus 9.0% (p<0.001) at 23 months	11.7% versus 4.7% (p=0.004)
CvLPRIT 2015[28]	296	CVO PCI versus MV primary or staged PCI	21.2% versus 10.0% (p=0.009) at 12 months	9.6% versus 4.0% (p=0.06)
DANAMI-3-PRIMULTI 2015[29]	627	CVO PCI versus MV staged FFR-guided PCI	22.0% versus 13.0% (p=0.004) at 27 months	8.0% versus 6.4% (p=0.47)
COMPARE-ACUTE 2017[30]	885	CVO PCI versus MV primary or staged FFR-guided PCI	20.5% versus 7.8% (p<0.001) at 12 months	6.4% versus 3.7% (p=0.10)
COMPLETE 2019[31]	4,041	CVO PCI versus MV primary or staged PCI	10.5% versus 7.8% (p=0.004) at 36 months	10.5% versus 7.8% (p=0.004)
FIRE 2023[32]	1,445	CVO PCI versus MV primary PCI	21.0% versus 15.7% (p=0.01)	13.5% versus 8.9% (p<0.05)

CR = complete revascularisation; CV = cardiovascular; CVO = culprit-vessel-only revascularisation; FFR = fractional flow reserve; MACE = major adverse cardiac events; MACCE = major adverse cardiac and cerebrovascular events; MV = multivessel; MVD = multivessel coronary artery disease; PCI = percutaneous coronary intervention; STEMI = ST-elevation MI.

Evidence for Revascularisation Methods for NSTEMI

There is limited evidence regarding the effectiveness of CR following NSTEMI, with most studies being observational. Several studies associate CR with better long-term outcomes compared with CVO, with reduced rates of MACE and repeat revascularisation. Some studies also report lower all-cause mortality. In a large, multicentre registry, CR was associated with greater in-hospital arterial complications and death, while in-hospital MACE rates were comparable to CVO. Despite this early failure, the same study showed that iCR was associated with improved all-cause mortality in a follow-up period of 4.6 years (HR 0.90; 95% CI [0.85–0.97]), suggesting that the upfront risk may be acceptable.[41]

Another retrospective study also reported better long-term outcomes with CR. During the index admission, there was no difference in a composite endpoint of all-cause death, MI and repeat revascularisation, but outcomes were better at 30 days (3.6% versus 10.2%; p=0.025).[15] At 12-month follow-up, patients receiving CR had improved outcomes (HR 0.56; 95% CI [0.31–0.99]). Tobias et al. showed CR was associated with a significant decrease in coronary re-intervention (11.1% versus 20%; p<0.001), urgent CABG (0.1% versus 0.4%; p=0.001) and target vessel revascularisation (5.2% versus 6.7%; p=0.003) but without a reduction in mortality.[42] Similarly, other retrospective data shows improvement in rates of repeat revascularisation with CR.[17] In older patients (aged 75 years and over), CR was associated with better long-term outcomes at the cost of greater in-hospital mortality.[43]

Despite this data, a large-scale meta-analysis of 12 observational studies found that CR did not reduce the need for future revascularisation.[44] Other observational studies have also not found the same benefits. In one study there was no difference in 2-year MACE rates between the strategies (CVO 13.1% versus CR 14.0%, p=0.735).[45] Confounding factors associated with all retrospective observational studies make it challenging to unpick the better strategy. Some NSTEMI patients have been included in trials of physiology-guided CR, but these have been in limited circumstances, such as only patients with ongoing pain and ECG changes in FULL REVASC, and in small numbers which makes any conclusion regarding this data impossible to draw.[46] The absence of randomised data makes a blanket recommendation difficult to formulate. It is clear that the CR strategy will increase the procedural risk after NSTEMI. However, this is traded against the potential to reduce the risk of future cardiac events.

Recent ESC guidelines recommend CR in NSTEMI patients with MVD, with functional invasive evaluation using intravascular ultrasound or fractional flow reserve (FFR) (IIb B recommendation), preferably during the index procedure (IIa C recommendation).[37,47–52] ACC/AHA guidelines recommend early invasive treatment without specifying the extent of revascularisation.[40,53] The lack of dedicated trials for NSTEMI can sometimes complicate evidence-based decision-making, necessitating individualised approaches and pragmatic approaches in some instances.[54] Further trials are warranted to ascertain the findings in patients with NSTEMI. Studies comparing CVO versus CR are outlined in *Table 2*.

Complete Revascularisation versus Culprit-vessel-only PCI in Cardiogenic Shock and Multivessel Disease

The CULPRIT-Shock trial compared the impact of iCR versus CVO in patients with AMI, MVD and cardiogenic shock. Of 699 patients, 27.9% (n=195) had NSTEMI.[55,56] The composite primary endpoint was death or the need for renal replacement therapy at 30 days. Patients receiving

Table 2: Observational Studies for Complete Revascularisation versus Culprit-vessel-only Revascularisation in Non-ST-elevation MI

Study title	Reference	Sample Size	Time Period	Design	Key Findings/Conclusion
Early and long-term outcomes of complete revascularisation with percutaneous coronary intervention in patients with multivessel coronary artery disease presenting with non-ST-segment elevation acute coronary syndromes	Hawranek et al. 2018[15]	1,592	2006–2014	Retrospective study	In patients with multivessel CAD and NSTE-ACS, CR PCI during index hospitalisation was independently associated with improved early and long-term prognosis without significant differences in periprocedural outcomes in comparison to incomplete revascularisation with PCI
What is the optimal revascularisation strategy in patients with multivessel coronary artery disease in non-ST-elevation MI? Multivessel or culprit-only revascularisation	Kim et al. 2011[17]	1,919	November 2005–January 2008	Retrospective multicentre study	Three-year MACE were decreased in CR PCI compared to CVO. Within CR, outcomes of single-stage CR were comparable to multi-stage PCI
Complete versus culprit-only lesion intervention in patients with acute coronary syndromes	Rathod et al. 2018[41]	37,491	2005–2015	Cohort study	In patients with MVD who had an NSTEMI, single-stage CR significantly reduced mortality compared to CVO.
Multivessel versus Culprit-only percutaneous coronary intervention in patients with non-ST-elevation acute coronary syndrome	Pustjens et al. 2022[42]	10,507	January 2017–October 2019	Multicentre cohort study	CR improved event-free survival with fewer coronary re-interventions. Mortality rates were similar for both interventions
Long-term prognostic benefit of complete revascularisation in elderly presenting with NSTEMI: real world evidence	Agra-Bermejo et al. 2021[43]	1,722	December 2003–December 2016	Retrospective study	CR significantly benefited those over 75 years with NSTEMI and MVD
Multivessel versus single vessel angioplasty in non-ST-elevation acute coronary syndromes: a systematic review and meta-analysis	Mariani et al. 2016[44]	117,685	2002–2014	Meta-analysis of 12 observational studies	CR PCI was not superior to CVO PCI when routinely performed
Long-term outcomes of single-vessel percutaneous coronary intervention on culprit vessel versus multivessel percutaneous coronary intervention in non-ST-segment elevation acute coronary syndrome patients with multivessel coronary artery disease	Li et al. 2021[45]	3,338	January 2013–December 2013	Retrospective cohort study	CR is not superior to CVO PCI during the index procedure

CAD = coronary artery disease; CR = complete revascularisation; CVO = culprit-vessel-only revascularisation; MACE = major adverse cardiac events; MVD = multivessel coronary artery disease; NSTE-ACS = non-ST-segment elevation acute coronary syndromes; NSTEMI = non-ST-segment elevation MI; PCI = percutaneous coronary intervention.

CVO performed better than those receiving iCR (45.9% versus 55.4%, RR 0.83; 95% CI [0.71–0.96]). A secondary analysis revealed there was 16% reduction in 30-day mortality in the CVO group. The study found no significant differences in other important outcomes, including the time to return to haemodynamic stability, need for mechanical circulatory support and a rise in biomarkers. These results suggest that a CVO strategy in the context of cardiogenic shock is the preferred option and should be the routine approach. It is essential to consider these results in the context of individual patient characteristics and it may be necessary to 'course correct' during a procedure if the clinical situation does not resolve with revascularisation of the presumed culprit. The trial did have some limitations in that it demanded immediate revascularisation of a chronic total occlusion, which prolonged the procedure and may have contributed to mortality in the CR group. Furthermore, the use of mechanical circulatory support was low (28%; n=194) and inconsistent between the groups. Recent advances in the evidence for mechanical circulatory support devices, such as Impella (Abiomed), may force a re-evaluation of the evidence for the best approach in the setting of cardiogenic shock.[57]

The ESC guidelines for ACS published in 2023 recommend immediate PCI of infarct-related artery only, and staged CR after primary PCI (IB recommendation).[37,55,58,59] This was consistent with ACC/AHA guidelines that stated that PCI of the non-culprit artery can be harmful in patients in cardiogenic shock/haemodynamically and are unstable and a staged procedure is recommended rather than CR during the index procedure (III B recommendation).[40,55,56,60]

Safety Outcomes in Studies of Complete Revascularisation

Clinical decisions around revascularisation of non-culprit lesions are often framed in the context of preventing clinical events over the long term, meaning months, years or even decades. However, these advantages need to be weighed against the risk of procedural events that may be equally (or more) important for patients. These safety outcomes include CIN, acute stent thrombosis, periprocedural MI, major bleeding and (perhaps most important of all) stroke.[22–32] Most clinical trials in STEMI have reported safety outcomes. Rates of complications such as procedure-related stroke, acute stent thrombosis, bleeding requiring transfusion or surgery and CIN requiring dialysis were similar in patients undergoing CR or CVO therapy across a number of trials.[25–27,30–32]

In the COMPARE-ACUTE trial, patients in the CVO group were more likely to have a net adverse clinical event (composite of cardiac death, AMI, any revascularisation, stroke and major bleeding) (HR 0.46; 95% CI [0.33–0.64]; p<0.001).[30] In the CvLPRIT cardiac magnetic resonance (CMR) sub-study, there was an increase in the incidence of MI in the non-culprit lesions territory seen with pre-discharge CMR (22.4% versus 10.5%; p=0.02).[51] This suggests that additional revascularisation may be

associated with increased periprocedural MI. However, there was no difference in total infarct size or ischaemic burden between treatment groups at the time of follow-up CMR.[61] Length of stay may be an important outcome, both for the patient and the overall healthcare system. This was not significantly different across a number of studies where this was recorded.[25,27,30–32] Overall, in the context of STEMI, RCTs indicate that CR is a safe strategy when compared to CVO PCI.[22–32] Once again, the absence of randomised data makes this conclusion harder to judge in the case of NSTEMI, but it is likely that we can draw evidence from the STEMI trials.

Staged versus Immediate Non-culprit Lesion Complete Revascularisation

The optimal timing of CR is also important since efficacy and safety may depend upon this. Timing has been addressed in several studies. The evidence for revascularisation of the non-culprit artery at the time of primary PCI remains limited. CR undertaken during the index procedure (iCR) may be feasible in stable patients with uncomplicated revascularisation of the culprit artery, low-complexity non-culprit artery disease and preserved renal function.[40] Some of these factors may be unclear, particularly where the presentation is with STEMI, and the definition of iCR usually includes a staged procedure during the index admission rather than mandating that all vessels are treated in a single procedure. It is worth noting that from the perspective of trial design, procedural MI is easier to identify in sCR since the biomarkers have returned to baseline while the patient has waited. Care is needed to ensure a fair comparison is made between the two strategies.

In most clinical trials of CR versus CVO, the timing of the CR has been at the discretion of the operating team, with an outer band placed for the limits of staged sCR. This includes the largest COMPLETE trial, which mandated CR of non-culprit lesions during the index hospitalisation or after hospital discharge (no later than 45 days after randomisation). The benefit of CR, in terms of cardiovascular death, MI and ischaemia-driven revascularisation, was consistently observed among patients who had non-culprit lesion PCI during the index hospitalisation (HR 0.77; 95% CI [0.59–1.00]); and those who had it after hospital discharge (HR 0.69; 95% CI [0.49–0.97]) when compared to CVO therapy. However, there were no differences in the treatment effects in prespecified subgroups.[31] These findings were consistent with the findings of Politi et al. and the CvLPRIT trial, which both showed no significant difference in terms of MACE, or survival-free period of adverse cardiac events.[25,28]

The MUTLISTARS-AMI trial has shown that among haemodynamically stable STEMI patients with MVD, iCR was both non-inferior and superior to sCR (which was performed between 19 and 45 days after revascularisation of the infarct-related artery) for a composite endpoint of all-cause mortality, non-fatal MI, stroke, ischaemia-driven revascularisation, or heart failure hospitalisation at 1 year (RR 0.52; 95% CI [0.38–0.72]; p<0.001) for non-inferiority and p<0.001 for superiority).[62] Additionally, the iCR group experienced less serious adverse events, such as cardiac, renal or vascular disorders, compared to the sCR group.[62]

The BIOVASC trial recruited patients with acute coronary syndromes including both STEMI and NSTEMI, with about one-third of the patients presenting with NSTEMI. The primary endpoint was that iCR was non-inferior to sCR. There was a significant reduction in the incidence of AMI (HR 0.41; 95% CI [0.22–0.76]) and ischaemia-driven revascularisation (HR 0.61; 95% CI [0.39–0.95]) in the patients with iCR compared to sCR.[63]

The ESC guidelines for the management of ACS highlight the lack of evidence on the optimal timing of multivessel PCI and further trials are warranted to reach a consensus.[37] Previous ESC STEMI guidelines from 2017 recommended non-IRA PCI during the index admission.[4] The primary rationale for this recommendation was that all available trials had performed PCI for MVD in that timeframe. However, in the COMPLETE trial, non-IRA PCI in patients allocated to complete revascularisation was performed either during hospitalisation (67% of cases; n=1285) or after discharge (33% of cases; n=596), at a mean time of 23 days after discharge but always within 45 days.[31] No treatment effect according to the timing of the PCI interaction was observed. Given that the optimal timing of revascularisation has still not been investigated in adequately sized randomised trials with a superiority design, no recommendation in favour of either iCR or sCR can be formulated.[37]

A retrospective observational study demonstrated a significantly lower rate of MACE and mortality in iCR and sCR, while also concluding that CR is superior to CVO, which is consistent with other studies.[64] It showed that sCR offered improved in-hospital mortality (0% versus 0.9%; p<0.0005), 1-year mortality (0% versus 2.7%; p<0.0005) and 3-year mortality (4.3% versus 5.4%; p<0.0005). Of the patients who received CR, those in the sCR group were found to have a significantly decreased risk of developing intrahospital MACE than those in the single-stage PCI group.[64]

Moreover, a prespecified sub-analysis of the BIOVASC trial investigated the comparative efficacy of iCR versus sCR in patients presenting with NSTEMI or unstable angina and MVD.[65] The study of 1,525 patients found that the incidence of MACE, including ischaemia-driven revascularisation at 1 year, was similar between iCR and sCR (7.9% versus 10.1%; risk difference 2.2% 95% CI [−1.5, 6.0]; p=0.15). However, iCR demonstrated a significant reduction in MIs compared to sCR, with incidence rates of 2.0% and 5.3%, respectively (risk difference 3.3%; 95% CI [0.9–5.7]; p=0.006). This reduction in MIs persisted even after excluding procedure-related MIs occurring during the index or staged procedure. Additionally, iCR was associated with a reduction in unplanned ischaemia-driven revascularisation compared to sCR, with incidence rates of 4.2% and 7.8%, respectively (risk difference 3.5%; 95% CI [0.4–6.6; p=0.018). The trial concluded that iCR is a safe strategy in patients with NSTEMI and multivessel disease and may lead to a reduction in MI and additional revascularisation at 1 year compared to sCR.[65]

Overall, iCR is a safe strategy and is effective in treating patients with NSTEMI and multivessel disease.[64,65] However, pragmatic decisions regarding the use of the Cath lab may require flexibility in the design of services, particularly where benefits remain small or theoretical.

A recent meta-analysis included 16 clinical trials with 11,876 patients with acute MI (both STEMI and NSTEMI) and MVD. It found that single-setting iCR significantly reduced cardiovascular mortality and MI compared to sCR and CVO in patients with AMI and MVD.[46] Specifically, iCR reduced cardiovascular mortality/MI (OR 0.70; 95% CI [0.55–0.91]; p<0.001) and MACE (OR 0.67; 95% CI [0.50–0.9]; p<0.01) MACE (OR 0.42; 95% CI [0.32–0.56]; p<0.001), and MI (OR 0.39; 95% CI [0.26–0.57]; p<0.001) compared to sCR. iCR ranked the best option of all strategies, followed by sCR and CVO.[46]

Physiology-guided versus Angiography-guided Percutaneous Coronary Intervention Strategies

One of the most important aspects of achieving CR is defining lesions that require revascularisation. Studies have compared angiography with invasive coronary physiology in decision-making strategies.[23,29,30,49,66,67] The COMPARE-ACUTE and DANAMI-3-PRIMULTI individually found that there was a reduction in a composite endpoint of cardiovascular death,

Table 3: Randomised Controlled Trials Comparing Physiology-guided versus Angiography Alone Strategies for the Assessment of Non-culprit Lesions

Trial	Sample Size	Non-culprit Lesions PCI Strategy	Key Findings
Ghani et al. 2012[23]	121	FFR-guided PCI MV primary PCI versus conservative treatment of non-infarct lesions in STEMI patients with MVD	MACE/MACCE 35.4% versus 35% (p=0.96) All-cause death/MI 5% versus 0% (p=0.29) at 36 months
DANAMI-3-PRIMULTI 2015[29]	627	MV staged FFR-guided PCI versus CVO PCI in STEMI patients with MVD	No significant difference between both arms (OR 0.55; 95% CI [0.18–1.65])
COMPARE-ACUTE 2017[30]	885	MV primary or staged FFR-guided PCI versus CVO PCI in STEMI patients with MVD	No significant difference between both arms (OR 1.00; 95% CI [0.25–4.03])
Frame-AMI 2023[49]	563	FFR-guided versus angiography-guided PCI in STEMI patients with MVD	At a median follow-up of 3.5 years, FFR-guided PCI displayed a significantly reduced primary composite endpoint of death, AMI and repeated revascularisation (p=0.003). Cardiac and all-cause death were significantly lower in the FFR-guided PCI group (p=0.010, 0.020, respectively). The incidence of AMI was significantly lower in the FFR-guided PCI group (p=0.009).
Flower-MI 2023[66]	1,171	FFR-guided versus angiography-guided PCI in STEMI patients with MVD	No significant difference in all-cause death, non-fatal AMI and unplanned hospitalisation leading to urgent revascularisation at 1 year in patients (with diameter stenosis of >50%) who underwent a preventive PCI compared to patients (with FFR<0.80) who did not (p>0.05)
FULL REVASC 2024[68]	1,542	FFR-guided versus angiography-guided PCI in STEMI and very high-risk NSTEMI patients with MVD	At a median follow-up of 4.8 years, the primary outcome – a composite of death from any cause, MI or unplanned revascularisation – occurred in 19.0% of the FFR-guided group and 20.4% of the angiography group (HR 0.93; 95% CI [0.74–1.17]; p=0.53). Secondary outcomes, including a composite of death or MI (HR 1.12; 95% CI [0.87–1.44) and unplanned revascularisation (HR 0.76; 95% CI [0.56–1.04]) showed no significant differences between groups.

AMI = acute MI; FFR = fractional flow reserve; MACE = major adverse cardiac events; MACCE = major adverse cardiac and cerebrovascular events; MV = multivessel; MVD = multivessel coronary artery disease; NSTEMI = non-ST-segment elevation MI; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation MI.

non-fatal MI and repeat revascularisation. This was mostly driven by a reduction of urgent repeat revascularisation.[29,30]

The FRAME-AMI trial compared patients with STEMI and MVD who had undergone a successful PPCI of the infarct-related artery and were randomly assigned to physiology-guided PCI (FFR ≤0.80) or angiography-guided PCI (diameter stenosis >50%) for non-culprit lesions.[49] At a median follow-up of 3.5 years, the physiology-guided strategy significantly improved the primary endpoint of all-cause death, non-fatal MI and repeat revascularisation (7.4% versus 19.7%; HR 0.43; 95% CI [0.25–0.75]; p=0.003).[49] Importantly, secondary endpoints, including CV death and all-cause death, were also significantly reduced.[49] There was also a reduction in the incidence of procedure-related MI.[49] The FRAME-AMI trial also compared patients with staged and immediate CR with the use of fractional physiology-guided PCI. The trial reported that the FFR assessment for non-culprit lesions during the index procedure could increase patient comfort and shorten hospital stays. It reduced medical costs and avoided possible complications from a staged invasive procedure.[49] From a safety perspective, the incidence of stent thrombosis, cerebrovascular accident and CIN were similar in both arms. Many intermediate coronary artery stenoses when assessed using angiographic appearance alone were not functionally significant. The severity of such lesions' severity may be overestimated in the acute phase of MI.[49,68,69] These findings may address the concern raised by the CvLPRIT CMR sub-study, in terms of increased incidence of AMI in non-culprit lesions on pre-discharge CMR.[61]

The findings of the FRAME-AMI trial were not concordant with the findings of the FLOWER-MI trial, which also evaluated patients (n=1171) with STEMI and MVD.[49,66] The primary outcome, a composite of death, non-fatal MI or urgent revascularisation at 1 year, occurred in 5.5% (n=32) of patients in the physiology-guided group and 4.2% (n=24) in the angiography-guided group (HR 1.32; 95% CI [0.78–2.23]; p=0.31) and was not significant, but angiographic assessment was numerically favoured. There were no significant differences between the strategies for the individual components of the primary endpoint. A major difference to the FRAME-AMI trial was the follow-up time, which was 1 year in the FLOWER-MI trial, compared to 3.5 years in FRAME-AMI. Additionally, there are significant differences in selection criteria and trial design. FLOWER-MI was substantially larger than FRAME-AMI although ultimately both trials were underpowered with small numbers of events. Furthermore, the FRAME-AMI trial included a mixture of STEMI and NSTEMI, with substantial iCR, while FLOWER-MI was exclusively STEMI patients and all had sCR.

In the recent FULL REVASC trial, a multinational, registry-based, randomised trial of 1,542 patients with STEMI or very high-risk NSTEMI and MVD, physiology-guided complete revascularisation was compared to CVO PCI.[67] At a median follow-up of 4.8 years, there was no difference in the MACE primary endpoint (19.0% CR versus 20.4% CVO; HR 0.93; 95% CI [0.74–1.17]; p=0.53). There were no differences in secondary outcomes, including a composite of death or MI (HR 1.12; 95% CI [0.87–1.44]). Thus, physiology-guided CR did not significantly reduce MACE compared to CVO PCI in this setting.[67] Network meta-analyses have suggested there were no significant differences between angiography-guided PCI and physiology-guided PCI although this may reflect contradictory results in the clinical trials included.[70]

Trials with greater power are needed to further analyse the role of physiology-guided PCI. This includes the COMPLETE 2 trial (NCT05701358), which is currently recruiting. More details regarding the timing of physiology post-MI are needed, as early FFR post-MI may be unreliable, and trials with more patients undergoing sCR would be able to display more benefits. Trials comparing physiology-guided versus angiography-alone PCI are outlined in *Table 3*.

Table 4: Ongoing Trials Comparing Complete Revascularisation versus Culprit-vessel-only Revascularisation in MI

Trial	Sample Size	Study Population	Design	Primary Endpoints
ASSIST-MI (NCT03263468)	3,520	STEMI	Immediate versus staged MV PCI	Death, MI, heart failure and repeat revascularisation within 1 year
iMODERN (NCT03298659)	1,146	STEMI	iFR-guided immediate MV PCI versus stress cardiac magnetic resonance-guided staged MV PCI	Death, MI and heart failure within 1 year
SLIM (NCT03562572)	414	NSTEMI	Immediate FFR-guided MV PCI versus staged MV PCI. Patients in the comparator group will be referred to treating cardiologist and/or heart team after culprit vessel PCI to decide whether staged PCI should be performed	Death, MI, stroke and repeat revascularisation within 1 year
OCT-CONTACT (NCT04878133)	460	STEMI	OCT-guided versus angiography-guided MV PCI	Death, MI and repeat revascularisation within 1 year
STAGED (NCT04918030)	1,700	STEMI	In-hospital versus out-hospital staged MV PCI. In-hospital staged PCI will be performed during the index hospitalisation (within 7 ±3 days), while out-hospital staged PCI will be performed upon rehospitalisation (within 30 ±15 days)	Death within 1 year
QFR-STEMI (NCT04259853)	1,016	STEMI	QFR-guided revascularisation versus angiography-guided MV PCI	Death, MI, stroke, repeat revascularisation and hospitalisation for heart failure within 1 year
SAFE STEMI (NCT02939976)	875	STEMI (age ≥60 years)	iFR-guided MV PCI versus CVO PCI	Cardiovascular death, MI and repeat revascularisation within 1 year
TERMINAL (NCT05231226)	426	STEMI	Immediate versus staged MV PCI	Death, MI, heart failure and repeat revascularisation within 1 year
OPTION-NSTEMI (NCT04968808)	676	NSTEMI	Immediate versus in-hospital MV PCI	Death, MI and repeat revascularisation within 1 year
MILESTONE (NCT01311323)	1,000	NSTE-ACS (SYNTAX score ≤33)	MV PCI versus coronary artery bypass grafting surgery	Death and repeat revascularisation within 1 year
OPTION-STEMI (NCT04626882)	994	STEMI	Immediate versus in-hospital MV PCI	Death, MI and repeat revascularisation within 1 year

FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; MV = multivessel; NSTE-ACS = non-ST elevation acute coronary syndrome; NSTEMI = non-ST-segment elevation MI; OCT = optical coherence tomography; PCI = percutaneous coronary intervention; QFR = quantitative flow ratio; STEMI = ST-segment elevation MI.

Revascularisation of Bystander Chronic Total Occlusions in Acute MI

An area of controversy in the field is whether chronic total occlusions (CTO) should be included as attempted CR. Multiple registries suggest that most CTOs are not attempted in clinical practice. Evidence is divergent, with some registry-based studies suggesting an improvement in outcome with successful CTO PCI leading to an improvement in survival at 1 and 3 years in a small registry, compared to those who had failed CTO PCI or in whom it was not attempted.[71] However, the EXPLORE trial showed no such differences. EXPLORE was a randomised study evaluating the effect of early CTO revascularisation after STEMI in 304 patients and the authors found no difference in left ventricular ejection fraction, which was the primary outcome, and no difference in mortality at 5 years.[72,73]

Data from wider trials remain limited. Only 2% of lesions treated in the COMPLETE trial were CTO and operators could leave these lesions at their discretion. Caution regarding the need for CTO revascularisation should be adopted, since risks of revascularisation may be higher and outweigh projected benefit and they should not be attempted as a primary PCI.[74]

Recommendations for Further Research for Revascularisation in MI

There are some important targets for further research that have already been highlighted in this paper. Evaluation of subgroups that would benefit more or less from a CR strategy will be important to guide holistic care of patients. Some of this work has begun with the assessment of older patients in the FIRE trial, but other groups, including women, are under-represented in these studies, which is often the case in cardiovascular research.

Larger, more robust trials are needed to evaluate whether there is a benefit to physiology-guided PCI over angiography alone. Additionally, trials using other modalities to identify high-risk lesions that may benefit from revascularisation, such as CT or intracoronary imaging, would also be welcome. There may also be consideration for the role of ischaemia testing, using stress echo, stress perfusion MRI or positron emission tomography. The usefulness of these modalities after STEMI will depend on the scientific basis for the benefit of CR. The relationship between a reduction in ischaemia and the benefit of CR is not certain and may simply be a surrogate for atherosclerotic plaque burden. If future clinical trials demonstrate that coronary physiology usefully selects lesions most likely to benefit, then there may also be a role for these modalities.

There are limited trials evaluating functional status and health-related quality of life when considering revascularisation strategies. Future studies might consider using different heart-specific measures and generic quality of life tools, such as the Kansas City cardiomyopathy questionnaire, EQ-5D, SF-12, SF-36, the Seattle Angina Questionnaire and

the Minnesota Living with Heart Failure Questionnaire. These can be beneficial in assessing patients' symptoms and how they are coping after the procedure. In addition, an improved understanding of the impact of CR on left ventricular function, and its impact on indications and timings of ICD devices would be welcome.

Emerging data indicates that there may be a benefit to CR in reducing the risk of arrhythmia in the long term.[75] This may reduce the need for device therapy but needs further study. Furthermore, cost-effectiveness analyses of the different approaches can be derived to assess the financial impact of the treatment offered on the healthcare system. Further ongoing trials comparing CR versus CVO strategies in MI are summarised in *Table 4*.

Conclusion

CR in STEMI with MVD has displayed a clear superiority over CVO in terms of overall clinical outcomes such as CV death, non-fatal MI and repeat revascularisation. There is less clarity regarding the benefit of iCR in patients with STEMI and MVD compared to sCR with conflicting and small-scale data. The role of physiological assessment in the guidance of revascularisation strategy for non-culprit vessels remains uncertain. More evidence is needed to ascertain the usefulness of physiology-guided PCI.

For patients with NSTEMI and MVD, a vast majority of the observational data favours CR, with associated improvements in long-term outcomes. However, it is difficult to produce a firm recommendation for CR in this circumstance in the absence of high-quality randomised data. ❑

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