Does the evidence really suggest that we should completely revascularise bystander disease in patients with ST elevation myocardial infarction undergoing primary angioplasty? Why we still need more definitive trial data to change routine practice

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Does the evidence really suggest that we should completely revascularise bystander disease in patients with ST elevation myocardial infarction undergoing primary angioplasty? Why we still need more definitive trial data to change routine practice

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**ABSTRACT**

**Introduction:** There remains considerable heterogeneity in the management of significant lesions in non-culprit coronary arteries in STEMI patients undergoing primary percutaneous coronary intervention (PPCI). Three recent randomised trials have shown clinical outcome benefit in a complete revascularisation approach when compared to PPCI of the culprit artery alone. By contrast, observational data suggest that an aggressive complete revascularisation may not confer clinical benefit and may, in some cases, be harmful.

**Areas covered:** In this review we discuss the three recent randomised trials that have advocated a complete revascularisation approach in addition to data available from registries.

**Expert commentary:** An adequately powered, randomised controlled trial is required to answer the question of whether complete revascularisation in STEMI patients is beneficial and, if so, whether it should be ischaemia directed and whether it should be at the index procedure or staged.

1. Introduction

Primary percutaneous coronary intervention (PPCI) of the infarct-related coronary artery (IRA) is the gold standard treatment for patients presenting with ST-segment elevation myocardial infarction (STEMI) [1–3]. In up to 30% of patients presenting with STEMI significant stenoses that are considered angiographically significant are also seen in 1 or more non-infarct-related arteries (N-IRA). The majority of these patients are asymptomatic prior to presenting with STEMI [4,5]. There is evidence demonstrating that these patients are at a higher risk of major adverse cardiac events (MACE) when compared to the patients with single vessel disease [4,6,7]. However, the optimal revascularization strategy for such patients remains contentious [8–12].

The uncertainty about the optimal management of N-IRA disease in STEMI patients results in considerable variation in the way in which such patients are treated. Historically, there have been three approaches that cardiologists have adopted. First, a conservative approach with revascularization of N-IRA only performed for refractory symptoms or objective evidence of ongoing ischemia. Second, an aggressive approach in which complete revascularization of N-IRA is undertaken at the index STEMI presentation (either at the same sitting as PPCI or before discharge), or third, an intermediate approach whereby revascularization of N-IRA is completed as staged procedure after discharge from the index PPCI.

The argument for the more aggressive approach of complete revascularization is dominated by the prospect of preserving left ventricular systolic function and preventing recurrent ischemia and infarction. The counter argument in favor of a conservative (i.e. IRA only) approach is based on the avoidance of longer procedure times with more contrast and radiation, increased procedural risk and increased risk of subsequent stent thrombosis. Above all, this argument focuses on lack of evidence of benefit.

The decision taken by interventional cardiologists about culprit-only or complete revascularization in these patients was, until recently, based largely upon observational data. Further, there is an awareness that in setting of an acute coronary syndrome, systemic inflammation and associated derangements in endothelial function and coagulation can exist which can ultimately lead to increased vulnerability of plaques [13,14]. In general, most operators employ a combination of a conservative and intermediate approach to the management of N-IRA in specific patients, which takes into consideration these data plus other factors including: extent and complexity of N-IRA disease; time of day of PPCI; comorbidities; presence of cardiogenic shock; level of patient (and operator) comfort/agitation. Figure 1 shows a coronary angiogram of an IRA and N-IRA in a STEMI patient.

1.1. The evidence base: our current dilemma

Prior to 2013, there were only 3 randomized trials looking at different revascularization strategies of N-IRA stenosis in STEMI patients [10,12,15]. These studies were limited by small sample
sizes and a lack of statistical power. In the largest study ($n = 214$), there was a significantly higher rate of MACE in patients allocated to complete revascularization compared to the IRA-only group [12]. Since 2013, however, a further three randomized trial have been published that all provide evidence in favor of complete versus culprit-only revascularization [16–18]. As a result of this, some international guidelines (AHA/ACC) have been altered to reflect the benefit of complete revascularization [19]. Table 1 summarizes the three recent trials that will be discussed in this article.

However, the results of these randomized trials are not consistent with evidence derived from observational studies [20–22]. Historically, the data from SHOCK [23], which showed some benefit from complete revascularization in STEMI patients with cardiogenic shock, was used by some interventional cardiologists to justify the treatment of N-IRA in STEMI patients without shock. However, recent contemporary observational evidence suggested no benefit for complete revascularization and potentially in some cases harm [22]. Specifically, this observational study looked at the management of 3984 STEMI patients with stenosis of $>50\%$ in 2 or more epicardial coronary arteries. These patients were admitted to 8 tertiary cardiac centers in London between January 2005 and November 2011. The study found IRA-only PCI to be an independent predictor for reduced in hospital MACE and survival at 1 year. It should be noted that only 14% of patients with N-IRA had complete revascularization in the study which is reflective of current clinical practice amongst interventional cardiologists.

Following the COURAGE trial, there has been a pattern toward favoring the conservative treatment of non acute lesions [24]. However, the population studied in COURAGE was those with stable coronary disease. What is not clear is whether the plaque disease and morphology in the N-IRA of STEMI patients is different to stable lesions studied in COURAGE. There is evidence to support a theory of pan-coronary inflammation in STEMI patients

![Coronary angiogram of a STEMI patient depicting the IRA (Proximal left anterior descending (LAD) artery) and N-IRA (Left circumflex artery).](image)

Table 1. The table summarizes and compares the three trials described in this review.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Study population</th>
<th>N-IRA stenosis</th>
<th>Primary end point</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRAMI</td>
<td>RCT, Open label</td>
<td>465 STEMI patients with MVD. Age (years) IRA: 62  Complete: 62</td>
<td>$\geq50%$</td>
<td>Composite of death from cardiac causes, nonfatal myocardial infarction, or refractory angina</td>
<td>Primary end point occurred in 21 complete revascularized patients vs. 53 IRA-only patients</td>
<td>Complete revascularization during the index procedure in STEMI patients with MVD reduces risk of cardiovascular events</td>
</tr>
<tr>
<td>CvLPRIT</td>
<td>RCT, Open label</td>
<td>296 STEMI patients with MVD. Age (years) IRA: 65.3±11.9 Complete: 64.6 +/-11.2 Killip II/III(n,%): IRA: 13 (9.4) Complete: 10 (6.8)</td>
<td>$\geq50%$</td>
<td>Composite of all-cause death, recurrent myocardial infarction (MI), heart failure, and ischemia-driven revascularization within 12 months</td>
<td>(1) The primary end point occurred in 10% of the complete revascularization group vs. 21.2% in the IRA-only revascularization group. (2) No significant reduction in death or MI, a nonsignificant reduction in all primary end point components within 12 months.</td>
<td>Index admission complete revascularization significantly lowered the rate of the composite primary end point at 12 months compared with treating only the IRA</td>
</tr>
<tr>
<td>PRIMULTI</td>
<td>RCT, Open label</td>
<td>627 STEMI patients with MVD. FFR DRIVEN. Age (years) IRA: 63 Complete: 64 Killip II–IV(n,%) IRA: 20 (6) Complete: 22 (7)</td>
<td>$\geq50%$</td>
<td>Composite of all-cause mortality, nonfatal reinfarction, and ischemia-driven revascularization of lesions in non-infarct-related arteries</td>
<td>Primary end point occurred in 13% of complete revascularized vs. 22% of IRA only</td>
<td>Complete revascularization guided by FFR measurements significantly reduces the risk of future events compared with no further invasive intervention after primary PCI</td>
</tr>
</tbody>
</table>
The focus for this review is the dilemma that faces the interventional cardiologist in relation to treatment of STEMI patients with significant NIRA who are undergoing PPCI: is the contemporary evidence from randomized trials applicable to the all-comers population that present routinely for treatment in these circumstances?

2. Preventive angioplasty in acute myocardial infarction (PRAMI)

The aim of PRAMI [16] was to determine whether performing ‘preventive PCI’ of N-IRA as part of the index procedure for patients presenting with STEMI would result in a lower incidence of death from cardiac causes, nonfatal myocardial, or refractory angina. A total of 465 patients were randomized in five UK centers between 2008 and 2013. Patients were randomized only after successful PPCI for the IRA was completed. To qualify they needed to have an angiographic eyeball stenosis of 50% or more in at least one N-IRA which was deemed to be treatable by PCI. Patients were ineligible if they were in cardiogenic shock, unable to give consent, had undergone coronary artery bypass grafting (CABG), had N-IRA involving the left main stem or ostia of both left anterior descending and circumflex arteries, or a chronic total occlusion.

Eligible patients were then randomized to either IRA only PCI (i.e. PPCI) or to undergo immediate complete revascularization of N-IRA, labeled as ‘preventive PCI’ in the IRA-only group, staged PCI was discouraged. In patients with subsequent symptoms of angina that failed medical therapy, there was a requirement in the protocol for objective evidence of ischemia prior to any further PCI. Follow-up information was collected at 6 weeks and then at yearly intervals. The primary outcome of the trial was a composite of death from cardiac causes, nonfatal myocardial infarction, or refractory angina. Secondary outcomes were death from non-cardiac causes and repeat revascularization procedures.

Of 2428 patients screened, 465 (19.2%) underwent randomization. Two hundred and thirty-four patients were randomized to have preventive PCI of N-IRA and the remaining 231 to IRA-only PCI group. Mean follow-up was 23 months. The trial demonstrated a significantly lower rate of the composite primary end point in the preventive PCI group (n = 21) group when compared to the IRA only group (n = 53, p < 0.001). A significantly lower rate was seen in nonfatal myocardial infarction (7 vs. 20, p = 0.009) and incidence of refractory angina (12 vs. 30, p = 0.002). Although there was a lower rate of cardiac mortality a reduction in the preventive PCI group, this did not reach statistical significance (p = 0.07). Thus, the data demonstrate a 65% lower rate of cardiac death, nonfatal myocardial infarction, or refractory angina with an absolute reduction of 14% over 23 months. In the secondary outcomes, there was a significant reduction in repeat revascularization in the preventive PCI group (16 vs. 46, p < 0.001).

However, whether these data support application of such an approach to all comers with STEMI and significant NIRA is open to scrutiny, in particular for the following reasons.

First, only 19% of the screened cases were randomized. Specifically, it took 5 years, in 5 high volume PPCI centers, to recruit 465 cases into the trial. Inevitably, this raises questions about selection and the generalizability of the results. This is, of course, a feature of any carefully constructed randomized trial but inevitably means that the results may not be applicable to 80% of the patients with STEMI and significant NIRA who are presented to us in routine practice.

Second, in PRAMI the decision to randomize a patient into the trial was only made once the IRA had been successfully treated. Obviously, some factors that might influence the decision to go ahead with randomization at this point could have included: the ease of completion of the PPCI to IRA; lack of PPCI complication; nature of NIRA lesion (length/bifurcation/calcification, etc.). Such factors were not measured or assessed in the trial: for example, there is no anatomical scoring system employed such as SYNTAX to describe the complexity of the IRA or the NIRA. Further, patients who were in the conservative arm were also unblinded to their treatment, thus being aware of the presence of ‘significant’ coronary disease apart from their IRA, which could potentially influence the event rate (n = 53) in this group.

The third limitation to the general applicability of PRAMI to all STEMI patients with N-IRA is that the trial was stopped early by the Data & Safety Monitoring Committee. The original power calculation indicated that enrolment of 600 patients would be required to provide a power of at least 80% to detect a reduction in risk of 30% in the preventive PCI group at a 5% significance level. Recruitment to this trial was stopped early after 465 patients were recruited based on a highly significant between-group difference (p < 0.001) in the incidence of the primary outcome favoring preventive PCI. Stopping a trial early based upon a statistically significant difference that it was not powered to detect is contentious and challenging. It was, of course, balanced against the potential for the trial causing harm to one cohort by the DSMB, but this was, strictly speaking, a theoretical possibility given the small numbers.

A fourth potential issue is that in PRAMI the decision about whether to intervene on N-IRA was based on a stenosis of 50% or more. There was no requirement to demonstrate evidence that the lesions were capable of inducing ischemia. Certainly, in other circumstances outside the context of STEMI, interventional cardiologists would rarely perform PCI on a lesion between 50%and 70%. Coronary angiography in isolation is known to have significant flaws, including particularly overestimating the significance of coronary lesions, using the currency of ischemia, potentially leading to inappropriate and harmful PCI [28]. Furthermore, it has also been shown that there is overestimation of N-IRA stenoses in the setting of PPCI where one fifth of >50% stenosis of N-IRA at the time of PPCI were less than 50% by the time of a staged procedure [29]. In addition, functional ischemia testing, such as flow fractional reserve (FFR), used in conjunction with coronary angiography has been shown to be associated with improved clinical outcomes as...
well as reduced resource utilization in patients with stable coronary artery disease [30,31] and also in the setting of an acute myocardial infarction [32,33]. The PRAMI protocol has therefore included some less severe angiographic lesions for PCI that interventionists would not commonly treat under other circumstances.

Finally, other potential confounding factors exist that could impact on the observed difference. For example, there were more anterior STEMI patients in the IRA-only group (39% vs. 29%), and there was also a greater incidence of diabetes mellitus in the IRA-only group (21% vs. 15%).

3. Complete versus lesion-only primary PCI trial (CvLPRIT)

CvLPRIT was an open-label randomized study conducted in 7 cardiac centers in the UK between May 2011 and May 2013. The aim of the trial was to test the feasibility, safety, and benefit of simultaneous complete revascularization of N-IRA in STEMI patients presenting for PPCI. Patients with N-IRA stenoses of more than 50–70% were recruited. In this trial, patients were randomized to either IRA-only PCI (n = 150) or in-hospital complete revascularization (n = 146) after angiography and before completion of the IRA PPCI. A total of 850 patients were screened with 296 randomized. In contrast to PRAMI, randomization in CvLPRIT was also stratified by infarct location (anterior/non anterior) and symptom onset (<3 h or >3 h). PPCI was undertaken according to routine practice. Unless clinically contraindicated drug eluting stents were recommended for IRA and N-IRA PCI. Provided there were no contraindications complete revascularization was recommended at the time of the index PPCI procedure. The operator was, however, allowed to stage the NIRA PCI if necessary for safety reasons but complete revascularization was mandated during the index hospital admission. Cardiovascular magnetic resonance imaging was performed on a prespecified subset of 205 patients at a median of 2.9 days after PPCI, with subsequent blinded analysis undertaken. All patients underwent myocardial perfusion scintigraphy (MPS) at 6 ± 2 weeks after discharge to assess residual ischemia, and the results were nested unless an independent review revealed an ischemic myocardial burden of 10% or more.

Patients were followed up at 6 months by telephone follow-up and were seen at 9 and 12 months. The primary end point was a composite of MACE comprising all-cause mortality, recurrent MI, heart failure (HF), and repeat revascularization. Safety end points were defined as stroke, major bleeding, and contrast-induced nephropathy.

MACE was statistically significantly lower in the complete revascularization group (n = 15, 10%) when compared to the IRA-only group (n = 31, 21.2%, p = 0.009). The separation in the event curves occurred early and was persistent throughout the follow-up period, see Figure 2. Although there was a significant difference in overall MACE rate between the groups, no significant differences were seen in any of the individual components of the composite primary end point.

Of the 150 patients randomized to complete revascularization in CvLPRIT 96 (64%) received N-IRA PCI at the index PPCI procedure, and in the remainder NIRA PCI was undertaken during the index admission before discharge. A higher incidence of all-cause mortality, MI, and HF was seen in the group who had delayed complete revascularization (n = 5, 11.9%) when compared to the patients who had complete revascularization done at the index PPCI procedure (n = 3, 3.1%), although this was not statistically significant (p = 0.06).

Thus, the overall results from CvLPRIT are consistent with those seen in PRAMI, despite some differences in methodology. Both trials show a benefit of N-IRA PCI in patients presenting with STEMI during the index admission. Again, however, the key question for the frontline clinician on behalf of the patients who present to them in this category is this: are the results from CvLPRIT relevant enough to an all-comers population that we should adopt complete revascularization in routine practice? In a similar way to PRAMI, there are features of the trial and its interpretation that mean the answer to this question probably cannot be ‘yes.’

First, over 2 years in 7 centers, 296 patients were recruited out of 850 who were screened. As in all randomized trials, this speaks of the entirely appropriate application of strict inclusion and exclusion criteria, but emphasizes that this is, of course, a luxury not available in routine STEMI care!

Second, the NIRA lesions needed to be at least 50% diameter severity in 2 angiographic views or at least 70% in a single view to be included, without objective evidence that they were causing ischemia. This leads again to the criticism that has been raised in relation to PRAMI, which is that in other populations treated with PCI, this is very uncommonly deployed in lesions of around 50%, particularly if there is no evidence they are causing ischemia.

Third, the very early event rate that drove the difference in outcome between the 2 groups is hard to explain. The abolute numbers of individual events that made up the overall composite end point in CvLPRIT was so small that it is difficult to understand what the ‘theme’ was for the early events… for example, there were 2 recurrent MI in one group and 4 in the other. Although the trial was appropriately powered, there has to be a concern that its size limits the confidence to apply the
results to all comers, rather to view it as hypothesis generating. Common themes of uncertainty, unanswered questions, and applicability arise.

4. DANAMI-3-PRIMULTI

DANAMI-3-PRIMULTI was an open-label randomized trial designed to assess, for the first time, the effect of ischemia-guided N-IRA PCI in STEMI patients. STEMI patients were randomized once the IRA PCI had been completed and if there was angiographic evidence of at least 50% stenoses of N-IRA. The treatment arms were (a) FFR-guided complete revascularization (using a cut off of ≤0.8) or (b) IRA PCI only. Patient randomized to FFR-guided complete revascularization had the NIRA PCI done 48 h after the index PCI procedure. Lesions with stenoses of greater than 90% did not have FFR assessment. Lesions deemed unsuitable for PCI were considered for CABG. The primary end point was a composite of all cause mortality, reinfarction, or ischemia-driven revascularization of N-IRA. A total of 627 patients were randomized, 314 in the FFR-guided complete revascularization arm and 313 in the IRA PCI-only arm. Median follow-up was 27 months.

The primary end point occurred in 68 (22%) patients in IRA PCI-only group compared to 40 (13%) in the FFR-guided complete revascularization group, which was highly statistically significant (p = 0.004). This difference was driven by ischemia-driven revascularization which was the only individual component of the composite primary end point to show a statistically significant difference (17% vs. 5%, p < 0.0001). Both urgent (6% vs. 2%, p = 0.03) and non-urgent PCI (9% vs. 3%, p = 0.002) were statistically higher in the IRA only group. Interestingly, 31% (n = 97) of the 314 patients randomized to FFR-guided N-IRA PCI had FFR readings greater than 0.80 and therefore had no further invasive treatment; a figure entirely consistent with the level of discrepancy between angiographic and FFR assessment of lesions in other studies including RIPCORD [34], FAME [30], FAMOUS-NSTEMI [32] and the series by Toth et al. [35]. No difference between the two groups was seen with regard to serious adverse events related to the revascularization procedures. It is also important to note that in the complete revascularization group, the 31% (n = 97) who had FFR readings above 0.8 (no further PCI) did not differ from the remainder of the complete revascularization group with regard to the occurrence of the primary end point (hazard ratio 1.54, 95% CI 0.82–2.90; p = 0.18). This provides a strong case for the validity of the FFR readings taken during the acute phase of acute coronary syndromes.

Clearly, PRIMULTI shares the same criticisms regarding generalizability of selected randomized trial populations to routine practice. Further, its principal finding that there was indeed benefit to FFR-guided NIRA revascularization but that this was driven by revascularization of the NIRA vessels is of great interest, but also, at the same time, challenging to correlate with the results of CvLPRIT and PRAMI. In PRIMULTI, the combined end point was achieved significantly less in the complete revascularization group as in the other trials, but in this case it was presumably by reducing the need for subsequent need for NIRA revascularization. A significant reduction in requirement for revascularization was also observed in PRAMI but there was a nonsignificant trend to that effect in CvLPRIT. One might assume, therefore, that the driver for the NIRA revascularization in the IRA-only groups was related to ischemia? And yet, here’s the thing: in the CvLPRIT patients all underwent a nuclear perfusion scan at 6 weeks after the index admission to look at their residual ischemic burden and there was no significant difference between the two groups! The conclusion from the authors was: therefore residual ischemia is unlikely to be an important driver of further events post PCI for STEMI, and its suppression alone cannot explain the reduced event rate in the complete revascularization arm of CvLPRIT [36]. Further to this the cardiac MRI (CMR) substudy to CvLPRIT [37] has shown that there is no significant difference in ischemic burden between the two groups at 9 months. There is therefore a curious discrepancy between the apparent benefit of targeting NIRA for PCI on the basis of a positive FFR and no detectable difference in the extent of reversible ischemia between groups in whom complete revascularization had been performed when compared to patients in whom only IRA was treated.

5. Expert commentary

Despite the data from PRAMI, CvLPRIT, and DANAMI-PRIMULTI 3 supporting a complete revascularization approach to N-IRA, there does not appear to have been a paradigm shift in practice toward complete revascularization in this group. The trials have produced important data and between them provide a strong signal that some patients with NIRA presenting with STEMI are likely to benefit from complete revascularization. However, despite all 3 trials showing apparent outcome benefit for the complete revascularization strategy, there remain several fundamental questions that still need to be answered before a wholesale shift to this approach can be objectively justified or taken up by the interventional community.

First, we know little about which patients are at risk of a subsequent MACE event. Our research endeavor has focused upon an intervention, in the form of complete revascularization, in all suitable NIRA patients. It should be obvious, however, that the presence of NIRA: the event rates in all 3 trials in the complete revascularization groups speak loudly to this point? One target for further research would be to better identify what factors render a particular patient at risk of the follow-up MACE event, and why? The advantage of this would be that it would facilitate a strategy of personalized intervention rather than a blanket alternative, which is what these trials have tested. Certainly, naïve assumptions, extrapolated from the extensive literature from elective and some acute coronary syndrome...
populations, that events are predicted according to lesion-level ischemia, are virtually unsustainable in the light of the data from the CvLPRIT nuclear substudy? The pathophysiological machinery yielding subsequent events in such patients should be systematically scrutinized in the hope of identifying biomarkers of the risk of such events.

Second, we do not know in enough detail the potential added value of measuring physiological surrogates for ischemia in NIRA vessels. Given that a 50% angiographic lesion is not considered a routine target for PCI in any other context, it is still tempting to speculate that lesion-level ischemia may have some value as a marker for risk, but in the light of the first point, the assumption must be that this risk is multifactorial. Ongoing and future trials will address the role of FFR assessment in much more detail.

Third, observational data have suggested a potential benefit in STEMI patients with NIRA for staged complete revascularization, within a few weeks of discharge. There will be persistent interest in this version of a complete revascularization strategy because it is attractive to interventionalists: completing the PPCI of the IRA in the middle of the night, allowing the patient home and bringing them back when they are settled is intuitively a more comfortable approach than doing all the PCI at the same emergency sitting. Staged complete revascularization is a strategy that requires formal testing in the context of a suitably powered randomized trial.

All three trials are modestly sized and not powered to detect a significant difference in individual end points of cardiac-related death and reinfarction. The results from all three trials PRAMI, CvLPRIT, and DANAMI-3-PRIMULTI show a significant reduction in the composite primary end point. However, when looking at hard end points such as cardiac-related death, no trial is able to show a significant benefit with a complete revascularization approach. This is largely due to the fact that all three trials are not statistically powered to show a significant reduction in such hard end points. Given this limitation and in addition to the open-label design of all three trials, it is clear that a definitive, adequately powered, randomized controlled trial is required to answer the question of whether complete revascularization in STEMI patients is beneficial and, if so, whether it should be ischemia directed and whether it should be at the index procedure or staged.

6. Five-year view

The conclusions from PRAMI, CvLPRIT, and DANAMI-3-PRIMULTI support a complete revascularization approach to the management of N-IRA in STEMI patients. This, however, is at odds with current clinical practice pursued by the vast majority of interventional cardiologists. Given the points of contention and uncertainty about current trial data, we envisage a large and definitive randomized trial reporting in around 5 years to address this issue.

Key issues

- Up to 30% of STEMI patients have significant N-IRA stenoses.
- Current clinical practice is based on clinical judgement with an emphasis on conservative treatment where possible.
- This is based on observational data which has shown complete revascularisation to be detrimental in some cases, and operator discretion/preference.
- Three recent randomised trials PRAMI,CvLPRIT and DANAMI-3-PRIMULTI have supported a complete revascularisation approach to the management of N-IRA.
- Both PRAMI and CvLPRIT have used coronary angiography as the only measure of determining whether PCI is required on N-IRA.
- No trial has been powered to detect significant differences in hard end points such as cardiac related death.
- Uncertainty remains about (a) the role of FFR-directed N-IRA and (b) the optimal timing of N-IRA PCI.
- A definitive randomised trial is still required to answer the areas of uncertainty listed and address whether complete revascularisation of N-IRA in STEMI patients is beneficial.

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References

Papers of special note have been highlighted as either of interest (€) or of considerable interest (€€) to readers.


**One of the three major trials discussed in the review.**


**The second major trial discussed in this review.**


**The final major trial discussed.**


**An important study on the validity of FFR in ACS.**


**The importance of FFR in the management of coronary artery disease is shown here.**

