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STEMI: is it time for COMPLETE revascularisation?

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Take Home Messages

- Half of patients presenting with ST-segment elevation myocardial infarction (STEMI) have multi-vessel coronary artery disease (CAD) at the time of presentation but the benefits of routine revascularisation of non-culprit lesions are uncertain.
- Previous trials have suggested that percutaneous coronary intervention (PCI) of non-culprit lesions reduces cardiovascular events but have been inadequately powered to detect hard outcomes such as myocardial infarction or death.
- The Complete versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early Percutaneous Coronary Intervention for STEMI (COMPLETE) trial provides evidence that complete revascularisation is superior to culprit lesion only PCI in reducing the composite risk of cardiovascular death, myocardial infarction, or ischemia-driven revascularisation.
- Revascularisation of non-culprit lesions can be safely deferred following discharge.
- This trial should aid interventionalists decision making and may help change clinical practice in the long term.

Background

Primary percutaneous coronary intervention (PCI) remains the gold-standard method of reperfusion for patients with ST-segment elevation myocardial infarction (STEMI) (1). Half of patients presenting with STEMI have multi-vessel coronary artery disease (CAD), which are additional angiographically significant lesions in locations separate from that of the culprit lesion that caused the acute event (2). These non-culprit lesions are often discovered at the time of primary PCI and may be angiographically stable or have complex morphologic features (3). Whether to routinely revascularise the non-culprit lesions or to manage them conservatively with optimal medical therapy is uncertain (4, 5).

The 2013 Preventive Angioplasty in Acute Myocardial Infarction (PRAMI) was a single-blinded, randomised trial which enrolled 465 patients with acute STEMI who underwent culprit lesion PCI (6). The patients were then randomly assigned to either non-culprit lesion PCI or no further PCI immediately after the culprit PCI procedure. The primary outcome was a composite of death from cardiac causes, nonfatal myocardial infarction, or refractory angina. Patients were followed up for 23 months. The results showed that in patients with STEMI and multi-vessel coronary artery disease undergoing culprit lesion PCI, PCI to the non-culprit lesions reduced the risk of adverse cardiovascular events, as compared with PCI limited to the culprit lesion.

The 2015 Complete versus Lesion-only Primary PCI (CvLPRIT) was a randomised trial comparing complete revascularisation at the time of index admission with treatment of only the culprit lesion

About the author

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artery (7). The trial enrolled 296 patients in 7 United Kingdom centres and patients were randomly assigned to the two treatment groups and followed up for 12 months. The primary endpoint was a composite of all-cause death, recurrent myocardial infarction (MI), heart failure, and ischemia-driven revascularisation within 12 months. The results showed that there was a non-significant reduction in all primary endpoints although there was no significant reduction in death or MI.

The Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3-PRIMULTI) trial assessed the impact of fractional flow reserve (FFR) guided treatment of non-culprit lesions in STEMI (8). After PCI of the infarct-related artery during STEMI, patients were randomly allocated to either receiving no further invasive treatment or complete FFR-guided revascularisation before discharge. The trial enrolled 627 patients with 313 allocated to no further invasive treatment and 314 assigned to have complete FFR-guided revascularisation. The primary endpoint was a composite of all-cause mortality, non-fatal reinfarction, and ischaemia-driven revascularisation of lesions in non-culprit arteries with a median follow-up of 27 months. The authors demonstrated that in patients with STEMI and multivessel disease, the patients in the FFR-guided complete revascularisation group needed significantly fewer repeat revascularisations compared with the patients in the group who had no further invasive intervention after primary PCI. All-cause mortality and non-fatal reinfarction did not differ between groups.

These trials provide evidence that PCI of non-culprit arteries after STEMI reduces the rate of nonfatal MI and future revascularisation (see **Table 1**). However all of the trials had small sample sizes and therefore were insufficiently powered to assess rates of death. In addition, the long-term benefits are unclear given that the longest follow up was approximately 2 years.

The COMPLETE Trial

The Complete versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early Percutaneous Coronary Intervention for STEMI (COMPLETE) trial was recently published in the New England Journal of Medicine (9). COMPLETE was a multinational, randomised trial that evaluated a strategy of complete revascularisation of all lesions, compared with a strategy of no further revascularisation in patients with STEMI and multi-vessel CAD who had already undergone successful culprit-lesion PCI. Complete revascularisation consisted of PCI of all suitable non-culprit lesions after PCI of the culprit lesion.

Patients presenting with STEMI were considered for inclusion in the trial provided they could be randomised within 72 hours after successful culprit-lesion PCI. Eligible patients had multivessel coronary artery disease, defined as having at least one angiographically significant non-culprit lesion. These non-culprit lesions were deemed angiographically significant if they had at least 70% stenosis of the vessel diameter on visual assessment or 50 to 69% stenosis accompanied by an FFR measurement of 0.80 or less. Patient inclusion and exclusion criteria are summarised in **Table 2**.

Patients who were randomly assigned to the complete revascularisation strategy had routine staged PCI of all suitable non-culprit lesions, regardless of symptoms or evidence of ischemia. Patients who were randomly assigned to the culprit lesion only PCI strategy received optimal medical therapy with no further revascularisation, regardless of whether there was evidence of ischemia on non-invasive testing.

Routine follow-up occurred at 6 weeks, 6 months, 1 year, and yearly thereafter up to a final follow-up visit. The first co-primary outcome was the composite of death from cardiovascular causes or new MI; the second coprimary outcome was the composite of death from cardiovascular causes, new MI, or ischemia driven revascularisation.

Outcomes

A total of 4041 patients from 140 centres in 31 countries were included in the trial and underwent randomisation, with 2016 patients assigned to the complete revascularisation group and 2025 patients assigned to the culprit lesion only PCI group. There was a low crossover rate (<5%) between the two treatment groups. After non-culprit lesion PCI, 90.1% of the patients in the complete revascularisation group had a Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) (10) score of 0, indicating that the PCI in these lesions were complete with no bystander disease.

Table 1. Comparison of the PRAMI, CvLPRIT and DANAMI-3-PRIMULTI Trials (adapted from (6-8))

	PRAMI	CvLPRIT	DANAMI-3-PRIMULTI
Number of patients	465	296	627
Mean age (years)	62	65	63
Median follow-up (months)	23	12	27
Median time from randomisation to second procedure (days)	0	<2	2
FFR measurement of non-culprit lesions	-	-	+
Primary outcome	Composite of death from cardiac causes, nonfatal MI, or refractory angina.	Composite of all-cause death, recurrent MI, heart failure, and ischemia-driven revascularization within 12 months.	Composite of all-cause mortality, non-fatal reinfarction, and ischaemia-driven revascularisation of lesions in non-infarct-related arteries.
Events with treatment of culprit lesion only [a]			
	PRAMI	**CvLPRIT**	**DANAMI-3-PRIMULTI**
Death	16/231	10/146	11/313
Cardiovascular death	10/231	7/146	9/313
Myocardial infarction	20/231	4/146	16/313
Revascularisation	46/231	16/146	52/313
Complete revascularisation v treatment of culprit lesion only [b]			
	PRAMI	**CvLPRIT**	**DANAMI-3-PRIMULTI**
Cardiovascular death or MI	0.36 (0.18–0.73)	Not reported	0.80 (0.45–1.45)
All-cause death, recurrent MI, heart failure, and ischemia-driven revascularisation	Not reported	0.45 (0.24-0.84)	Not reported
All cause mortality	Not reported	0.38 (0.12-1.20)	1.40 (0.63-3.00)

[a] number/total number of patients. [b] Hazard ratio (95% confidence interval)
CvLPRIT Complete versus Lesion-Only Primary Percutaneous Coronary Intervention Trial, DANAMI-3–PRIMULTI Third Danish Study of Optimal Acute Treatment of FFR fractional flow reserve, FFR fractional flow reserve, MI myocardial infarction, PRAMI Preventive Angioplasty in Acute Myocardial Infarction.

At a median follow up period of 3 years, the first coprimary outcome (death from cardiovascular causes or new MI) had occurred in 158 patients (7.8%) in the complete revascularisation group compared to 213 patients (10.5%) in the culprit lesion only PCI group (hazard ratio, 0.74; 95% confidence interval [CI], 0.60 to 0.91; P=0.004). The benefit was driven by a lower incidence of new MI in the complete-revascularisation group. Cardiovascular mortality was similar in the two groups (2.9% in complete revascularisation group and 3.2% in the culprit lesion only PCI group), as was all cause mortality (4.8% in the complete revascularisation group and 5.2% in the culprit lesion only PCI group).

The second coprimary composite outcomes (death from cardiovascular causes, new MI, or ischemia-

Table 2. Inclusion and exclusion criteria for the COMPLETE trial

Inclusion	Exclusion
Men and women within 72 hours after successful PCI to culprit lesion for STEMI.	Intent to revascularise non-culprit lesion(s) irrespective of randomised allocation.
Multivessel disease defined as at least 1 additional non-infract related coronary artery lesion that meets the following criteria: a) ≥2.5 mm in diameter that has not been stented as part of the index PCI b) is amenable to successful treatment with PCI c) ≥70% diameter stenosis by visual estimation or 50-69% diameter stenosis by visual estimation plus FFR ≤0.80.	Planned surgical revascularisation.
	Non cardiovascular co-morbidity reducing life expectancy to less than 5 years.
	Any other medical, geographic, or social factor making study participation impractical or precluding 5 year follow-up.
	Prior CABG surgery.

CABG coronary artery bypass grafting, COMPLETE Complete versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early Percutaneous Coronary Intervention for STEMI, FFR fractional flow reserve, PCI percutaneous coronary intervention, STEMI ST-segment elevation myocardial infarction.

driven revascularisation) was significantly lower in the complete-revascularisation group than in the culprit lesion only PCI group, occurring in 179 patients (8.9%) in the complete-revascularisation group as compared with 339 patients (16.7%) in the culprit-lesion only PCI (hazard ratio, 0.51; 95% CI, 0.43 to 0.61; P<0.001).

The risk of adverse events (including stroke, major bleeding, and acute kidney injury) was similar in the two groups indicating no major safety concerns from an additional PCI procedure.

Discussion

The COMPLETE trial showed the benefits of complete revascularisation (i.e. culprit and non-culprit lesions) on cardiovascular outcomes in patients with STEMI and multivessel disease (9). The main benefit shown by COMPLETE revascularisation were reductions in new MI or ischaemia driven revascularisation with no differences in death (cardiovascular or all cause). These results suggest that patients with significant bystander coronary artery disease should have their non-culprit lesions treated to reduce the risk of future MI and future revascularisation. The data confirms what has been suggested in previous trials which were smaller and unable to give definitive results that this strategy leads to a clinical benefit (6-8, 11). Currently the American College of Cardiology guidelines (12) and the European Society of Cardiology guidelines (13, 14) have a class IIb recommendation for the treatment of non-culprit lesions. The COMPLETE trial was a large and positive trial but there are a few limitations that should be considered before interventionalists change their clinical practice based on these results.

Limitations

In the COMPLETE trial, patients who were already planned to have revascularisation of non-culprit lesions were excluded from the trial. That means that there was a selection bias for patients included into the trial. In addition, the total number of patients included was just over 4000 which seems low considering patients were selected from 140 centres over 4 years. There has been no indication of what proportion of STEMI patients with multivessel disease were included. The question remains as to how representative is the trial of real-world patients if patients were preselected.

In addition, there were no patients in the trial with cardiogenic shock and patients had a low average SYNTAX score, giving an increased chance of successful revascularisation. More complex non-culprit lesions which are associated with higher SYNTAX scores may be more challenging to treat successfully and therefore could lead to higher rates of adverse outcomes (15).

Timing of intervention

Two thirds of patients in the COMPLETE trial had deferred revascularisation of non-culprit lesions. The benefit of complete revascularisation was similar whether non-culprit PCI was conducted early (median of one day during the index hospitalisation) or several weeks following hospital discharge. One of the possible reasons for this is because the benefit of complete revascularisation seems to emerge over long term as shown by the survival curves diverging at 1 year (for the first coprimary endpoint) and continuing to separate at 4 years (9). Most early events after STEMI are likely due to the underlying severity of the index infarction itself, rather than the non-culprit lesion. Being able to bring patients back for their non-culprit PCI allows patients time to recover physically and psychologically from their STEMI (16). Furthermore, it allows patients an early discharge from hospital, which is both good for patients and also reduces burden on hospitals, critically important in the current NHS climate.

Use of FFR

Another aspect to consider in the COMPLETE trial was the use of FFR to guide treatment of non-culprit lesions. A recent meta-analysis demonstrated that FFR-guided PCI of non-culprit arteries along with primary PCI was associated with lower rate of major adverse cardiovascular events compared with PCI of only the culprit artery in patients with STEMI and multivessel disease (17). The meta-analysis suggested that the difference was driven by lower rate of repeat revascularisation in FFR-guided PCI of the non-culprit group. In the COMPLETE trial, almost all non-culprit lesions were treated on the basis of angiographic findings, but 60% of the lesions had at least 80% stenosis of the vessel diameter on visual estimation. Thus, most lesions were angiographically significant and only 1% of lesions were guided by FFR. The COMPLETE trial therefore does not add significantly add to what we already know about the use of FFR in multivessel coronary disease in the context of STEMI but suggests that FFR may still have an important role in diagnosing lesions of intermediate severity and should be used if available.

Use of Clopidogrel

A further point to consider was the use of Clopidogrel. In the COMPLETE trial a quarter of patients received Clopidogrel which has been shown to be inferior to Ticagrelor for the treatment of STEMI (18). Patients who did not have complete revascularisation and were treated with Clopidogrel (rather than Ticagrelor) were more likely to have increased risk of future adverse outcomes.

Conclusions

In the COMPLETE trial, a strategy of complete revascularisation was superior to culprit lesion only PCI in reducing the composite risk of cardiovascular death or myocardial infarction, as well as the composite risk of cardiovascular death, myocardial infarction, or ischemia-driven revascularisation. The reduction in coprimary outcomes were driven by reductions in recurrent MI and revascularisation. Given the evidence for benefit and no signals of harm, it appears to be appropriate to recommend complete revascularisation for patients similar to those included in the COMPLETE trial. Such revascularisation can be safely deferred following hospital discharge. Further studies are needed to reproduce these findings and longer follow up to evaluate whether the tendency toward a small reduction in all-cause mortality becomes significant over time.

Disclosures

None.

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