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FFR-guided multivessel stenting reduces urgent revascularization compared with infarct-related artery only stenting in ST-elevation myocardial infarction: A meta-analysis of randomized controlled trials[☆]

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Abstract

Background—Randomized controlled trials (RCTs) have shown fractional flow reserve-guided (FFR) multivessel stenting to be superior to infarct-related artery (IRA) only stenting in patients with ST-elevation myocardial infarction (STEMI) and multivessel disease. This effect was mainly driven by a reduction in overall repeat revascularization. However, the ability to assess the effect of this strategy on urgent revascularization or reinfarction was underpowered in individual trials.

Methods—We searched Pubmed, EMBASE, Cochrane CENTRAL, and Web of Science for RCTs of FFR-guided multivessel stenting versus IRA-only stenting in STEMI with multivessel disease. The outcomes of interest were death, reinfarction, urgent, and non-urgent repeat

[☆]All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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revascularization. Risk ratios (RR) were pooled using the DerSimonian and Laird random-effects model.

Results—After review of 786 citations, 2 RCTs were included. The pooled results demonstrated a significant reduction in the composite of death, reinfarction, or revascularization in the FFR-guided multivessel stenting group versus IRA-only stenting group (RR [95% Confidence Interval]: 0.49 [0.33–0.72], $p < 0.001$). This risk reduction was driven mainly by a reduction in repeat revascularization, both urgent (0.41 [0.24–0.71], $p = 0.002$) and non-urgent revascularization (0.31 [0.19–0.50], $p < 0.001$). Pooled RR for reinfarction was lower in the FFR-guided strategy, but was not statistically significant (0.71 [0.39–1.31], $p = 0.28$).

Conclusions—This systematic review and meta-analysis suggests that a strategy of FFR-guided multivessel stenting in STEMI patients reduces not only overall repeat revascularization but also urgent revascularization. The effect on reinfarction needs to be evaluated in larger trials.

Keywords

FFR; Multivessel; PCI; Stenting; STEMI; Meta-analysis

1. Introduction

Approximately 50% of patients with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) have multivessel disease with involvement of non-infarct related artery (IRA) [1]. Several randomized controlled trials (RCTs) have evaluated the efficacy and safety of PCI of angiographically severe non-culprit lesion(s) either during the index procedure or as a staged procedure [2–5]. Previous synthesis of evidence from these trials demonstrated that multivessel PCI, whether at the time of the index procedure or staged, leads to a reduction in the composite of death, reinfarction, or repeat revascularizations compared with IRA-only PCI [6,7]. These results were mainly driven by a reduction in repeat revascularizations without a significant reduction in death or reinfarction [6,7]. Additionally, angiographic severity may not reliably estimate the functional significance of a lesion [8]. As FFR-guided PCI has been shown to be superior to medical therapy alone in stable coronary disease to reduce urgent revascularizations [9,10], it was postulated that FFR-guided multivessel PCI in STEMI might reduce urgent revascularizations compared with IRA-only PCI.

A recently published RCT (Compare-Acute) investigated FFR-guided multivessel PCI versus IRA-only PCI in 885 STEMI patients with multivessel disease who underwent primary PCI [11]. It showed that FFR-guided complete revascularization led to a reduction in the composite endpoint of death, reinfarction, revascularization, or stroke that was mainly supported by a reduction in repeat revascularizations. The reinfarction rate was 50% lower with an FFR-guided strategy; however, this difference did not reach statistical significance (FFR-guided multivessel PCI versus IRA-only PCI: 2.4% versus 4.7% at 1 year, $p = 0.10$). We hypothesized that these results may be due to a relatively modest sample size and low statistical power. Therefore, we conducted a systematic review to identify RCTs comparing FFR-guided multivessel PCI versus IRA-only PCI in patients with STEMI and multivessel disease, with the goal that pooling these RCTs will result in an increase of power to

investigate the effect on outcomes — especially the risk of urgent revascularization and reinfarction.

2. Methods

2.1. Search strategy

We carried out a systematic search of published RCTs using Pubmed, EMBASE, Cochrane CENTRAL, and Web of Science from inception to March 2017. We used free text and MeSH terms to represent myocardial infarction, PCI, FFR, and multivessel disease. The studies of interest were RCTs evaluating FFR-guided multivessel stenting versus IRA-only stenting in STEMI with multivessel disease. The study quality was assessed using the Cochrane Collaboration's risk of bias in RCTs [12].

2.2. Data synthesis and statistical analysis

Two reviewers (A.G. and N.S.B.) independently extracted data from the included studies. The outcomes of interest were death, reinfarction, and repeat revascularizations, both urgent and non-urgent, and a composite of these outcomes. The composite endpoint of death, reinfarction, or repeat revascularization in the Compare-Acute Trial was calculated by excluding stroke events (4 events) from the reported composite endpoint of death, reinfarction, repeat revascularization, or stroke. Risk ratios (RR) were pooled using the DerSimonian and Laird random-effects model using STATA version 14.2.

We also evaluated the power of the Compare-Acute Trial to detect a significant difference for a composite of death or reinfarction between the two strategies of FFR-guided multivessel PCI or IRA-only PCI. Power at 1-year follow-up was calculated for a log-rank test based on the reported trial characteristics with an observed annual event rate of 3.7% in the FFR-guided strategy and 6.4% in the IRA-only strategy in 885 patients with 2:1 randomization, 0.5% observed dropout rate (4/885). For subsequent follow-up years, a dropout rate of 5% was assumed. Power analysis was done using SAS version 9.4.

3. Results

3.1. Study selection

We retrieved 786 records in addition to the recently published Compare-Acute Trial [11]. After removing duplicates and screening based on title and abstracts, four full-text articles were examined that evaluated FFR-guided multivessel PCI versus IRA-only PCI in STEMI with multivessel disease — two were short-term and long-term follow-ups of the same RCT by Dambrink et al. [13,14], and the other two RCTs were Compare-Acute and DANAMI-3-PRIMULTI trials [11,15]. The Dambrink et al. study was a small RCT of 121 patients with enrollment of only 40% of the target sample size and no publication of a clinical trial design paper to our knowledge. The study was deemed of low quality for the purpose of this meta-analysis (Cochrane's risk of reporting bias = High) and thus was excluded. Finally, two trials, DANAMI-3-PRIMULTI and Compare-Acute, were included in the meta-analysis.

3.2. Characteristics of included studies

Both the DANAMI-3-PRIMULTI and Compare-Acute trials were contemporary RCTs utilizing drug-eluting stenting predominantly (Table 1). Although both trials were multicenter, DANAMI-3-PRIMULTI was done in two university hospitals in Denmark whereas the Compare-Acute Trial involved 24 participating sites across Europe and Asia. In both trials, the ischemic FFR threshold was 0.80. In DANAMI-3-PRIMULTI, multivessel PCI of the non-IRA vessel(s) was performed 2 days after the index procedure but prior to discharge. In the Compare-Acute Trial, multivessel PCI of non-IRA vessel(s) was performed at the time of the index procedure in most of the patients. Patient characteristics in both trials were similar with enrollment of predominantly middle-aged white men with a high burden of cardiovascular risk factors (Table 1).

3.3. Pooled results

The pooled results demonstrated a significant reduction in the composite of death, reinfarction, and revascularization in the FFR-guided multivessel PCI group versus IRA-only PCI group (RR [95% Confidence Interval (CI)]: 0.49 [0.33–0.72], $p < 0.001$), Fig. 1A. This risk reduction in the composite endpoint was driven mainly by a reduction in repeat revascularization, both urgent (RR [95% CI]: 0.41 [0.24–0.71], $p = 0.002$) and non-urgent revascularization (RR [95% CI]: 0.31 [0.19–0.50], $p < 0.001$). Pooled RR for reinfarction was lower in the FFR-guided strategy, but the difference was not statistically significant (RR [95% CI]: 0.71 [0.39–1.31], $p = 0.28$).

3.4. Power analysis

Based on the reported trial characteristics of the Compare-Acute Trial, there was only 38% power to detect a significant difference in the composite of death or reinfarction at 1-year follow-up, Fig. 1B. The estimated length of follow-up time in Compare-Acute Trial to reach 80% or 90% power for the composite endpoint of death or reinfarction is 3.3 years and 4.7 years, respectively.

4. Discussion

In this systematic review and meta-analysis, we found that a strategy of FFR-guided multivessel PCI was superior to IRA-only PCI in patients with STEMI and multivessel disease for reducing the composite endpoint of death, reinfarction, or repeat revascularization. This risk reduction was mainly driven by a reduction in repeat revascularization, as was also found in the included individual RCTs as well. However, reduction in repeat revascularization is sometimes considered a “soft” end-point. Therefore, the main argument in favor of multivessel PCI at the time of STEMI that could be made based on current evidence from RCTs had been that in relatively stable STEMI patients with multivessel disease, performing multivessel PCI at the time of the index procedure would save the patient another cardiac catheterization in the future. The results of this meta-analysis, however, suggest that FFR-guided multivessel PCI may lead to a reduction specifically in the risk of urgent revascularization, a more important or “harder” endpoint from both the patient and physician perspectives.

Our meta-analysis also showed a lower point estimate for the risk of reinfarction with FFR-guided multivessel PCI, however, the confidence intervals remained wide and this difference was not statistically significant. Therefore, it remains unclear if there is a true lack of biologic effect of FFR-guided multivessel stenting on reinfarction risk versus an issue of statistical power in these modest-size trials. Our power estimates show that, at the current event rates, it would take over three years of follow-up of Compare-Acute Trial to reach 80% power to detect a significant difference between the two arms for the endpoint of death or reinfarction, though if the potential benefits occur relatively early after PCI, only a much larger trial would resolve the issue. The ongoing Ffr-gUidance for compLete Non-cuLprit REVAScularization (FULL REVASC, NCT02862119), and Complete vs Culprit-only Revascularization to Treat Multi-vessel Disease After Primary PCI for STEMI (COMPLETE, NCT01740479) trials are powered for the endpoint of death or reinfarction and will shed further light on this issue.

4.1. Limitations

As a meta-analysis of published literature, our study has inherent limitations with regards to the differences in trial design and outcome definitions in individual trials. We did not have access to patient-level data. In addition, the two trials had differences in the timing of FFR measurement with FFR performed at the time of primary PCI in the Compare-Acute Trial versus performed two days later in the DANAMI-3-PRIMULTI trial. FFR at the time of primary PCI can be potentially affected by transient microcirculatory changes in the non-IRA territory in the setting of acute coronary syndromes [16]. However, a clinical study evaluating FFR values in non-IRA territories at the time of primary PCI versus 6 weeks later found no significant differences in the FFR values between the two time-points [17]. Therefore, the clinical impact of a two-day difference in the timing of FFR measurement in the two trials is likely minimal [18]. Furthermore, the instantaneous wave-free ratio (iFR) merits study in this setting [19].

5. Conclusion

In this systematic review and meta-analysis, we provide evidence to support that a strategy of FFR-guided multivessel stenting in STEMI patients reduces not only overall repeat revascularizations but also urgent revascularizations. Whether the benefit provided by FFR-guided multivessel stenting would translate into a reduction in reinfarction or mortality remains to be established. A longer follow-up of the Compare-Acute Trial at the predefined 36 months of follow-up duration [11,20] and the ongoing FULL REVASC (NCT02862119) and COMPLETE (NCT01740479) trials will shed light on the effect of an FFR-guided multivessel PCI strategy on the rates of death or reinfarction.

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Fig. 1.

A) The top panel shows pooled effect estimates for randomized controlled trials of an FFR-guided multivessel PCI strategy versus IRA-only strategy. It demonstrates a reduction in the composite of death, reinfarction, or revascularization with an FFR-guided complete revascularization strategy. The reduction in the endpoint was mainly driven by a reduction in not only overall repeat revascularization but also specifically urgent revascularization. B) The bottom panel shows estimated power of the Compare-Acute Trial [11] with years of follow-up to detect a significant difference for a composite of death or reinfarction between the two strategies of FFR-guided multivessel PCI or IRA-only PCI. Power at 1-year follow-up was calculated for a log-rank test based on the reported trial characteristics with an observed annual event rate of 3.7% in the FFR-guided strategy and 6.4% in the IRA-only strategy in 885 patients with 2:1 randomization and a 0.5% observed dropout rate (4/885). For subsequent follow-up years, a dropout rate of 5% was assumed. The vertical dashed lines indicate the estimated length of follow-up of the Compare-Acute Trial to reach 80% or 90% power for the composite endpoint of death or reinfarction (3.3 years and 4.7 years, respectively). FFR, fractional flow reserve; IRA, infarct-related artery; MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention.

Table 1

Trial and patient characteristics of included studies.

	DANAMI-3-PRIMULTI, 2015 [15] (N = 627)	Compare-Acute, 2017 [11] (N = 885)
<i>Trial characteristics</i>		
Randomization	1:1 (314 FFR-guided; 313 IRA-only)	2:1 (295 FFR-guided; 590 IRA-only)
Trial sites	2 university hospitals in Denmark	24 participating centers in Europe/Asia
FFR		
Ischemic threshold	0.80	0.80
FFR in IRA-only group	No	Yes (patients and referring cardiologists were blinded to FFR results)
Non-culprit PCI		
Timing	2 days after the initial PCI procedure before discharge	83.4% during index procedure; 16.6% before discharge (mean = 2.1 days)
Number of stents per patient in multivessel PCI group	2 (Median)	1.6 (Mean)
Drug eluting stent	93.8%	97.6%
Follow-up, months	12–44 (Median = 27)	12
Reinfarction		
Definition	Typical chest pain accompanied by a substantial rise in troponins, development of new Q-waves on the electrocardiograph, or both	<i>Peri-procedural:</i> 2–5 times rise in CK-MB above upper limit of normal <i>Spontaneous:</i> Rise and fall of troponin or CK-MB with ischemic symptoms or ST changes or new pathologic Q waves
Periprocedural	2 (0.3%)	13 (1.5%)
Spontaneous	29 (4.6%)	22 (2.5%)
Repeat revascularizations		
Definition	Ischemia-driven (subjective or objective) revascularization of lesions in non-infarct related arteries	Repeat revascularizations except clinically indicated elective revascularizations within 45 days after primary PCI in IRA-only PCI arm
<i>Patient characteristics</i>		
Age, years	64 (Median)	61 (Mean)
Males	81%	77%
Diabetes	11%	15%
Hypertension	44%	47%
Current smoker	50%	46%
Previous myocardial infarction	7%	8%
Three-vessel disease	31%	32%
Anterior infarct	35%	35%

FFR, fractional flow reserve; IRA, infarct-related artery; PCI, percutaneous coronary intervention.