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FFR-Guided PCI VS CABG for Multivessel Coronary Artery Disease: Lessons from FAME 3

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Take Home Messages

- FAME 3 is a randomised controlled trial which compared FFR-guided PCI to CABG for multi vessel coronary artery disease.
- FFR-guided PCI failed to achieve non-inferiority to CABG surgery in managing multivessel CAD (primary endpoint was major adverse cardiac and cerebrovascular events).
- The previous FAME trial proved that FFR-guided PCI was associated with better outcomes compared to angiography-guided PCI in management of multivessel CAD.
- The study limitations include a short follow-up period, lack of diversity (in terms of sex and ethnicity), exclusion of patients with acute MI, and limited use of other modalities like IVUS which can improve precision and outcomes of PCI in general.

Introduction

Fractional flow reserve (FFR) has now become widely used in percutaneous coronary intervention (PCI) as it gives more accurate information about the physiological significance of the coronary lesions (1). Studied in the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) trial (2), FFR-guided PCI was proven to have better outcomes than angiography-guided PCI for managing multivessel coronary artery disease (CAD) (2). Subsequently, the FAME 3 trial was conducted to assess the non-inferiority of FFR-guided PCI to coronary artery bypass graft (CABG) surgery in the management of multivessel CAD (3).

FAME 3 study design

FAME 3 trial was an investigator-initiated, multicentre, international, randomised controlled trial, conducted at 48 sites with 1, 6 and 12-months follow-up (3). Patients' randomisation and characteristics are summarised in **Table 1**. All patients were preloaded with aspirin and high-dose statin, while for the PCI group a second antiplatelet agent was added for at least 6 months. FFR cut off for PCI was <0.8 and polymer zotarolimus-eluting stents were used. The primary endpoint of the study was the major adverse cardiovascular and cerebrovascular event (MACE), which included death, myocardial infarction (MI), stroke and repeat revascularisation. Inclusion and exclusion criteria are summarised in **Table 2**.

About the author

Mohammed Ahmed is currently working as an ST4 cardiology registrar at the Grange University hospital. He graduated from Elgezira University, Sudan and finished his internship in Sudan. He has completed four years of training in internal medicine and was awarded an MD in internal medicine from Sudan medical specialization board. He plans to pursue subspecialty training in interventional cardiology.

Table 1. Patient baseline characteristics from the FAME 3 trial		
	FFR guided PCI	**CABG**
Number of patients	757	747
Number of stents	3.7 ± 1.9	NA
Number of anastomoses	NA	3.4 ± 1
Age (years)	65.2 ± 8.6	65.1 ± 8.3
Male sex %	81.4	83.3
Diabetes %	28.3	28.8
Low ejection fraction[a] %	18.2	17.7
Syntax score	26 ± 7.1	25.8 ± 7.1

Values expressed as frequency, mean±standard deviation or percentage.
FAME3 = Fractional Flow Reserve Versus Angiography for Multivessel Evaluation 3; SYNTAX = Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.
[a] defined as ≤50%.

Table 2. Inclusion and exclusion criteria	
Inclusion Criteria	**Exclusion criteria**
• Three vessel CAD, defined as ≥ 50% diameter stenosis by visual estimation and amenable to revascularisation by both PCI and CABG • Angina and/or evidence of myocardial ischemia	• Cardiogenic shock and/or need for haemodynamic/mechanical support • Recent STEMI (< 2 years) • Ongoing Non-STEMI with rising biomarkers • Left main disease requiring revascularisation • >1 major chronically occluded epicardial vessel

CABG = Coronary artery bypass graft; CAD = coronary artery disease; PCI = percutaneous coronary intervention; STEMI = ST elevation myocardial infarction.

FAME 3 Results

At one year, the incidence of the primary endpoint was 10.6% in the FFR-guided PCI group compared to 6.9% in the CABG group (hazard ratio, 1.5; 95% confidence interval, 1.1 to 2.2; P=0.35 for noninferiority).

The secondary endpoints, death, MI, repeat revascularization and stroke, were more common in the PCI group compared to the CABG group (1.6% vs 0.9%, 5.2% vs 3.5%, 5.9% vs 3.9% and 1.1% vs 0.9% respectively). However, the safety endpoints which included Bleeding Academic Research Consortium type 3–5, acute kidney injury, rehospitalisation, development of atrial fibrillation and arrhythmias, were all higher in the CABG group.

Discussion

The FAME 3 Trial failed to show non-inferiority of FFR-guided PCI to CABG in managing multivessel CAD(3). The patient numbers and characteristics were well matched in both trial arms. However, the trial had its limitations. The follow up period was limited to one year which might affect late outcomes assessment. Patients with acute MI, ongoing non-STEMI and EF< 30% were excluded which means those patients who were randomised were relatively stable and fewer procedural complications are expected. In contrast to other trials comparing PCI to CABG, such as the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) (4) and Nordic-Baltic-British left main revascularisation study (NOBLE) (5), FAME 3 trial excluded patients with left main stem (LMS) disease (4). Therefore, the outcomes of FFR-guided PCI in patients with LMS disease was not assessed in this trial.

Table 3. Comparison between the outcome of FAME 3 and SYNTAX trial

	FAME 3	SYNTAX
Number of patients	1500	1800
Number of stents	3.7	4.6
Repeat revascularisation (%)	4.9	13.9
Mortality (%)	1.6	4.4
MACCE among CABG group	6.9	12.4
Medical therapy: **- Statins %** **- β-blockers %**	 94 83	 70 75

CABG = coronary artery bypass graft; MACCE = Major Adverse Cardiac and Cerebrovascular Events.

While patients had an average of 4.3 lesions, and average of 3.7 +/- 1.9 stents, it was not clear if complete revascularisation was actually achieved. The COMPLETE trial showed that complete inpatient or staged revascularization was superior to treating the culprit lesion only with less incidence of death from cardiovascular causes or new MI (6). This might have affected the result among the PCI group. Furthermore, it appears that 24% of patients with a negative FFR still went on to have PCI. This might have influenced the results, and led to inappropriately higher complications rate in patients where intervention may not have been indicated.

While FFR was measured in only 60% post-PCI with an average of 0.88, it is worth noting that FFR was not measured pre-PCI in about one quarter of cases mainly due to total or subtotal occlusion. Other possible reasons for deviation from protocol were not stated. Intravascular imaging (not specified) was used in only 12% of the cases and the percentage of stenoses requiring revascularisation was assessed visually regardless of evidence from the REACT study which found that the use of IVUS-guided post-PCI optimisation significantly improved post-PCI FFR (7).

It is relevant to compare the results of the FAME 3 study with the SYNTAX study which was carried out more than a decade ago and compared angiographically-guided PCI to CABG for multivessel or LMS CAD. FAME 3 demonstrated better outcomes among the PCI cohort than the SYNTAX study, as outlined in **Table 3**. This could be attributed to more effective medical therapy in FAME 3 trial with more than 80% of the patients using statins and beta-blockers (8).

Conclusion

In the FAME 3 trial FFR guided PCI failed to meet non-inferiority compared to CABG surgery in multivessel CAD. FAME 3 was a high-quality randomized trial and reflected the previous evidence of better outcome of FFR guided PCI over angiography guided PCI. The trial has some limitations such as lack of diversity and short follow up duration, however extended three and five years follow up is ongoing and might change the outcome particularly in terms of late MI and repeat revascularization.

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