

REVIEW

The Aftermath of a Negative Third FAME

Dimitrios Oikonomou, MD, Catherine Liontou, MD, Konstantinos Triantafyllou, MD*

First Department of Cardiology, Evangelismos General Hospital, Athens, Greece

* Email: kontriad@gmail.com

Abstract

The current guideline recommendations regarding myocardial revascularization of patients with multivessel coronary artery disease (CAD) mostly advocate coronary artery bypass grafting (CABG) over percutaneous coronary intervention (PCI), especially for patients with diabetes. However, in certain clinical cases, PCI can be considered. FAME and FAME 2 studies had demonstrated the superiority of functional flow reserve (FFR)-guided PCI over angiography-guided PCI and over optimal medical therapy (OMT) alone respectively. FAME 3 study (Fractional Flow Reserve versus Angiography for Multivessel Evaluation), published early in 2022, was a study that investigated how PCI guided by FFR measurements can perform compared to CABG guided mostly by coronary angiography for the revascularization of patients with three-vessel CAD. Stable patients with an average SYNTAX score of 26 were randomized, while patients with left main disease, recent ST segment elevation myocardial infarction (STEMI), left ventricular ejection fraction <30% or cardiogenic shock were excluded. Regarding the composite primary endpoint of major adverse cardiovascular events (MACE), including death, non-fatal myocardial infarction, stroke or repeat revascularization, at 1 year follow-up, FFR-guided PCI failed to be proven as non-inferior compared to CABG. The findings of FAME 3 as added to those of FAME and FAME 2 should be considered in the context of current guidelines for myocardial revascularization and do not seem practice changing. Relevant limitations, possible implications and future perspectives are also briefly discussed herein. *Rhythm* 2022;17(2): 32-35.

Key words: fractional flow reserve; revascularization; multivessel coronary artery disease

Abbreviations: CABG: coronary artery bypass grafting; CAD: coronary artery disease; DM: diabetes mellitus; MACE: major adverse cardiovascular events; OMT: optimal medical treatment; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction

Running (brief) title: FAME 3 and revascularization implications.

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Introduction

Randomized trials have shown better outcomes with coronary artery bypass grafting (CABG) over

percutaneous coronary intervention (PCI) among patients with higher coronary artery disease (CAD) burden and lesion complexity, and also in the presence of diabetes mellitus.^{1,2} The European Society of Cardiology (ESC) guideline recommendations for the mode of myocardial revascularization according to CAD severity as published in 2014 (around the time period of conception of FAME 3) and as updated in their 2018 version are summarized in **Table 1**.^{3,4} Those recommendations have been clearly in favor of CABG over PCI for patients with left main or multivessel CAD and SYNTAX score > 22, while PCI could be proposed as a reliable treatment solution in the following scenarios:

- Significant stenoses in one or two coronary arteries with or without implication of the proximal left anterior descending (LAD)
- Left main significant stenosis with a SYNTAX score ≤ 22
- Significant three-vessel CAD with a SYNTAX score ≤ 22

However, for patients with diabetes and three-vessel CAD and a SYNTAX score ≤ 22, the recommendation for PCI was downgraded from 2014 to 2018 guidelines from IIa – B to IIb – A, which means that for this category of patients CABG should be preferred (indication I – A).

FAME and FAME 2

The FAME and FAME 2 studies had demonstrated the superiority of PCI guided by FFR versus conventional angiography-guided PCI (FAME) and versus optimal medical treatment (OMT) alone (FAME 2).^{5,6}

FAME randomized 1050 patients with multivessel CAD to FFR-guided PCI versus traditional angiography-guided PCI. Regarding the primary endpoint which was the composite of death, non-fatal myocardial infarction or repeat revascularization FFR-guided PCI was superior regarding the abovementioned composite of major adverse cardiovascular events (MACE) at 1 year (13.2% vs 18.3%, HR 0.72) and at 5 years (28% vs 31%, HR 0.91).^{5,7} A strategy of FFR-guided PCI resulted in a significant decrease of MACE for up to 2 years after the index procedure. From 2 years to 5 years, the risks for both groups developed similarly. These clinical outcomes in the FFR-guided group were achieved with a lower number of stented arteries and less resource use. Those results suggested that FFR guidance of multivessel PCI should be the standard of care in most patients.⁷

FAME 2 randomized 1120 patients with CAD to FFR-guided PCI versus OMT alone having as primary endpoint the composite of death, non-fatal myocardial infarction or urgent revascularization. At 1 year FFR-guided PCI was largely superior with far less MACE (4.3% vs 12.7%, HR 0.32).⁶ At 3 years MACE were also significantly fewer in

the FFR-guide PCI group compared with the OMT group (10.1% versus 22.0%), primarily as a result of a lower rate of urgent revascularization (4.3% versus 17.2%).⁸

Table 1. ESC 2014 & 2018 guidelines for the type of revascularization (CABG or PCI) in patients with stable CAD with suitable coronary anatomy for both procedures and low predicted surgical mortality (period of conception of FAME 3)

Recommendations per extent of CAD CABG vs PCI	2014 ESC Guidelines		2018 ESC Guidelines	
	CABG Class - LOE	PCI Class - -LOE	CABG Class - LOE	PCI Class - -LOE
1VD without proximal LAD stenosis	Ib - C	I - C	Ib - C	I - C
1VD with proximal LAD stenosis	I - A	I - A	I - A	I - A
2VD without proximal LAD stenosis	Ib - C	I - C	Ib - C	I - C
2VD with proximal LAD stenosis	I - B	I - C	I - B	I - C
Left main disease with a SYNTAX score ≤22	I - B	I - B	I - A	I - A
Left main disease with a SYNTAX score 23–32.	I - B	Ia - B	I - A	Ia - A
Left main disease with a SYNTAX score >32.	I - B	III - B	I - A	III - B
3VD with a SYNTAX score ≤22	I - A	I - B	I - A	?DM status
3VD with a SYNTAX score 23–32	I - A	III - B	I - A	III - A
3VD with a SYNTAX score >32	I - A	III - B	I - A	III - A
3VD without DM* with SYNTAX score ≤22	I - A	I - B	I - A	I - A
3VD without DM* with SYNTAX score >22	I - A	III - B	I - A	III - A
3VD with DM* with SYNTAX score ≤22	I - A	Ia - B	I - A	Ib - A
3VD with DM* with SYNTAX score >22	I - A	III - B	I - A	III - A

CABG = coronary artery bypass grafting; DM = diabetes mellitus; ESC = European Society of Cardiology; LAD = left anterior descending; LOE = level of evidence; PCI = percutaneous coronary intervention; 1VD = one-vessel (coronary) disease; 2VD = two-vessel disease; 3VD = three-vessel disease

These two studies had determined the place held by FFR in the 2014 and the last 2018 myocardial revascularization guidelines (Table 2).^{3,4}

FAME 3: Study Design and Results

The international, multicenter FAME 3 trial has enriched the FAME studies program having as objective to compare and possibly demonstrate non-inferiority of FFR-

guided PCI versus CABG for patients with three-vessel CAD that would be technically eligible for both.⁹ Thus 1500 such patients were randomized between the two strategies (having excluded patients with recent ST-segment elevation myocardial infarction (STEMI), left main disease, left ventricular ejection fraction <30% or cardiogenic shock) and their outcomes compared, having as primary end-point the composite of death, non-fatal myocardial infarction, stroke or repeat revascularization at 1 year follow-up. Noninferiority of FFR-guided PCI to CABG was prespecified as an upper boundary of less than 1.65 for the 95% confidence interval of the hazard ratio. The patients in the CABG arm were supposed to receive preferentially arterial grafts, while assessment of the FFR to guide CABG was not mandated, but if it was performed at the time of the diagnostic coronary angiogram the information could be used to define surgical targets. Patients in the FFR-guided PCI arm were supposed to receive second generation drug-eluting stents with zotarolimus (Resolute Integrity or Resolute Onyx) with a dual antiplatelet therapy duration for at least 6 months. The protocol specified that only stenoses with an FFR ≤ 0.80 were to be treated with PCI, while intravascular imaging was performed as deemed necessary by the treating physicians.

Table 2. FAME Studies

Year	Study	Recommendation	Class / LOE
2009	FAME	FFR to identify hemodynamically relevant coronary lesion(s) in stable patients when evidence of ischemia is not available	I - A
2012	FAME 2	FFR-guided PCI should be considered in patients with multi-vessel CAD undergoing PCI	Ia - B
2022	FAME 3	FFR-guided PCI for relatively stable patients with 3-vessel CAD (without left main involvement or recent STEMI) is inferior and is not preferred compared to CABG	?(Iib-B)

CABG = coronary artery bypass grafting; CAD = coronary artery disease; FFR = fractional flow reserve; LOE = level of evidence; PCI = percutaneous coronary intervention;

Patients included were on average 65-year-old, the percentage of diabetics among them was 29% and were admitted for an acute coronary syndrome (but not STEMI) in 40% of cases. At least one vessel with chronic total occlusion was met in 22% of the patients and at least one bifurcation lesion in 68% among them. The average SYNTAX score was 26 (33% of patients had < 23, 49% between 22 and 32 and the remaining 18% had >33). The average number of significant coronary lesions to be

treated was 4.2 - 4.3 for both groups. In the FFR-guided PCI group 82% of the lesions were evaluated with FFR (which could not be measured for lesions with subtotal or total occlusion) and the average measurement was 0.70, while 24% of the lesions “interrogated” by pressure wire before treatment had a measured FFR > 0.80. Patients assigned to undergo PCI received a mean of 3.7 stents with median stented length of 80mm and intravascular imaging guidance in only 12% of cases. In the CABG group the average number of anastomosed grafts was 3.4, FFR during coronary angiogram to determine appropriate target lesions was used in 10% and the left internal mammary artery was utilized in 97% of cases. A quarter of CABG treated patients had multiple arterial grafts and also a quarter had CABG without extracorporeal circulation.

The results regarding the primary endpoint at 1 year demonstrated that FFR-guided PCI compared to CABG was related to more MACE (10.6% versus 6.9%, HR: 1.5, CI 95%: 1.1-2.2) and thus failed to reach the non-inferiority criterion ($p=0.35$). There was no clear evidence of between-group differences in the incidence of each individual component of the primary end-point or the composite of death, myocardial infarction, or stroke. The incidence of death, myocardial infarction, or stroke was 7.3% in the FFR-guided PCI group and 5.2% in the CABG group (HR: 1.4; 95% CI: 0.9 to 2.1). Repeat revascularization was deemed necessary in 5.9% in the PCI versus 3.9% in the CABG arm (HR: 1.5, 95% CI: 0.9-2.1). The incidences of major bleeding (BARC 3-5), arrhythmia (mainly atrial fibrillation) and acute kidney injury were significantly higher in the CABG group than in the FFR-guided PCI group. Finally, the median duration of hospitalization was almost 4 times longer (11 days versus 3 days in the PCI group) and the need for repeat hospitalization twice as likely within 30 days after CABG (10.2% versus 5.5% after PCI).⁹

FAME 3: Considerations and Implications

As a measure of the pressure gradient across a coronary lesion, FFR is most of the time technically simple to assess, and FAME study has shown better outcomes when PCI is guided by FFR than when it is guided by angiography alone.⁵ However FFR is still used infrequently in everyday practice, while its value has been challenged in recent studies.¹⁰⁻¹² The FLOWER-MI study demonstrated that among patients with STEMI undergoing complete revascularization, an FFR-guided strategy did not have a significant benefit over an angiography-guided strategy with respect to the risk of death, myocardial infarction, or urgent revascularization at 1 year.¹¹ In the FUTURE study among patients with multivessel CAD there was no evidence that an FFR-guided treatment strategy reduced the risk of ischemic cardiovascular events

or death at 1-year follow-up.¹² Moreover, it has not been clear whether FFR guidance might make PCI a reasonable alternative to CABG for patients with multivessel CAD, a question that FAME 3 tried to answer with the abovementioned mostly negative and disappointing, but not incomprehensible results.

Many limitations of FAME 3 are to be noted. The patients were highly selected since those with left main disease or recent STEMI were excluded and the lesions to be treated with PCI were supposed to also be “crossable” with the FFR guidewire. Thus, these results cannot be considered as applicable to all comer patients with multivessel CAD, but on the other hand FFR-guided PCI logically could not be expected to have better results over CABG among patients with multivessel CAD and even more complex anatomy than patients included in FAME 3. It should be emphasized that most of FAME 3 study patients had quite advanced CAD, since only 1 out of 3 had a SYNTAX score <23, which means that 2 out of 3 should be treated with CABG and not PCI, according to the previous (2014) or the most recent (2018) myocardial revascularization guidelines.^{3,4}

FFR was not mandated and measured in only 10% the patients assigned to undergo CABG; however, trials comparing FFR-guided CABG with angiography-guided CABG have not shown the same benefit as seen with FFR-guided PCI.^{13,14} Intravascular imaging was used in only 12% of the patients treated with PCI, while recent studies indicate that repeat revascularization is less common and clinical outcomes substantially improved when intravascular imaging guides PCI as shown in the ULTIMATE study and advocated in the SYNTAX II “state-of-the-art PCI” paradigm.^{15,16} A relatively low percentage of CABG procedures in FAME 3 involved multiple arterial grafts (24.5%) and since they have been reported to be associated with better outcomes, this may have led to an underestimation of the relative benefit of CABG.¹⁷ Also to be mentioned is the fact that in this study the MACE rate was far lower than expected in the initial study design for the CABG treated patients (6.9% versus predicted around 12%). Finally, the comparisons regarding quality of life and medico-economic aspects related to each of the two strategies are not yet published and importantly one year follow-up is considered too short for definitive evaluation.

It seems that for the relatively low surgical risk patients with mostly complex multivessel CAD as represented in FAME 3, CABG is the preferred approach despite its inherent increased short-term risks. A putative and probably unbeatable advantage of CABG in this context is that the use of surgical grafts bypasses a substantial length of coronary vessel beyond the flow-limiting lesion, and subsequent atherothrombotic events along that length are rendered less harmful. This advantage

cannot be neutralized by the improved selection of lesions by FFR guidance for PCI.

Conclusion

Among patients with three-vessel CAD (without left main disease, recent STEMI, LVEF<30% or cardiogenic shock) revascularization with FFR-guided PCI is inferior to CABG, which remains the preferred strategy since it is related in FAME 3 with fewer MACE (6.9% vs 10.6% at 1 year), despite more serious bleeding complications, post-operative arrhythmias (mainly atrial fibrillation), longer index hospitalization duration (x4) and need for rehospitalization in 30 days (x2) compared to PCI. According to the most recent revascularization guidelines PCI remains a credible option for non-diabetic three-vessel disease CAD patients with SYNTAX score ≤ 22 . The most modern approach would be to use FFR in order to define the functional SYNTAX score and accordingly guide revascularization targets by CABG or PCI (the latter reserved for non-diabetics with SYNTAX score ≤ 22 and performed under intravascular imaging guidance). After FAME 3 trial CABG remains the dominant revascularization strategy for low surgical risk patients with multivessel CAD.

However, a Heart Team approach and shared decision making remain fundamental to the management of multivessel CAD in our daily practice, which frequently demands care for patients with multivessel CAD that would be excluded from FAME 3 due to high surgical risk, advanced age or comorbidities that would render the dilemma between CABG or PCI more difficult or even tip the scale towards PCI after surgical rejection.

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