



A protocol update of the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) 3 trial: A comparison of fractional flow reserve–guided percutaneous coronary intervention and coronary artery bypass graft surgery in patients with multivessel coronary artery disease

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The FAME 3 Trial: A comparison of fractional flow reserve–guided percutaneous coronary intervention and coronary artery bypass graft surgery in patients with multivessel coronary artery disease, started recruitment in August 2014 and as of January 2019 has enrolled 1240 (83%) out of total 1500 patients. The design of the FAME 3 trial has been previously published in the American Heart Journal.¹

In the beginning of 2018, the members of the FAME 3 steering committee, including both cardiothoracic surgeons and interventional cardiologists, under the guidance of the US Food and Drug Authority (FDA), elected to amend the protocol. The purpose of this report is to inform the medical community of the most important changes:

1. Change in the non-inferiority margin from hazard ratio 1.45 to 1.65

2. Extension of the long-term follow-up from 3 years to 5 years.

Since the initial design of the FAME 3 protocol, the BEST, EXCEL, and NOBLE trials have been published.²⁻⁴ These studies demonstrate a 1 year MACCE rate which is in the 10% or lower range in the CABG arm, compared with the SYNTAX and FREEDOM trials which were in the 12% range.^{5,6} In addition, in EXCEL, a clinically acceptable non-inferiority margin for only death, CVA and MI (excluding revascularization) was a hazard ratio in the 1.4 range. Because of the lower event rates after CABG in more recent studies and because we will also be including revascularization as part of MACCE, the FAME 3 Steering Committee feels a hazard ratio of 1.65 is more appropriate for defining a clinically acceptable non-inferiority margin. Based on this change, 1290 total subjects will be necessary to reject the null hypothesis if it is false. To account for subject drop-out and loss of follow-up and to maximize our statistical power, the original sample size of 1500 subjects will remain unchanged.

It is important to note that the decision to change the non-inferiority margin was made by the steering committee without knowledge of the event rates in either of the randomized arms or input from Medtronic or Abbott, which are providing financial support for the study. In addition, we want to emphasize that a claim of non-inferiority can only be made when the upper 95% confidence interval (CI) of the hazard ratio does not exceed the non-inferiority margin. As an example of the difference between the hazard ratio and the upper limit of its 95% CI, in the recent non-randomized SYNTAX II study, contemporary PCI was compared to the equipoise-derived CABG cohort of the SYNTAX I trial.⁷

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While the rate of major adverse cardiac and cerebrovascular events (MACCE) was numerically lower in the PCI arm, resulting in a hazard ratio of 0.81, the upper limit of the 95% CI was 1.49.

Finally, since the initiation of the study it was planned to have long-term follow-up to 5 years if funding allowed.¹ During the enrolment period this additional funding became available allowing long-term follow-up through 5 years. Longer term follow-up will be critical in understanding the clinical implications of any differences between the two treatment strategies.

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