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

Protocol

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1. Protocol Summary

Title	A Comparison of Fractional Flow Reserve-Guided Percutaneous Coronary Intervention and Coronary Artery Bypass Graft Surgery in Patients with Multivessel Coronary Artery Disease: Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) 3 Trial.
Hypothesis	Fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) in patients with multivessel coronary artery disease (CAD) will result in similar outcomes to coronary artery bypass graft surgery (CABG).
Objective	Compare outcomes after FFR-guided PCI to CABG in patients with multivessel CAD.
Design	The FAME 3 trial is a multicenter, international, randomized, controlled noninferiority trial. All patients with multivessel CAD (not involving the left main) will be screened by the site's Heart Team (including but not limited to an interventional cardiologist, cardiac surgeon and research coordinator). If all agree that the patient can be treated either with FFR-guided PCI or CABG, and all inclusion criteria are met and no exclusion criteria are met, then the patient will be randomized. Baseline clinical, functional, laboratory and electrocardiographic data will be obtained. Patients will receive treatment within 4 weeks of randomization. Patients randomized to CABG will receive state of the art therapy at the discretion of the local surgeon with a strong emphasis on arterial revascularization. Patients undergoing PCI will have FFR measured with a Abbott coronary pressure wire across all lesions. If the FFR is ≤0.80, then PCI will be performed with the Medtronic Resolute Integrity/Onyx drug-eluting stent (DES) as per usual routine. If the FFR is >0.80 then PCI will be deferred. Post procedure laboratory tests will be obtained including troponin within 12-24 hours after the procedure. Resource utilization will be obtained. All patients will receive medical therapy as per published guidelines. Patients will follow-up at 1 and 6 months, and 1, 2, 3, and 5 years with an evaluation of clinical status, functional status, medications and events. Core lab analyses will include formal quantitative coronary angiography (QCA) of the baseline angiograms with calculation of the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score and Functional SYNTAX Score.
Population	A complete listing of all inclusion and exclusion criteria can be found in section 5 of the protocol.
Duration	Ten years: 5 years of enrollment and 5 years follow-up from last patient enrolled.
Primary Endpoint	Death, MI, stroke and any repeat revascularization (MACCE) will be evaluated at 1 year, where subjects contribute data from time of randomization until the occurrence of MACCE or one year follow-up,

	whichever occurs first. Subjects who die or are lost to follow up before 1 year will be censored at their last recorded activity.
Key Secondary Endpoint	Death, MI, and stroke will be evaluated at 3 years, where subjects contribute data from time of enrollment until the occurrence of one of the above events or three year follow-up, whichever occurs first. Subjects who die or are lost to follow up before this time will be censored at their last recorded activity.
Statistics	The study will use a noninferiority design. For the primary endpoint, assuming 12% of subjects experience MACCE in the CABG arm by 1 year post randomization, given a clinically irrelevant hazard ratio of 1.65, a one-sided 2.5% significance level and 90% power to reject the null hypothesis if it is false, the sample size necessary is 645 patients per group (1290 for the entire study). To account for loss to follow-up and subject withdrawal, up to 1500 patients will be enrolled from 50 sites.
Principal Investigators	William F Fearon, MD (PI), Bernard De Bruyne, MD, PhD (Co-PI) and Nico HJ Pijls, MD, PhD (Co-PI)
Steering Committee	William F. Fearon, MD, Bernard De Bruyne, MD, PhD, Nico HJ Pijls, MD, PhD, Keith Oldroyd, MD, Alan C. Yeung, MD, Joseph Woo, MD, Olaf Wendler, MD, Michael Reardon, MD.
Clinical Events Committee	Kenneth Mahaffey, MD, (Chair) Stanford University Medical Center [redacted], MD, Duke University Medical Center [redacted], MD, Duke University Medical Center [redacted], MD, Stanford University Medical Center
Data Safety Monitoring Board	[redacted], MD, (Chair) University of California, Irvine [redacted], MD, New York Presbyterian Hospital/Weill-Cornell Medical Center [redacted], MD, UCLA Medical Center
Statistical Analysis	Manisha Desai, PhD, Quantitative Sciences Unit, Stanford University Medical Center
FFR Core Lab	Stanford University Medical Center
Angiography Core Lab	Stanford University Medical Center
Economic and Quality of Life Analyses	Mark Hlatky, MD, Department of Health Research and Policy Stanford University Medical Center
Clinical Research Organization	genae
Sponsor(s)	Investigator Initiated Trial, with Leland Stanford Jr. University as the official Sponsor.
Support	Study is supported through research grants by Medtronic Corp. and Abbott Vascular.

2. Summary of Investigational Plan Changes

Revision History	Effective Date
1.0	28Feb2014
2.0	15May2015
2.1	15Jun2016
3.0	27Feb2018

Version 2.0, 15May2015

Section	Change From	Change To	Rationale for Change
1.0 Protocol Summary table, Steering Committee		Added Steering Committee members Woo and Reardon	Updated to include new Steering Committee members that agreed to participate after initial CIP version.
5.0 Design, subheading Follow-up	after randomization	after the index procedure	To harmonize follow up schedule across sites. Time to procedure from randomization could vary significantly depending on site waiting times..
9.0 Appendix A, Definitions	(ii) angiographic documented new graft or new native coronary occlusion	(ii) angiographic documented new graft or new major native coronary occlusion	Update definition of periprocedural MI to be in line with the 3rd Definition of periprocedural MI.

Version 2.1, 15Jun2016

Section	Change From	Change To	Rationale for Change
1.0 Protocol Summary table, Duration	Five years: 2 years of enrollment and 3 years follow-up.	Eight years: 5 years of enrollment and 5 years follow-up from last patient enrolled.	Extend enrolment period due to slower than expected enrolment rate
5.0 Design, subheading study enrolment	an enrollment period of 2 years	an enrollment period of up to 5 years	Extend enrolment period due to slower than expected enrolment rate

Version 3.0, 27Feb2018

Section	Change From	Change To	Rationale for Change
Table of Contents			Fix numbering of sections
1. Protocol Summary table, Design	Patients undergoing PCI will have FFR measured with a St. Jude Medical coronary pressure wire	Patients undergoing PCI will have FFR measured with a Abbott coronary pressure wire	Device manufacturer change of name
1. Protocol Summary table, Design	PCI will be performed with the Medtronic Resolute Integrity drug-eluting stent (DES)	PCI will be performed with the Medtronic Resolute Integrity/Onyx drug-eluting stent (DES)	The Onyx stent has now replaced the Integrity stent

1. Protocol Summary table, Design	Patients will follow-up at 1 and 6 months, and 1, and 3 years with an evaluation of clinical status, functional status, medications and events. Follow up may be extended to 5 years, if funding allows.	Patients will follow-up at 1 and 6 months, and 1, 2, 3, and 5 years with an evaluation of clinical status, functional status, medications and events.	Correct follow up description and remove text related to possible 5 year follow up. Funds now available.
1. Protocol Summary table, Duration	Eight years: 5 years of enrollment and 3 years follow-up from last patient enrolled. Note: 5 year follow up will be performed if funding allows.	Ten years: 5 years of enrollment and 5 years follow-up from last patient enrolled.	Funding for follow-up through 5 years post procedure available.
1. Protocol Summary table, Statistics	clinically irrelevant hazard ratio of 1.45	clinically irrelevant hazard ratio of 1.65	See new text in the statistical analysis section
1.0 Protocol Summary table, Statistics	the sample size necessary is 712 patients per group (1424 for the entire study). To account for loss to follow-up, 1500 patients will be enrolled from 50 sites over 2 years.	the sample size necessary is 645 patients per group (1290 for the entire study). To account for loss to follow-up and subject withdrawal, up to 1500 patients will be enrolled from 50 sites.	Based on the new non-inferiority margin and the expected event rate in the control arm
1.0 Protocol Summary table, Sponsor(s)	Investigator Initiated Trial and supported through research grants by Medtronic Corp. and St. Jude Medical, Inc.	Investigator Initiated Trial, with Leland Stanford Jr. University as the official Sponsor.	Clarification of who Sponsor is.
1.0 Protocol Summary table, Support			Newly added to indicate study is supported through research grants.
2. Summary of Investigational Plan Changes			Newly added.
3. Background	the Medtronic Resolute Integrity stent has been shown to be safe and effective. Thus, one might hypothesize that a comparison of PCI with the second generation Medtronic Resolute Integrity stent technology	the Medtronic Resolute Integrity/Onyx stent has been shown to be safe and effective. Thus, one might hypothesize that a comparison of PCI with the second generation Medtronic Resolute Integrity/Onyx stent technology	Added for inclusion of Onyx stent.
Multiple sections	Medtronic Resolute Integrity stent	Medtronic Resolute Integrity/Onyx stent,	Added for inclusion of Onyx stent.
4. Objective	St. Jude Medical Coronary Pressure Wire	Abbott Coronary Pressure Wire	To account for change in name of device manufacturer

5. Population, exclusion criteria 1	Requirement for other cardiac or non-cardiac surgical procedure (e.g., valve replacement, carotid revascularization)	Requirement for other cardiac or non-cardiac surgical procedure (e.g., valve replacement, carotid revascularization), however a MAZE procedure or pulmonary vein ablation is allowed	The MAZE and pulmonary vein ablation are frequent add-on procedures at the time of CABG and not felt to increase the risk of the procedure significantly
5. Population, exclusion criteria 11	Inability to take dual antiplatelet therapy for six months	to take dual antiplatelet therapy or anticoagulation and single antiplatelet therapy for at least six months	Single antiplatelet therapy with anticoagulation is now an accepted treatment after PCI for patients requiring anticoagulation
5. Population, exclusion criteria 16		More than one major epicardial vessel which is chronically occluded	Newly added
6. Design, PCI Strategy	PCI may be staged if necessary, but this is not encouraged. The plan to stage the PCI of a particular lesion should be declared before instrumenting the lesion. The second portion of the PCI procedure should be performed within four weeks of the first portion.	PCI may be staged if necessary, but this is not encouraged. The plan to stage the PCI of a particular lesion should be declared before instrumenting the lesion and can be contingent upon the patient having persistent symptoms. The second portion of the PCI procedure should be performed within four weeks of the first portion.	Clarification
6. Design, Medications table		For patients who require anticoagulation, single antiplatelet therapy is acceptable	Newly added row.
6. Design, Follow-up	Patients will be seen and evaluated at 1 month (±7 days), and 1 and 3 years (±30 days) after the index procedure with the specific assessments as outlined in the follow-up table below. (5 year follow up will be performed if funding allows). Phone call follow-up will occur at 6 months, 2 years (and 4 years, if funding allows).	Patients will be seen and evaluated at 1 month (±7 days), and 1, 3 and 5 years (±30 days) after the index procedure with the specific assessments as outlined in the follow-up table below. Phone call follow-up will occur at 6 months and 2 years .	Correction to account for changes to follow-up schedule with addition of 5 year follow-up.
6. Design, Follow-up Schedule table	Follow-Up Schedule (including the potential for 4 and 5 year)	Follow-Up Schedule	Change of table heading to account for addition of 5 year follow-up.

6. Design, Electrocardiography	at discharge[1], 1 month, 1, and 3 years post index procedure.	at discharge, 1 month, 1, 3 and 5 years post index procedure.	Change to account for addition of 5 year follow-up visit
6. Design, Blood Sampling	At 1 year and 3 year follow-up if assessed locally, per standard of care	At 1, 3 and 5 year follow-up if assessed locally, per standard of care	Change to account for addition of 5 year follow-up visit
6. Design, Quality of Life Assessment	Data collection will include the completion of the EQ-5D questionnaire prior to the procedure and at the different follow-up time points as indicated inFollow Up Schedule (including the potential for 4 and 5 year).	Data collection will include the completion of the EQ-5D questionnaire prior to the procedure and at the different follow-up time points as indicated in the Follow-Up Schedule.	Change to account for addition of 5 year follow-up visit
8. Organization, Support	The study is supported by research grants provided by Medtronic Corporation and St. Jude Medical.	The study is supported by research grants provided by Medtronic Corporation and Abbott Vascular.	To account for change in name of device manufacturer
8. Organization, Steering Committee			Added names of 3 Steering Committee members
Study Flow Chart			Correction to account for inclusion of 5yr follow up.
10. Statistics	a hazard ratio of 1.45 or less is not clinically meaningful.	a hazard ratio of 1.65 or less is not clinically meaningful.	See new text in statistical analysis section
10. Statistics	All patients will be followed for 3 years post-randomization (5 years if funding allows) or until they die, whichever comes first.	All patients will be followed for 5 years post-randomization or until they die, whichever comes first.	Change to account for addition of 5 year follow-up visit
10. Statistics, Sample Size and Power Considerations	We anticipate that within 1 year of follow up the PCI arm will have a 12% event rate based on the 18% rate in SYNTAX and the decrease in death, MI and revascularization seen with FFR guidance in FAME and with second generation drug eluting stents, like the Resolute Integrity stent. Thus, assuming 12% of subjects in the CABG arm experience MACCE (from the SYNTAX study and FREEDOM trial), given a clinically	Recently, the EXCEL, NOBLE and BEST trials have been published. These studies demonstrate a one 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. In addition, in EXCEL, a clinically acceptable non-inferiority margin for death, CVA and MI was a hazard ratio in the 1.4 range. Because of the lower event rates after	Include new information related to recently published Trial results and rationale for changes in hazard ratio.

	irrelevant hazard ratio of 1.45, a one-sided 2.5% significance level and 90% power to reject the null hypothesis if it is false, the sample size necessary is 712 patients per group (1424 for the entire study). These calculations are based on assumptions of uniform accrual over time, no loss to follow-up, exponentially distributed death times, and a Wald test statistic. Thus, to account for patients lost to follow-up we will enroll 1500 patients from up to 50 medical centers.	CABG in more recent studies and because we will also be including revascualrzation as part of MACCE, we feel a hazard ratio of 1.65 is more appropriate for defining a clinically acceptable non-inferiority margin. We assume a 10% of subjects in the CABG arm experience MACCE, and further that patients in the PCI arm will not experience a higher rate than those in the CABG arm. We would deem an increase in event rate up to and including a 16% event rate as not clinically inferior. Thus, given a clinically irrelevant hazard ratio of 1.65, a one-sided 2.5% significance level and 90% power to reject the null hypothesis if it is false, the sample size necessary is 645 patients per group (1290 for the entire study). These calculations are based on assumptions of uniform accrual over time, no loss to follow-up, exponentially distributed death times, and a Wald test statistic. Thus, to account for patients lost to follow-up and subject withdrawal we will enroll up to 1500 patients from up to 50 medical centers.	
11. Appendix A, Definitions		**Acute Kidney Injury** AKI (acute kidney injury) is defined as any of the following: • K Increase in SCr (Serum creatinine) by ≥0.3 mg/dl (≥26.5 µmol/l) within 48 hours; • or K Increase in SCr to≥1.5 times baseline, which is known or presumed to have	Newly added definition

		occurred within the prior 7 days; • or K Urine volume <0.5 ml/kg/h for 6 hours.	
11. Appendix A, Definitions		**Cross-over** If, during the first month after randomization, a patient receives as the initial revascularization therapy the alternative form of revascularization than the assigned treatment (i.e. Randomized to CABG but receives PCI), this will be defined as a cross-over and not a repeat revascularization event, unless the reason for the alternative revascularization strategy is due to a change in the patient's clinical status resulting in urgent/emergent revascularization.	Newly added definition

3. Background

Both United States and European guideline statements recommend coronary artery bypass graft surgery (CABG) over percutaneous coronary intervention (PCI) for patients with multivessel coronary artery disease (MVD), defined as angiographically significant disease involving all three major epicardial vessels. [1,2] This recommendation is based primarily on the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) study, which randomized 1800 patients with MVD or significant left main coronary disease to either PCI or CABG and demonstrated significantly higher rates of the primary endpoint, a composite of the major adverse cardiovascular and cerebrovascular events (MACCE), death, myocardial infarction (MI), cerebrovascular accident (CVA) and repeat revascularization at one year in the PCI arm (17.8 vs. 12.4%, p=0.002).[3] This difference was driven primarily by a significant difference in the need for repeat revascularization (13.5 vs. 5.9%, p<0.001), although there was a strong trend towards lower rates of cardiac death (3.7 vs. 2.1%, p=0.05) and MI (4.8 vs. 3.3%, p=0.11) in the CABG arm. These events were counterbalanced to some degree by a significantly lower rate of CVA in the PCI arm (0.6 vs. 2.2%, p=0.003).

The three year follow-up in these patients continued to show a significantly higher rate of MACCE in the PCI arm (28.0 vs. 20.2%, p<0.001), as well as a now significantly higher rate of cardiac death (6.0 vs. 3.6%, p=0.02) and MI (7.1 vs. 2.6%, p=0.002) in the PCI arm.[4] When comparing the 1095 patients with MVD not involving the left main coronary, the same significant differences were noted in MACCE between the two groups at both one and three years (19.2 vs. 11.5%, p<0.001) and (28.8 vs. 18.8%, p<0.001).

Another development of the SYNTAX trial was the application of the SYNTAX score as a method for identifying patients with complex disease, who might benefit more from CABG. The SYNTAX score is an angiography-based scoring system which assigns points to lesions based on their features of complexity, such as ostial location, length, morphology, severity and involvement of sidebranches. After dividing the population into tertiles, based on the SYNTAX score, the investigators demonstrated that outcomes were significantly improved after CABG when compared to PCI in patients falling in the intermediate (SYNTAX score >22 and <33) and high (SYNTAX score >33) tertiles.[3,4]

The recently published Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial adds further support to the findings from SYNTAX.[5] The FREEDOM trial randomized 1900 diabetic patients to PCI or CABG and found a significantly higher rate of the primary endpoint, death, MI or CVA in the PCI arm at 5 year follow-up (26.6 vs. 18.7%, p=0.005). This difference was driven by higher rates of death and MI in the PCI arm and higher rates of CVA in the CABG arm.

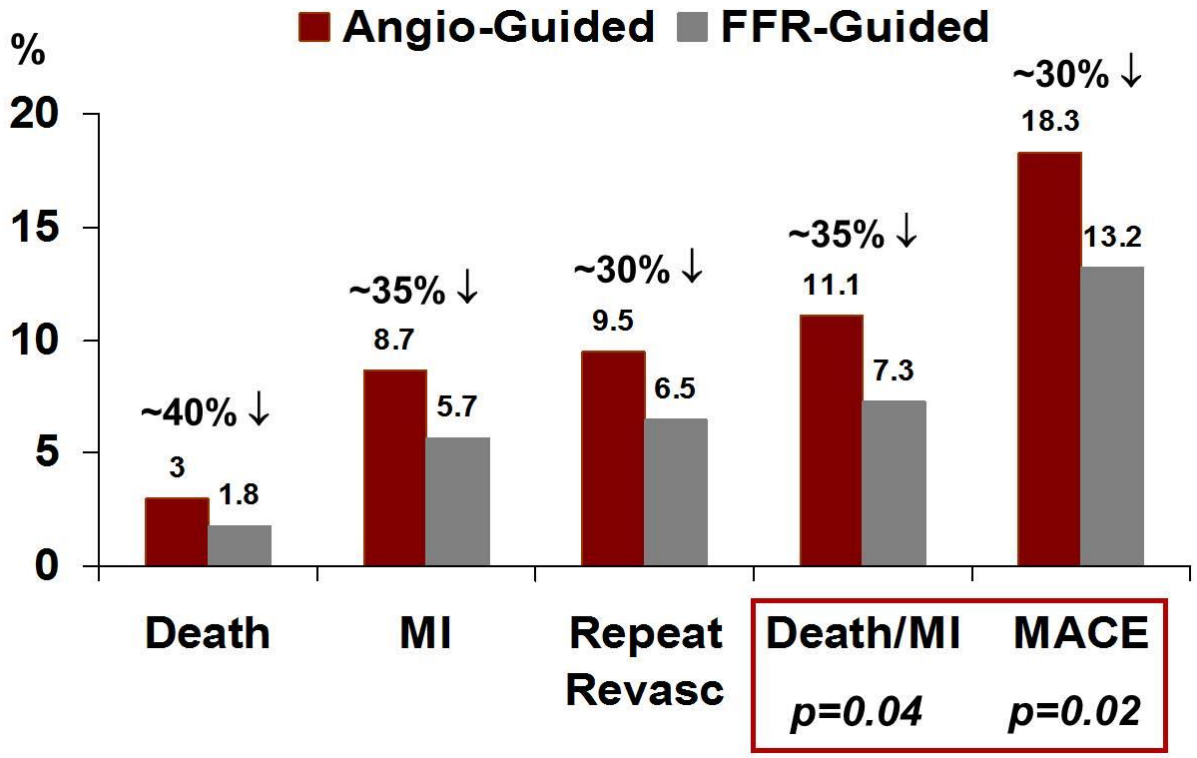
Based on these two studies, most patients with multivessel CAD are now routinely referred to CABG, particularly if they have an intermediate or high SYNTAX score. However, the inferior results of PCI demonstrated by both SYNTAX and FREEDOM might be explained by the use of inferior stent technology, and even more importantly, by the lack of application of fractional flow reserve (FFR)-guided PCI.

Patients undergoing PCI in SYNTAX received the paclitaxel-eluting Taxus stent and patients in the FREEDOM trial received predominantly the sirolimus-eluting Cypher stent and the Taxus stent. These stents have now been shown to be inferior to second generation drug-eluting stents, which have lower rates of stent thrombosis, target lesion revascularization, and in some cases, death or myocardial infarction.[6,7,8] Studies directly comparing second generation drug-eluting stents to each other have shown no appreciable difference in these endpoints.[9,10] In addition, in over 1,000 patients with multivessel CAD, the Medtronic Resolute Integrity/Onyx stent has been shown to be safe and effective.[7,9,10] Thus, one might hypothesize that a comparison of PCI with the second generation Medtronic Resolute Integrity/Onyx stent technology to CABG might result in lower rates of death, MI and the need for repeat revascularization as compared to what was seen with the Taxus stent, and which are more similar to those seen after CABG.

The second reason outcomes may have been inferior with PCI in SYNTAX and FREEDOM relate to the lack of FFR-guided PCI. FFR is a coronary pressure wire-based index for assessing the ischemic potential of a coronary lesion. It is defined as the mean distal coronary pressure divided by the mean proximal coronary pressure during maximal hyperemia. Numerous studies have demonstrated that if the FFR is ≤0.80, then significant ischemia is present and revascularization is warranted. If the FFR is >0.80, then the lesion can be safely treated with medication, despite its angiographic appearance, and one can expect an excellent outcome.[11]

The Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) trial, randomized 1005 patients with two or three vessel coronary disease and stable symptoms or non ST elevation acute coronary syndromes in whom PCI was indicated to either angiography-guided PCI or to FFR-guided PCI, in which case FFR was measured across every lesion and PCI was performed only if the FFR was ≤ 0.80.[12] The one year primary endpoint of death, MI or the need for repeat revascularization occurred in significantly fewer patients randomized to the FFR-guided strategy (13.2 vs. 18.3%, p=0.02). This was driven by numerical reductions in all three components of the primary endpoint: death (1.8 vs. 3.0, p=0.19), MI (5.7 vs. 8.7%, p=0.07) and repeat revascularization (6.5 vs. 9.5, p=0.08). The composite of death and MI was significantly reduced by FFR-guided PCI (7.3 vs. 11.1, p=0.04).

Figure 1 One year outcomes from FAME 1 Trial

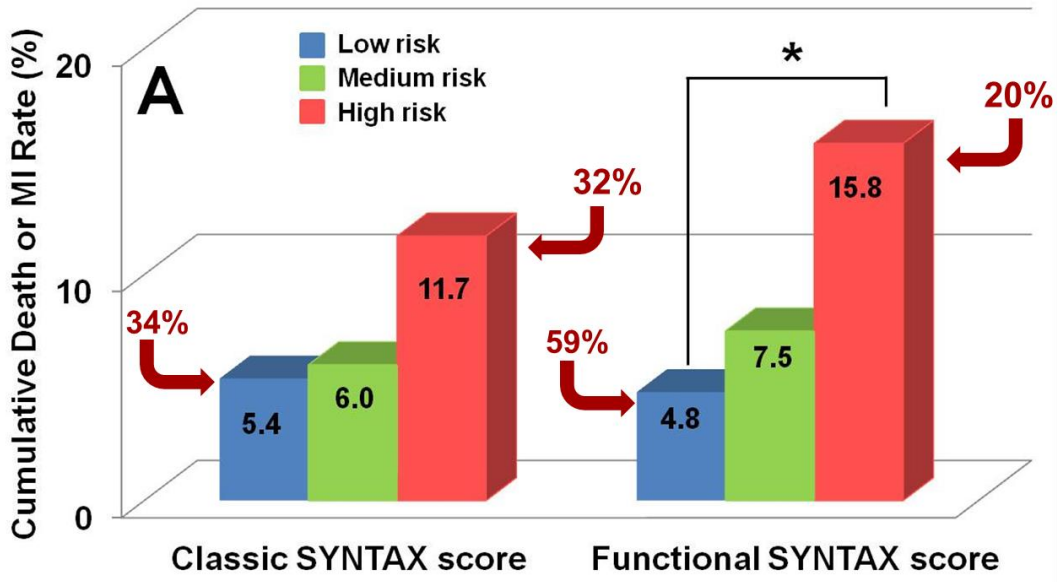


At two year follow-up, there continued to be a significant reduction in death and MI with FFR-guided PCI (8.4 vs. 12.9%, p=0.02) and a trend towards a lower rate of death, MI or the need for repeat revascularization (17.9 vs. 22.4%, p=0.08).[13] The improved outcomes with FFR-guided PCI are likely a result of more judicious PCI whereby ischemia-producing lesions are

revascularized and non-ischemia producing ones are treated medically. In this manner, the benefit of PCI can be maximized by relieving ischemia and the risks can be minimized by avoiding unnecessary PCI.

This difference between functional complete revascularization with FFR-guided PCI and anatomic complete revascularization with angiography guidance was further demonstrated by a substudy from FAME evaluating the so-called Functional SYNTAX Score (FSS).[14] In this substudy, the SYNTAX score was calculated in the usual fashion in the 497 patients in FAME who were randomized to FFR guidance. The FSS was then calculated in these patients by subtracting the points for any lesions incorporated into the SYNTAX score in which the FFR was >0.80. The FSS resulted in reclassification of 32% of patients from a higher risk SYNTAX score tertile to a lower risk FSS tertile. The FSS was a better discriminator of the risk for death and MI or death, MI and the need for repeat revascularization as compared to the SYNTAX score.

Figure 2 Comparison of Functional SYNTAX Score and SYNTAX Score in FAME 1 Trial



If one compares the results of the FAME study to the results of SYNTAX (excluding the left main subset), the major adverse event rate (excluding stroke) was similar between the angiography-guided arm in FAME and the PCI arm in SYNTAX, reflecting the fact that PCI in SYNTAX was performed primarily with angiography guidance alone. On the other hand, the FFR-guided arm in FAME had similar event rates to the CABG arm in SYNTAX. Based on this

comparison and the trials showing improved outcomes with the Medtronic Resolute Integrity/Onyx stent, one can hypothesize that a comparison between FFR-guided PCI with the Resolute stent and CABG in patients with multivessel coronary disease would be favorable.

4. Objective

The primary objective of the FAME 3 Trial is to demonstrate that FFR-guided PCI is noninferior to coronary artery bypass graft surgery in patients with multivessel CAD. If we fail to reject the null hypothesis that FFR-guided PCI is worse than CABG, this study will be considered negative. The FAME 3 study is not intending to support a label change for either the Resolute Integrity
Zotarolimus-Eluting Coronary Stent System or the Abbott Coronary Pressure Wire.

5. Population

Inclusion Criteria

1. Age ≥ 21 years with angina and/or evidence of myocardial ischemia
2. Three vessel CAD, defined as ≥ 50% diameter stenosis by visual estimation in each of the three major epicardial vessels or major side branches, but not involving left main coronary artery, and amenable to revascularization by both PCI and CABG as determined by the Heart Team. Patients with a non-dominant right coronary artery may be included if only the left anterior descending artery (LAD) and left circumflex have ≥50% stenosis
3. Willing and able to provide informed, written consent

Exclusion Criteria

1. Requirement for other cardiac or non-cardiac surgical procedure (e.g., valve replacement, carotid revascularization), however a maze procedure or pulmonary vein isolation is allowed
2. Cardiogenic shock and/or need for mechanical/pharmacologic hemodynamic support
3. Recent STEMI (<5 days prior to randomization)
4. Ongoing Non STEMI with biomarkers (cardiac troponin) still rising
5. Known left ventricular ejection fraction <30%

6. Life expectancy < 2 years
7. Requiring renal replacement therapy
8. Undergoing evaluation for organ transplantation
9. Participation or planned participation in another clinical trial, except for observational registries
10. Pregnancy
11. Inability to take dual antiplatelet therapy or anticoagulation and single antiplatelet therapy for at least six months
12. Previous CABG
13. Left main disease requiring revascularization
14. Extremely calcified or tortuous vessels precluding FFR measurement
15. Any target lesion with in-stent drug-eluting stent restenosis
16. More than one major epicardial vessel which is chronically occluded

6. Design

FAME 3 is an investigator-initiated, multicenter, international, randomized, controlled trial including up to 50 sites worldwide. Consecutive patients with multivessel CAD (not involving the left main coronary) who meet the inclusion criteria and none of the exclusion criteria outlined above will be randomized in a 1:1 fashion to either CABG or FFR-guided PCI.

Study Enrolment

With a goal of including 1500 patients from up to 50 sites and an enrollment period of up to 5 years, each site is expected to include ≥ 2 patients per month. We anticipate 20-25 US sites will enroll 40-50% of patients in the trial. Consecutive patients will be screened at each participating center and those with multivessel CAD, defined as ≥ 50% diameter stenosis in each of the three major epicardial vessels, and not involving the left main coronary will be eligible. After the baseline angiogram has been performed, the Heart Team will review the patient's case to determine if all of the inclusion criteria and none of the exclusion criteria are met. In particular, the Heart Team will evaluate whether or not both FFR-guided PCI and CABG are reasonable treatment alternatives. This may involve the calculation of the SYNTAX score or any other scores predicting outcomes after CABG or PCI, but these are not mandated. The SYNTAX

score and other scores will be calculated by a core laboratory after patient enrolment. The study will be discussed with the patient, and if the patient provides informed, written consent, then the patient will be enrolled.

Randomization

Randomization will occur via a web-based system stratified by diabetes status and site. Once a patient has been randomized, treatment should occur within 2 weeks, and no longer than 4 weeks. A patient will be considered enrolled once randomization has occurred.

Baseline Data

Every patient will undergo baseline assessment as outlined below.

- Baseline demographics and clinical characteristics will be recorded as outlined in the case report form.
- Medications
- Laboratory studies including complete blood count, basic metabolic panel, lipid panel and glycosylated hemoglobin (HgbA1C); all hospitalized patients will have cardiac markers, including troponin checked, and if elevated, repeated 4-12 hours later to determine if they are stable or declining
- Electrocardiogram
- Quality of life (EQ-5D) assessment

Coronary Artery Bypass Graft Surgery (CABG)

CABG will be performed as per clinical routine at each participating center. FFR assessment of lesions to help guide bypass is not mandated, but if performed at the time of the diagnostic angiogram, the information can be used by the surgeon. We expect this will occur in approximately ¼ of cases, and in most of these cases we expect the decision to place a bypass graft will be based on the FFR result. Adjunctive pharmacologic therapy during and immediately after the CABG should be prescribed as per the clinical routine at each participating center. Recommendations are described in the section Medications.

Both off-pump and on-pump surgery are acceptable, as long as the surgeon and the site are experienced in the particular technique. An internal mammary graft to the LAD should be attempted in all cases, if feasible. Complete arterial revascularization is strongly recommended,

however, each center should use a conduit strategy with which they are most comfortable. All vessels ≥ 1.5 mm in diameter and with ≥ 50% stenosis should undergo bypass procedure, if technically feasible.

Fractional Flow Reserve-Guided PCI

Access:

- PCI can be performed via the radial artery or the femoral artery, as per the site's usual routine.

Performance of FFR:

- Only those sites with prior experience measuring FFR will be included in the FAME 3 trial. Intracoronary pressure measurements should be obtained with a guiding catheter and a St Jude Medical Pressure Wire. For correct use of the pressure guidewire, refer to the instructions for use provided by St Jude Medical along with the product. The FFR tracings from the first 10 patients at every site will be recorded on the RADIANALYZER and reviewed by the FFR core lab at Stanford immediately after each patient is treated. The Steering Committee will provide feedback to the Interventional Cardiology site Principal Investigator. We expect measurement of FFR will not be possible in 5% of lesions due to technical or anatomic reasons. These patients in whom FFR of a particular lesion was not possible will be included in all analyses based on the intention to treat principle.
- Ensure correct calibration of all equipment, the aortic pressure transducer and the pressure guidewire.
- Before introducing the guidewire into the coronary artery, intracoronary nitroglycerin (100-200 micrograms, or its equivalent) should be administered.
- Before advancing the pressure guidewire sensor past the stenosis, baseline pressure as measured by the guide catheter and the pressure guidewire should be equalized, with the pressure wire sensor positioned at the tip of the guiding catheter. At this point, the pressure tracing of the guiding catheter and of the pressure guidewire should be equalized electronically.
- The sensor is then advanced across the stenosis.

- Administer hyperemia according to standard practice. It is recommended that hyperemia is induced by intravenous adenosine (140 µg/kg/min for at least 2 minutes or until a steady state is obtained) via central venous access. If intravenous adenosine cannot be given, it is recommended that intracoronary adenosine is given by a bolus injection of at least 100 µg and repeated twice.
- FFR should be recorded once steady state maximal hyperemia has been achieved based on examination of the pressure and heart rate tracing and based on symptom development in the case of intravenous adenosine. The lowest Pd/Pa ratio during steady state hyperemia in the absence of any artifact or arrhythmia should be recorded as the FFR.
- Only those lesions with an FFR ≤0.80 should be stented.
- If the FFR in a vessel is ≤0.80, the operator is not obligated to stent. For example, if on pullback of the wire, diffuse disease is diagnosed without an obvious focal step-up, stenting is not mandated. Or if a small sidebranch of a bifurcation lesion has an FFR ≤0.80, stenting is not mandated. In other words, operators should use their good clinical judgment and follow their routine practice.
- In case of serial stenoses, FFR "of the complete vessel" should be ≤0.80 to warrant PCI of one of more of these stenoses. Long stents to cover a segment or multiple shorter stents, can be placed at the discretion of the operator. After treating one stenosis, FFR should be remeasured to determine whether the second stenosis warrants therapy.
- In the case in which the operator decides to revascularize a chronic total occlusion, FFR measurement is not mandatory and a default FFR value of 0.50 can be applied.
- It is strongly advocated to measure the final post DES implantation FFR, to document the degree of resolution of the pressure gradient achieved by the revascularization. A pullback should be performed to address the source of any residual gradient and to check for drift in the pressure wire.
- Based on the literature and clinical experience, we expect a <1% complication rate from FFR measurement.[15]

PCI Strategy:

- PCI will be performed solely with the Medtronic Resolute Integrity/Onyx stent. If the Resolute stent cannot be delivered, an alternative current generation drug-eluting stent can be substituted, preferably an everolimus eluting stent.
- Covering the entire diseased portion of the lesion with a single drug-eluting stent is recommended.
- A single cross-over stent strategy for bifurcation lesions is recommended, with provisional sidebranch stenting only if < TIMI 2 flow is persistent after kissing balloon inflation of the sidebranch.
- It is not recommended to revascularize a chronic total occlusion (CTO) unless a patient has persistent symptoms after the initial PCI, documented ischemia on noninvasive testing involving the region subtended by the vessel with the CTO, and visible collaterals which fill a vessel >2.5 mm in diameter. If the operator is considering bringing the patient back for revascularization of a CTO, this should be documented in the CRF at the time of the baseline procedure. The operator is not obligated to bring the patient back, but this will avoid confusion regarding whether or not the follow-up procedure is planned.
- PCI may be staged if necessary, but this is not encouraged. The plan to stage the PCI of a particular lesion should be declared before instrumenting the lesion and can be contingent upon the patient having persistent symptoms. The second portion of the PCI procedure should be performed within four weeks of the first portion.

Medications

Type of medication	**CABG**	**FFR-guided PCI**
Aspirin 80-100 mg once a day for the duration of the study	Pre- and post-procedure	
High dose statin (e.g., atorvastatin 80 mg)	≤ 24 hours before the procedure	
Clopidogrel or its equivalent (i.e. prasugrel or ticagrelor)[2] for 6 months (12 months recommended)	-	Pre-loading with 600 mg or equivalent
Bivalirudin for anticoagulation	-	Recommended
Beta blockers or amiodarone to prevent atrial fibrillation	At site's discretion	

For patients who require anticoagulation, single antiplatelet therapy is acceptable		

[1] Ticlopidine should not be used.

Follow-up

Patients will be seen and evaluated at 1 month (±7 days), and 1, 3 and 5 years (±30 days) after the index procedure with the specific assessments as outlined in the follow-up table below. . Phone call follow-up will occur at 6 months and 2 years . One month is defined as 30 days (i.e. 6 months equals 180 days). Each year will be defined as 360 days. During follow-up patients will be assessed for any MACCE, angina severity, and quality of life (EQ-5D).

Follow-Up Schedule

	Base-Line	12-24 Hours Post Proc.	Dis-charge	1 month (±7 days)	6 month (±30 days)	1 year (±30 days)	2 years (±30 days)	3 years (±30 days)	5 years (±30 days)
	Hosp.	Hosp.	Hosp.	Visit	Call	Visit	Call	Visit	Visit
Medical History	X								
QOL (EQ-5D)	X			X		X		X	X
Working Status	X			X	X	X	X	X	X
ECG	X	X[1]	X	X		X		X	X
Lab Studies	X	X[1]	X			X		X	X
Cardiac Medications	X		X	X	X	X	X	X	X
Resource Utilization			X	X	X	X	X	X	X
MACCE			X	X	X	X	X	X	X

[1] The 12-24 hour assessment is sufficient in case discharge is within 36 hours post-procedure

Recording of Adverse Events

For the purpose of this trial, only MACCE events will be reported. In case a patient does not attend the final visit, all efforts should be made to obtain a complete inventory of these events.

Electrocardiography

Twelve lead electrocardiograms (ECGs) are recorded before the procedure (within 24 hours), 1 day after the procedure (12 to 24 hours post procedure) and at discharge[3], 1 month, 1, 3 and 5 years post index procedure.

Recording of Cardiac Medication

Cardiac medications prescribed during the initial hospital stay and at the time of follow-up visits must be recorded. Investigators should review all medications carefully at every out-patient clinic visit.

Angina Assessment

The anginal status of the patient will be assessed according to the Canadian Cardiovascular Society (CCS) Classification at all follow-up contacts (calls or visits).

Blood Sampling

Baseline blood samples: Pre catheterization analyses, assessed locally, per standard of care should include:

- Total Cholesterol
- HDL Cholesterol
- LDL Cholesterol
- Triglycerides
- Creatinine
- Hemoglobin
- Glycosylated hemoglobin

Mandatory post PCI or CABG blood sampling will include 12 – 24 hours post index procedure:

- Troponin (and CK and CK-MB if available)
- Hemoglobin
- Creatinine

If elevated, cardiac markers will be measured every 8 hours until they begin to decline. The highest creatinine and the lowest hemoglobin during the hospitalization will be recorded.

At 1, 3 and 5 year follow-up if assessed locally, per standard of care

- Total Cholesterol
- HDL Cholesterol
- LDL Cholesterol
- Triglycerides,
- Creatinine
- Hemoglobin
- Glycosylated hemoglobin

Resource Utilization

Resource utilization data will be collected for each patient at the time of each follow-up contact. Specific data to be collected will include:

1. Resource use concerning the initial procedure
2. Hospital readmissions
3. Major procedures after the initial procedure
    - revascularization procedures (CABG, PCI)
    - diagnostic procedures (angiography, echocardiography, exercise testing, etc.)
4. Medication
    - Anti anginal medication
    - Medication for treatment of other cardiovascular conditions (hypertension, CHF, arrhythmia)
    - Antiplatelet agents and anticoagulants

Quality of Life Assessment

Data collection will include the completion of the EQ-5D questionnaire prior to the procedure and at the different follow-up time points as indicated in the Follow-Up Schedule.

Working Status

In addition to the quality of life assessment prior to treatment allocation and at all planned clinical follow-up visits, the patient will be requested to provide information relative to his/her working status or any change therein.

7. Reporting of Events

The study will evaluate two different common treatments. For the purpose of this study, only endpoint related events and other possible vascular events are reported.

Trial personnel must report any of the following events within 1 business day of learning of the event.

- Death
- Myocardial infarction
- Cerebrovascular event (TIA, CVA)
- Revascularization (PCI, CABG)
- Bleeding event
- Acute renal failure
- Atrial fibrillation or other arrhythmia
- Rehospitalization

The notification is by preference performed via the electronic CRF (eCRF). Alternatively e-mail or phone may be used for immediate notification, however the eCRF must be completed as soon as possible. Detailed procedures will be listed in the manual of operations. Study personnel must update any follow-up information in the completed adverse event CRF as the event continues and/or resolves. It is the responsibility of the Site Principal Investigator to inform the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of the adverse event as required by local procedure.

Vigilance Reporting

Since commercially available products are used in this study, reporting relative to device malfunctions must be reported to the relevant manufacturer according to the procedure as defined by the relevant entity.

8. Organization

Sponsor

This is an investigator initiated trial. The Principal Investigators are considered to be the sponsors of this study. The Principal Investigators will be supported by the clinical research organization, genae, for the financial and logistic aspects of this clinical trial.

Support

The study is supported by research grants provided by Medtronic Corporation and Abbott Vascular.

Steering Committee

The Steering Committee (SC) is the main decision making committee of the trial and has final responsibility for the medical and scientific conduct of the trial. The SC will approve the trial protocol and any amendment (if applicable). The SC further will review all reported adverse events on a regular basis. The Committee may request that the trial be put on hold or even terminated for safety, ethical or other reasons.

The Committee will be comprised of physician-investigators:

- William F. Fearon, MD, Stanford, CA, USA, Chairperson and Coordinating Clinical Investigator (CCI)
- Bernard De Bruyne, MD, PhD, Aalst, BE, Co-CCI
- Nico HJ Pijls, MD, PhD, Eindhoven, NL, Co-CCI
- Keith Oldroyd, MBCHB, MD, Glasgow, UK, Co-CCI
- Michael Reardon, MD, Houston, TX, USA, Co-CCI
- Olaf Wendler, MD, PhD, London, UK, Co-CCI
- Joseph Woo, MD, Stanford, CA, USA, Co-CCI
- Alan C. Yeung, MD, Stanford, CA, USA, Co-CCI

Monitoring

Central clinical and statistical monitoring will be the primary monitoring method of FAME 3 with a commercially available approved device widely used in clinical practice and using techniques outlined by FDA.[16] The Steering Committee believes this risk-based monitoring approach will be effective because the majority of the investigators in FAME 3 are established investigators who have worked with the Principal Investigators in other recent large clinical

randomized trials (FAME 1 and FAME 2). Factors for selection of Investigators include their experience in clinical research and experience with the sponsor or members of the Steering Committee. The Steering Committee also believes this monitoring approach is appropriate because the two treatment strategies being tested are accepted clinical approaches performed routinely; the device being tested (the Medtronic Resolute Integrity/Onyx stent) has a robust safety record in prior human studies; and because the treatment after the initial procedure will be according to routine practice. All sites will enter data or upload electronic records into a secure electronic CRF. Investigators will receive training from the CRO on the protocol and study requirements including data collection and event reporting. The objective clinical outcomes of FAME 3 will undergo central adjudication.

The electronic CRF will not allow randomization into the study unless all inclusion criteria have been met and no exclusion criteria have been met. The CRF will not allow submission unless all of the data elements have been successfully entered. Drop down selections in the electronic CRF will only allow selection of data within a specific expected range for each data point. This will help to eliminate human error in entering data. All sites will electronically upload the signed consent page for each patient enrolled into FAME 3. A minimum of 10% of the CRFs will be randomly selected and monitored to identify inconsistent data, data outliers, and potential protocol deviations that may be indicative of systemic or significant errors in data collection and reporting at a site. If this is identified, targeted on-site monitoring will be conducted. In addition, on site monitoring may occur if the number of adverse events, protocol deviations, subject withdrawals or missed follow-up visits exceeds a pre-defined threshold. Root cause analysis will be performed as necessary to identify appropriate corrective or preventive actions. All adverse events which occur during the study will trigger monitoring which will include review of source documents. Statistical analyses of the entered data will be performed to identify unusual trends, such as too little variance in data at a particular site, too many withdrawals or screen failures, and delays in reporting. Regular videoconferences and email communication will occur between the CRO and the sites to ensure compliance with the above monitoring plan. In person, biannual investigators' meetings will further reinforce the monitoring plan. The monitoring results will be documented and communicated to the Steering Committee by the CRO on a quarterly basis or more frequently, as necessary. The Steering Committee will provide reports to FDA as requested.

Investigator responsibilities

As this is an investigator Initiated Clinical Trial, it is expected that each involved investigator is responsible for obtaining the relevant approvals and to provide the required reporting throughout the trial.

Clinical Events Committee

The Clinical Events Committee is made up of interventional and non-interventional cardiologists and cardiac surgeons who are not participants in the trial. A stroke consultant will be available to review neurologic event adjudication as necessary. The Clinical Events Committee is charged with the development of specific criteria used for the adjudication of clinical events and clinical endpoints in the trial which are based on protocol.

The Clinical Events Committee will establish explicit rules outlining the minimum amount of data required, and the algorithm followed in order to classify a clinical event. All members of the Clinical Events Committee will be blinded to the primary results of the trial.

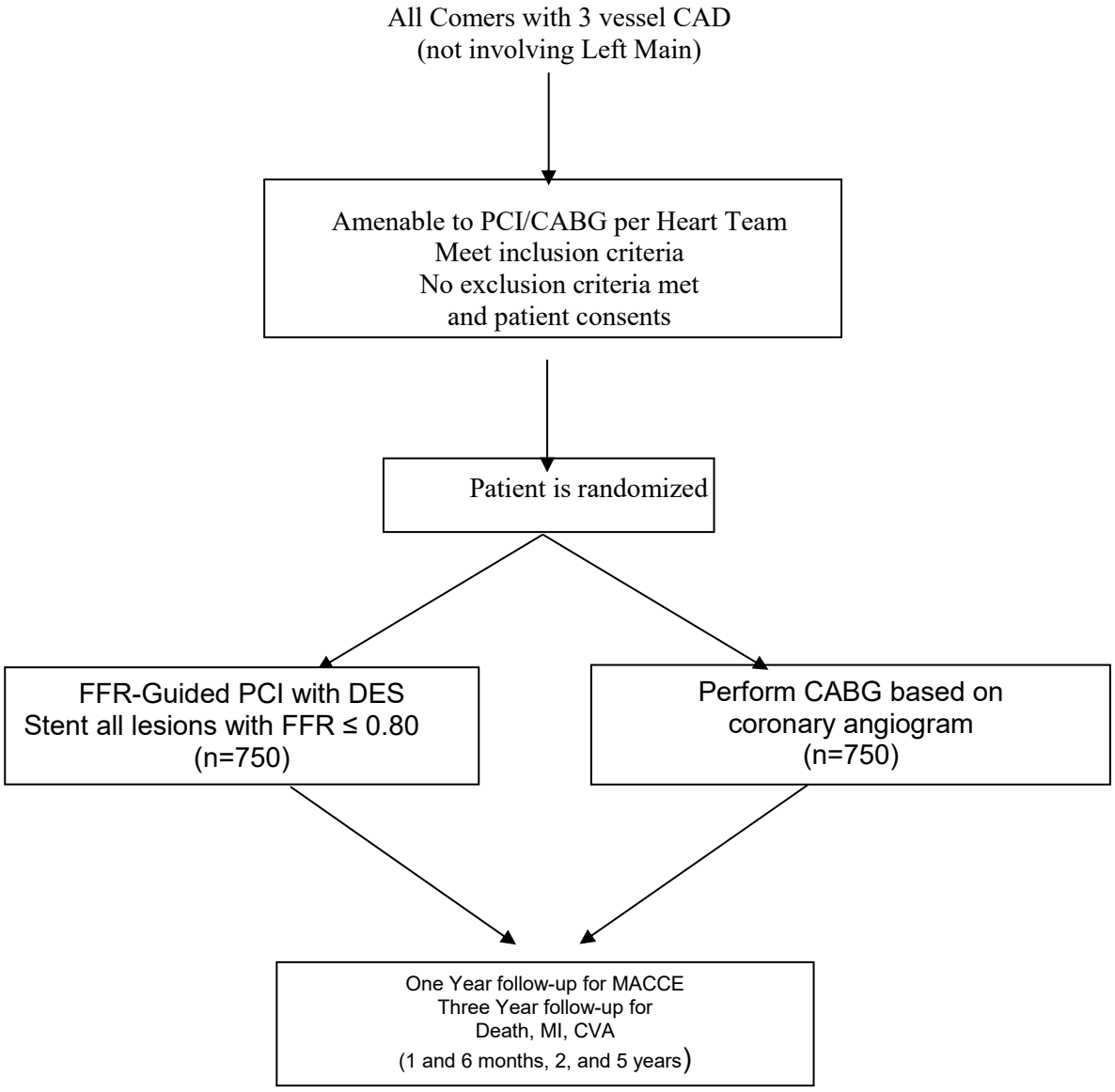
The Clinical Events Committee will meet regularly to review and adjudicate all clinical events in which the required minimum data is available blinded to treatment group assignment. The Committee will also review and rule on all deaths that occur throughout the trial.

All events will be reviewed by the Steering Committee only.

Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) will be an independent group of physicians including an interventional cardiologist, cardiac surgeon and statistician. The DSMB, in conjunction with the Steering Committee, will develop a charter with specific guidelines regarding monitoring the safety of the subjects enrolled in FAME 3. In brief, this group will initially convene quarterly during the first year of enrolment and then every 6 months for the remainder of the trial and have complete access to the adverse events in each arm of the trial. Based on their clinical judgment, the DSMB can recommend stopping the trial. The final decision regarding stopping enrollment will rest with the Steering Committee.

Study Flowchart



9. Endpoints

Primary Endpoints

Death, MI, stroke and any repeat revascularization (MACCE) will be evaluated at 1 year from the last patient randomized, where subjects contribute data from time of enrollment until the occurrence of MACCE or one year follow-up, whichever occurs first. Subjects who die or are lost to follow up before this time will be censored at their last recorded activity.

Key Secondary Endpoint

Death, MI, and stroke will be evaluated at 3 years from the last patient randomized, where subjects contribute data from time of enrollment until the occurrence of MACCE or three year follow-up, whichever occurs first. Subjects who die or are lost to follow up before this time will be censored at their last recorded activity. This secondary endpoint is not a co-primary endpoint because we would need to adjust for multiplicity and this would increase our sample size.

Other Secondary Endpoints

- Comparison of proportion of patients in each arm with MACCE at one year, excluding patients lost to follow-up from each arm
- MACCE rate at each time point besides one year
- Rate of each individual component of MACCE at each time point
- Rate of death, MI, and stroke at each time point
- Rate of death and MI at each time point
- Rate of cardiac death alone and in combination with other end points
- Rate of death, MI, stroke and all repeat revascularizations at each time point
- Stent thrombosis (ARC definition) and graft occlusion at each time point
- Bleeding complication
- Significant arrhythmia
- Development of acute renal failure
- Length of hospital stay
- Rehospitalization within 30 days and 1 year of the primary procedure

- Usefulness of the STS, logistic Euroscore, SYNTAX score, clinical SYNTAX score, ACEF score, Functional SYNTAX score and other scoring systems for predicting outcomes
- Outcomes based on left internal mammary artery use alone versus multiple arterial conduits
- Cost and cost-effectiveness at each time point
- Health-related quality of life index (EQ-5D) at each time point
- Functional class at each time point
- Number of anti-anginal medications at each time point.

Pre-specified Subgroup Analyses

These analyses will be performed between the PCI and CABG arms, as well as within each arm, as appropriate.

- Comparison of outcomes by baseline features including diabetes status, sex, age, ejection fraction, kidney function, acute coronary syndrome, prior MI, and geographic location (within or outside of the United States).
- Comparison of outcomes by STS, logistic Euroscore, SYNTAX score, clinical SYNTAX score, ACEF score and Functional SYNTAX score
- Comparison of outcomes by revascularization status (i.e., complete or incomplete as defined by angiogram)
- Compare complete arterial revascularization to incomplete arterial revascularization in the CABG group
- Compare on-pump to off-pump CABG results
- Comparison of outcomes by proximal LAD versus non proximal LAD
- Comparison of surgical results between patients with FFR measured before CABG and angiography-guided CABG

10. Statistics

Null and Alternative Hypotheses to Address Primary Question

The study makes use of a noninferiority design and assumes that a hazard ratio of 1.65 or less is not clinically meaningful. More specifically, the null hypothesis is that the hazard of MACCE for PCI patients is greater than that of CABG patients and the alternative hypothesis is that the hazard of MACCE for PCI is not worse (not greater) than that for CABG patients. Let HR_0 be the non-inferiority margin – i.e., the maximum ratio of clinical insignificance. Then the null (H0) and alternative (H1) hypotheses can be expressed as:

$$H_0: HR \geq HR_0 \ \ vs \ H_1: \ HR < HR_0$$

Primary Analysis Plan: Statistical Tools and Test Statistic

The primary analysis will be based on the intention-to-treat (ITT) principle, whereby all randomized patients will be included in the analysis and according to the treatment group to which they were originally allocated. Patients will be encouraged to remain in the trial until completion of up to 5 years follow-up. All patients will be followed for 5 years post-randomization or until they die, whichever comes first. If a patient refuses further clinical follow-up, the follow-up evaluation will be conducted using telephone interviews. For patients who drop out or are lost to follow-up, the reason for dropping out or being lost will be recorded. Importantly, for the primary analysis the patient will be censored at the time when the last follow-up examination or telephone contact took place if the subject did not experience MACCE, allowing the subject to be included in the analysis according to the ITT analysis plan.

Kaplan-Meier curves will be used to graphically display differences in MACCE by treatment arm and by diabetes status. In addition, we will use survival analytic techniques such as a log-rank test or, if appropriate, a Cox proportional hazards (PH) model to estimate the difference in hazard of MACCE by treatment arm, stratified by center, and with diabetes status included as a term in the model. The test for non-inferiority of fractional flow reserve-guided PCI will be one-sided and assessed at the 0.025 level of significance. For example, a Cox PH model for the hazard of MACCE can be expressed as:

$$\lambda_1 = \lambda_{0i} \exp(\beta_1 PCI + \beta_2 DM)$$

for i=1, 2, …, 50 where i indexes the clinical sites involved in the study, PCI represents an indicator for whether a subject has been randomized to the PCI arm, DM is an indicator for whether the subject has been diagnosed with diabetes at baseline, λ_1 , represents the hazard of MACCE, and λ_{0i} represents the baseline hazard of MACCE at the i^{th} clinical site. Our model allows the baseline hazard of MACCE to vary by clinical site. Our interest lies in inference about β_1 , which represents the difference in log-hazard between the treatment arms. A Wald test statistic that is a function of β_1 can then be used to assess whether the hazard ratio for the treatment arms is within the non-inferiority margin. For this purpose, we will conduct a one-sided test at the 0.025 level of significance.

Model Diagnostics: Assessing heterogeneity of hazards across levels of confounders and assessing adherence to the proportional hazards assumption

We will perform a number of tests to confirm that the assumptions in the above model are reasonable. If the number of subjects per site is too small, we will pool smaller sites so that there are at least 10 subjects per site. Then, to confirm that the hazard of MACCE does not vary by pooled site, diabetes status and gender, we will include an interaction term between pooled site, PCI and diabetes and test whether the corresponding coefficient is greater than zero using a two-sided Wald test statistic at the 0.15 level of significance. We will take a similar approach by including an interaction term between gender and PCI. If homogeneity of the hazard by a feature is rejected, the corresponding interaction term will be included in the model. The test statistic corresponding to the primary question of interest (i.e., the treatment effect) will be evaluated in the presence of the interaction term to describe the overall treatment effect. We will additionally present the hazard ratios by levels of the modifying factor.

The proportional hazards assumption will be evaluated through graphical techniques including plots of transformed survival estimates (i.e., log(-log(survival at time t))) by log-transformed time and Kaplan-Meier curves by treatment arm. Should the assumption be violated, we can relax the assumption through inclusion of an interaction term between treatment arm and log-transformed time.

Sample Size and Power Considerations[17]

Recently, the EXCEL[18], NOBLE[19] and BEST[20] trials have been published. These studies demonstrate a one 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. In addition, in EXCEL, a clinically acceptable non-inferiority margin for death, CVA and MI 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 Steering Committee feels a hazard ratio of 1.65 is more appropriate for defining a clinically acceptable non-inferiority margin. We assume a 10% of subjects in the CABG arm experience MACCE, and further that patients in the PCI arm will not experience a higher rate than those in the CABG arm. We would deem an increase in event rate up to and including a 16% event rate as not clinically inferior. Thus, given a clinically irrelevant hazard ratio of 1.65, a one-sided 2.5% significance level and 90% power to reject the null hypothesis if it is false, the sample size necessary is 645 patients per group (1290 for the entire study). These calculations are based on assumptions of uniform accrual over time, no loss to follow-up, exponentially distributed death times, and a Wald test statistic. Thus, to account for patients lost to follow-up and subject withdrawal we will enroll up to 1500 patients from up to 50 medical centers.

Sensitivity Analyses

Our current approach is to do an intent-to-treat analysis and include all randomized subjects in the analysis. Subjects who are lost to follow-up will be included in the analysis up to the time they are censored. An alternative set of analyses that will serve as sensitivity analyses will be to compare the proportion of subjects who experience the primary event at one year of follow-up by treatment arm using logistic regression techniques, where subjects who are lost to follow-up are excluded from the analysis, or included with an imputed outcome using multiple imputation techniques that rely on missing at random and missing not at random techniques. Auxiliary variables to be used in the multiple imputation include all baseline variables such as age, gender, site, diabetes status, etc. This will allow comparisons to our primary analysis. If results are similar across analyses, this will bolster our findings. If they are different, we will report the discrepancy. The results from our primary analysis, however, will be reported as our final analysis.

Secondary Analyses

Secondary analyses will be performed to inform future studies and are therefore considered hypothesis-generating. For example, we will use Cox proportional hazards regression techniques to assess whether the differences in hazard of the key secondary outcome of death, MI, and stroke (censored at 3 years) is different by treatment arms. Similarly, we will use these tools to investigate whether relationships between outcome and treatment vary by baseline features such as age, sex, geographic location, etc.

11. Appendix A.

Definitions

Death is defined as all cause death. Cardiac death is defined as any sudden death, death related to acute myocardial infarction, arrhythmia or congestive heart failure, death secondary to a cerebrovascular accident, or death directly related to PCI or CABG, even if the ultimate cause of death is not clearly a cardiac event (e.g., infection). Non-cardiac death is any death which is not clearly cardiac in etiology.

Myocardial infarction is defined in two ways, depending on whether or not it is PCI or CABG-related or a spontaneous event, as recently described in the literature.[21]

Spontaneous myocardial infarction (>72 hours after PCI or CABG):

Detection of rise and/or fall of cardiac biomarkers (CK-MB or troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:

- Symptoms of ischemia
- ECG changes indicative of new ischemia [new ST-T changes or new, persistent, non rate-related left bundle branch block (LBBB)]
- Development of pathological Q waves (≥ 0.03 seconds in duration and ≥ 1 mm in depth) in ≥ 2 contiguous precordial leads or ≥ 2 adjacent limb leads of the ECG
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

PCI or CABG-related MI (<72 hours after PCI or CABG):

Elevation of the cardiac troponin value > 10 x 99th percentile of the URL in patients with a normal baseline reference level, or an increase of > 20%, if the baseline values are elevated, but are stable or falling. In addition, at least one of the following:

(i) new pathologic Q waves or new left bundle branch block
(ii) angiographic documented new graft or new major native coronary occlusion
(iii) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormalities is required.

Stroke (cerebrovascular accident or CVA) is the rapid onset of a focal or global neurological deficit. If the duration is <24 hours, the event is deemed a transient ischemic attack (TIA), except if an intervention is performed as defined below. If the duration is ≥24 hours, it is deemed a stroke. Stroke is subdivided as ischemic, hemorrhagic, or undetermined. Ischemic stroke refers to acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of the central nervous system tissue. Hemorrhagic stroke is an acute symptomatic episode of focal or global cerebral or spinal dysfunction caused by nontraumatic intraparenchymal, intraventricular or subarachnoid hemorrhage. Undetermined stroke is one with insufficient information to allow categorization as either of the above two.

Stroke is diagnosed when the following criteria are met:

1. Rapid onset of a focal/global neurological deficit with at least one of the following:
    - Change in level of consciousness
    - Hemiplegia
    - Hemiparesis
    - Numbness or sensory loss affecting one side of the body
    - Dysphagia/aphasia
    - Hemianopia
    - Amaurosis fugax
    - Other new neurological sing(s)/symptom(s) consistent with stroke

2. Duration of focal/global neurological deficit is ≥24 hours, or it can be <24 hours if a therapeutic intervention is performed, brain imaging clearly documents a new hemorrhage or infarct, or the neurological deficit results in death.
3. Confirmation of the diagnosis by at least one of the following:
    - Neurology or neurosurgical specialist
    - Brain imaging (CT, MRI, or cerebral vessel angiography)
    - Lumbar puncture diagnostic of intracranial hemorrhage

Urgent revascularization is defined as an unplanned hospitalization for an acute coronary syndrome with at least one of the following: electrocardiographic changes, biomarker elevation, or new perfusion/wall motion abnormalities to document ischemia and which results in revascularization during the hospitalization.

Repeat revascularization is defined as any unplanned (elective or urgent) revascularization, whether PCI or CABG. Planned staged PCI procedures do not qualify.

Bleeding is defined as per the Bleeding Academic Research Consortium (BARC).[22] Other descriptions of bleeding, such as TIMI, will be applied as well.

BARC Bleeding Definitions:

Type 0: no bleeding

Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

Type 2: any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation

Type 3

Type 3a

Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed)

Any transfusion with overt bleeding

Type 3b

Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed)

Cardiac tamponade

Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)

Bleeding requiring intravenous vasoactive agents

Type 3c

Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)

Subcategories confirmed by autopsy or imaging or lumbar puncture

Intraocular bleed compromising vision

Type 4: CABG-related bleeding

Perioperative intracranial bleeding within 48 h

Reoperation after closure of sternotomy for the purpose of controlling bleeding

Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period†

Chest tube output ≥2 L within a 24-h period

Type 5: fatal bleeding

Type 5a

Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

Type 5b

Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

Stent thrombosis is defined as per the Academic Research Consortium.[23]

ARC Definitions:

Definite stent thrombosis

1. Angiographic confirmation of stent thrombosis
2. The presence of a thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:

- Acute onset of ischemic symptoms at rest
- New ischemic ECG changes that suggest acute ischemia
- Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)
- Nonocclusive thrombus
- Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary

stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.
- Occlusive thrombus
- TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).
- Pathological confirmation of stent thrombosis
- Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

Probable stent thrombosis

Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

- Any unexplained death within the first 30 days
- Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

Possible stent thrombosis

Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up.

Graft Occlusion is defined based on an ARC-like definition[24]

Definite graft occlusion

1. Clinical presentation of acute coronary syndrome with graft occlusion confirmed by angiography, multi-slice CT or autopsy
2. Q-wave MI in the territory of one or more of the treated vessels within the first 30 days

Probably graft occlusion

1. Any unexplained death within 30 days of CABG
2. Any MI that is related to documented acute ischemia in the territory of the anastomosed graft without angiographic confirmation of graft occlusion

Possible graft occlusion

1. Any unexplained death beyond 30 days

Significant Arrhythmia consists of ventricular tachycardia or fibrillation requiring cardioversion, atrial fibrillation lasting > 24 hours, or need for a permanent pacemaker.

Acute Kidney Injury AKI (acute kidney injury) is defined as any of the following:

K Increase in SCr (Serum creatinine) by ≥0.3 mg/dl (≥26.5 µmol/l) within 48 hours;
or K Increase in SCr to≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days;
or K Urine volume <0.5 ml/kg/h for 6 hours.

Rehospitalization is defined as a hospital stay of >36 hours.

Cross-over

If, during the first month after randomization, a patient receives as the initial revascularization therapy the alternative form of revascularization than the assigned treatment (i.e. Randomized to CABG but receives PCI), this will be defined as a cross-over and not a repeat revascularization event, unless the reason for the alternative revascularization strategy is due to a change in the patient's clinical status resulting in urgent/emergent revascularization.

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