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ORIGINAL INVESTIGATIONS

A Prospective Natural History Study of Coronary Atherosclerosis Using Fractional Flow Reserve

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ABSTRACT

BACKGROUND In patients with coronary artery disease, clinical outcome depends on the extent of reversible myocardial ischemia. Whether the outcome also depends on the severity of the stenosis as determined by fractional flow reserve (FFR) remains unknown.

OBJECTIVES This study sought to investigate the relationship between FFR values and vessel-related clinical outcome.

METHODS We prospectively studied major adverse cardiovascular events (MACE) at 2 years in 607 patients in whom all stenoses were assessed by FFR and who were treated with medical therapy alone. The relationship between FFR and 2-year MACE was assessed as a continuous function. Logistic and Cox proportional hazards regression models were used to calculate the average decrease in the risk of MACE per 0.05-U increase in FFR.

RESULTS MACE occurred in 272 (26.5%) of 1,029 lesions. Target lesions with diameter stenosis ≥70% were more often present in the MACE group ($p < 0.01$). Median FFR was significantly lower in the MACE group versus the non-MACE group (0.68 [interquartile range: 0.54 to 0.77] vs. 0.80 [interquartile range: 0.70 to 0.88]; $p < 0.01$). The cumulative incidence of MACE significantly increased with increasing FFR quartiles. An average decrease in MACE per 0.05-unit increase in FFR was statistically significant even after adjustment for all clinical and angiographic features (odds ratio: 0.81; 95% confidence interval: 0.76 to 0.86]). The strongest increase in MACE occurred for FFR values between 0.80 and 0.60. In multivariable Cox regression analysis, FFR was significantly associated with MACE up to 2 years (hazard ratio: 0.87; 95% confidence interval: 0.83 to 0.91]).

CONCLUSIONS In patients with stable coronary disease, stenosis severity as assessed by FFR is a major and independent predictor of lesion-related outcome. (FAME II - Fractional Flow Reserve [FFR] Guided Percutaneous Coronary Intervention [PCI] Plus Optimal Medical Treatment [OMT] Verses OMT; NCT01132495) (J Am Coll Cardiol 2016;68:2247–55)

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CV = cardiovascular

FFR = fractional flow reserve

HR = hazard ratio

MACE = major adverse cardiovascular event

MI = myocardial infarction

MT = medical therapy

PCI = percutaneous coronary intervention

Q = quartile

TVR = target vessel revascularization

The extent of stress-induced myocardial ischemia is an important determinant of outcome in patients with stable coronary artery disease. The natural history of atherosclerotic lesions was previously investigated with intracoronary imaging, mainly focusing on plaque composition without accounting for the potential impact of mechanical stress exerted on the plaque itself by intracoronary pressure gradients (1). Fractional flow reserve (FFR) uniquely relates hyperemic pressure loss over a stenosis to the potential maximum flow in the absence of the lesion (2). In addition, FFR identifies coronary stenoses able to induce reversible myocardial ischemia (3,4) and optimizes the risk stratification of patients with chest pain undergoing coronary angiography. Patients with preserved FFR have an excellent very long-term prognosis with medical therapy (MT) alone (5) whereas patients with abnormal FFR benefit from revascularization (6–8). A meta-analysis suggested a risk continuum between the actual FFR value and clinical outcome, offering mechanistic insight into local plaque progression (9), yet these data were obtained retrospectively in patients in whom FFR had significantly altered the management strategy.

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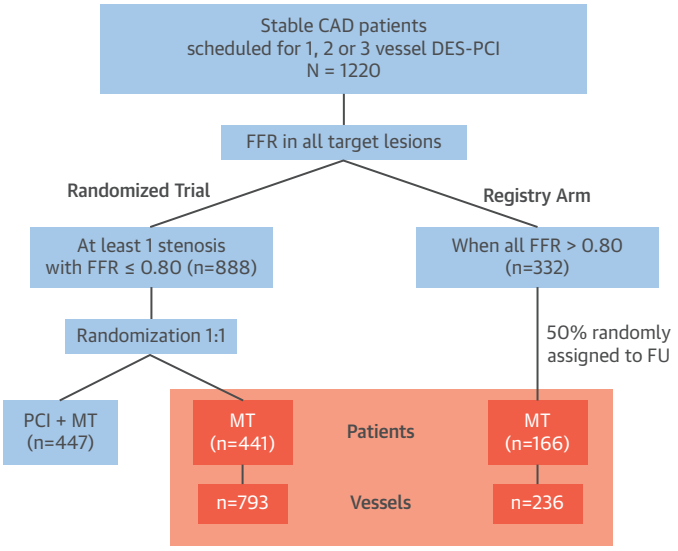
In the FAME-2 (Fractional Flow Reserve versus Angiography for Multivessel Evaluation-2; NCT01132495) trial (funded by St. Jude Medical), patients were randomized to percutaneous coronary intervention (PCI) or to MT alone when at least 1 coronary stenosis showed an abnormal FFR (7,8). Patients with angiographically significant stenoses that appeared to be hemodynamically nonsignificant were not randomized but treated with MT alone and followed in a registry.

The present report analyzes the outcome of all patients in whom the lesions were assessed with FFR and initially received MT alone, thus describing the natural history of coronary atherosclerosis from a coronary hemodynamic perspective.

FIGURE 1 Study Flow Diagram



Flow diagram of the FAME-2 (Fractional Flow Reserve-guided PCI Versus Medical Therapy-2) trial highlighting the patients treated with medical therapy (MT) only and included in the present vessel level subanalysis **(orange)**. CAD = coronary artery disease; DES = drug-eluting stent(s); FFR = fractional flow reserve; FU = follow-up; PCI = percutaneous coronary intervention.

METHODS

PATIENTS. The study design and the results of the FAME-2 trial have been previously reported (7). In short, the FAME-2 trial randomized consecutive patients with stable angina and angiographically assessed 1-, 2-, or 3-vessel coronary disease suitable for PCI. FFR was measured with a coronary guidewire (PressureWire Certus or PressureWire Aeris, St. Jude Medical, St. Paul, Minnesota) during adenosine-induced hyperemia to assess the hemodynamic severity of each indicated stenosis. Patients who had at least 1 stenosis in a major coronary artery with an FFR

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