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**Citation for published version (APA):**

Barbato, E., Toth, G. G., Johnson, N. P., Pijls, N. H. J., Fearon, W. F., Tonino, P. A. L., Curzen, N., Piroth, Z., Rioufol, G., Jüni, P., & de Bruyne, B. (2016). A prospective natural history study of coronary atherosclerosis using fractional flow reserve. *Journal of the American College of Cardiology*, 68(21), 2247-2255.  
<https://doi.org/10.1016/j.jacc.2016.08.055>

**DOI:**

[10.1016/j.jacc.2016.08.055](https://doi.org/10.1016/j.jacc.2016.08.055)

**Document status and date:**

Published: 29/11/2016

**Document Version:**

Publisher's PDF, also known as Version of Record (includes final page, issue and volume numbers)

**Please check the document version of this publication:**

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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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  $\geq 70\%$  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](https://doi.org/10.1016/j.jacc.2016.08.055)) (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.

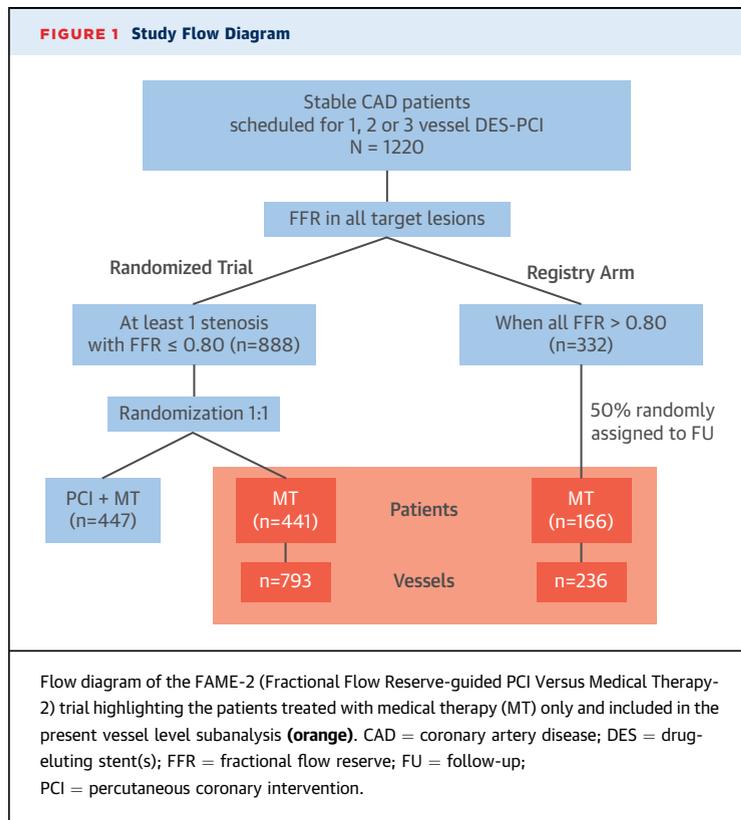
SEE PAGE 2256

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.

**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 Aerus, 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



Dr. Fearon has received research grant support from St. Jude Medical, Medtronic, and Acist Medical; and has served as a consultant for Medtronic, Heartflow, and CathWorks. Dr. Curzen has received unrestricted grant support from Boston Scientific, St. Jude Medical, and Heartflow; an education grant from Volcano; and speaker fees from Boston Scientific and Heartflow. Dr. Jüni has received research grants to his institution from AstraZeneca, Biotronik, Biosensors International, Eli Lilly, and The Medicines Company; and has served as an unpaid member of the steering group of trials funded by AstraZeneca, Biotronik, Biosensors, St. Jude Medical, and The Medicines Company. Dr. De Bruyne is a shareholder for Siemens, GE, Bayer, Philips, Heartflow, Edwards Lifesciences, Sanofi, and Omega Pharma; his institution (Cardiovascular Center, Aalst, Belgium) has received grant support from Abbott Vascular, Boston Scientific, Biotronik, and St. Jude Medical; and he has received consulting fees from St. Jude Medical, Opsens, and Boston Scientific not related to this publication. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

of 0.80 or less were randomly assigned to FFR-guided PCI plus the best available MT or to the best available MT alone. Patients with an FFR of more than 0.80 in all vessels were enrolled in a registry and received the best available MT. A random sample of 50% of the registry patients underwent the same follow-up as the patients in the randomized trial. In this analysis, we included all of the patients who were treated only with best available MT alone and who had 2 years of clinical follow-up—namely, patients randomized to best available MT plus patients enrolled in the registry who underwent clinical follow-up (Figure 1). All patients provided written informed consent, and local Institutional Review Boards approved the study protocol.

**VESSELS.** This study investigated the relationship between FFR values and clinical outcome at the vessel or lesion level. Angiographic characteristics and endpoints are reported at the vessel level. Coronary stenosis severity was assessed by visual estimation, and reported according to the main FAME-2 trial (7) in the following strata of diameter stenosis: <50%, 50% to 69%, 70% to 90%, and >90%. We excluded vessels with chronic total occlusions from our analysis (n = 28), as FFR was not measured in these vessels, and an arbitrary value of 0.50 was assigned according to the FAME-2 trial protocol.

**ENDPOINTS.** This is a pre-specified subanalysis of the FAME-2 study. The primary endpoint is major adverse cardiovascular event (MACE) at 2 years, defined as the composite of cardiovascular (CV) death, target vessel-related myocardial infarction (MI), and ischemia-driven target vessel revascularization (TVR) (both urgent and nonurgent). All outcomes were previously adjudicated by an independent clinical events committee whose members were unaware of the treatment assignments. All the narratives of the patients experiencing an event at follow-up were blindly reviewed and the event was unequivocally assigned to the culprit vessel in case of MI and ischemia-driven TVR. When the identification of the culprit vessel was not possible/feasible (i.e., in case of CV death, no coronary angiography performed, or non-ST-segment elevation MI in patients with multivessel disease), the endpoint was assigned to all the stenotic vessels of those patients. This was the case in a very small minority of events, the culprit vessel could not be identified in 3 of 272 cases (1%), while the culprit vessel was identified in all the cases where FFR was available at the baseline. The culprit lesion could not be identified in 23 of the 272 cases (8%), and in 19 cases where FFR was available at the baseline. Given this negligible dependence among the events per vessel of the same subject, we did not pursue a mixed effects model.

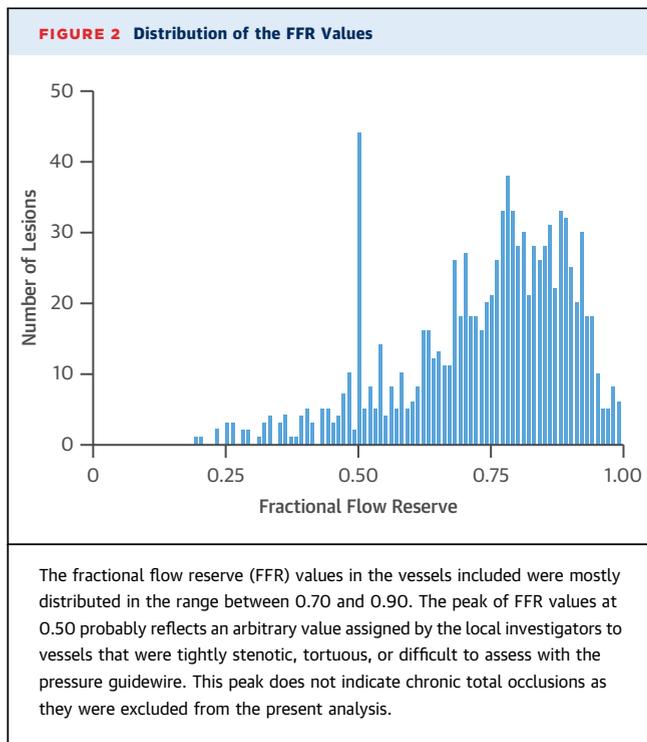
**TABLE 1 Univariable Predictors of MACE**

	MACE	HR (95% CI)	p Value
<b>Patients (n = 607)</b>			
Median age (64 yrs)			
Below median	93 (31)	Ref.	—
Above median	92 (29)	0.93 (0.69-1.24)	0.63
Sex			
Female	44 (28)	Ref.	—
Male	141 (31)	1.09 (0.78-1.54)	0.59
Median BMI (28 kg/m <sup>2</sup> )			
Below median	98 (30)	Ref.	—
Above median	86 (30)	1.02 (0.76-1.36)	0.91
Risk factors			
Smoker	39 (31)	1.01 (0.71-1.44)	0.95
Hypertension	144 (30)	0.89 (0.63-1.27)	0.55
Hypercholeolemia	139 (29)	0.90 (0.65-1.26)	0.55
Diabetes overall	55 (35)	1.19 (0.87-1.63)	0.27
Diabetes ID	20 (41)	1.46 (0.92-2.32)	0.11
Renal insufficiency	7 (37)	1.32 (0.62-2.80)	0.47
History			
Previous PCI	33 (30)	0.97 (0.67-1.42)	0.89
Previous MI	67 (30)	0.89 (0.66-1.21)	0.47
Presentation			
MVD	126 (29)	0.86 (0.63-1.17)	0.34
EF <50%	24 (29)	0.85 (0.56-1.32)	0.48
CCS angina class ≥III	133 (33)	1.39 (1.01-1.91)	0.04
<b>Vessels (n = 1,029)</b>			
Vessel location			
LCx/RCA	133 (24)	Ref.	—
LMCA/LAD	139 (29)	1.25 (0.98-1.58)	0.07
DS strata			
<50%	6 (8)	Ref.	—
50%-69%	92 (18)	2.32 (1.01-5.29)	0.046
70%-90%	142 (38)	5.62 (2.48-12.73)	<0.001
>90%	32 (40)	5.99 (2.50-14.35)	<0.001
Lesion type*			
A	54 (18)	Ref.	—
B1	84 (23)	1.33 (0.95-1.88)	0.10
B2	87 (35)	2.21 (1.57-3.10)	<0.001
C	44 (44)	2.8 (1.89-4.17)	<0.001

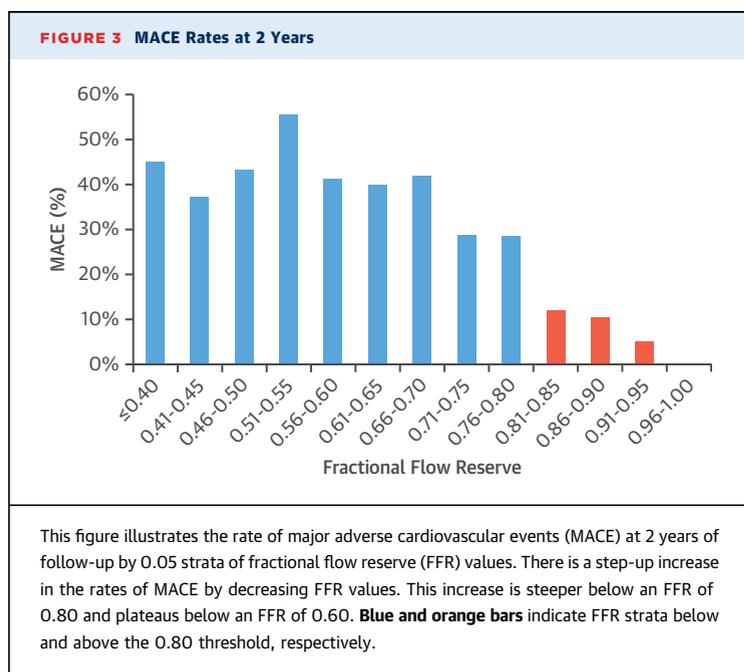
Values are n (%) unless otherwise indicated. \*For 6 lesions in patients without major adverse cardiovascular events (MACE), and 3 lesions in patients with MACE, data on lesion type was unavailable.

BMI = body mass index; CI = confidence interval; CCS = Canadian Cardiovascular Society; DS = diameter stenosis; EF = ejection fraction; HR = hazard ratio; ID = insulin dependent; LAD = left anterior descending artery; LCx = left circumflex artery; LMCA = left main coronary artery; MI = myocardial infarction; MVD = multivessel disease; PCI = percutaneous coronary intervention; RCA = right coronary artery.

**STATISTICAL ANALYSIS.** Continuous variables are presented as mean ± SD or median (interquartile range). Categorical data are presented as numbers and percentages. Normal distribution was tested with the D’Agostino-Pearson omnibus K2 test. Comparisons between continuous variables were performed using the Student *t* test or Mann-Whitney *U* test, as appropriate. Comparisons between categorical variables were evaluated using Fisher exact test or Pearson chi-square test, as appropriate. To select an appropriate



statistical model for the relationship between FFR and MACE, we used nonparametric regression with locally weighted scatterplot smoothing in SPSS (version 20, IBM, Armonk, New York). Cox regression analysis was used to calculate the hazard ratio (HR) and 95% confidence interval (CI) for 0.05 FFR strata, and



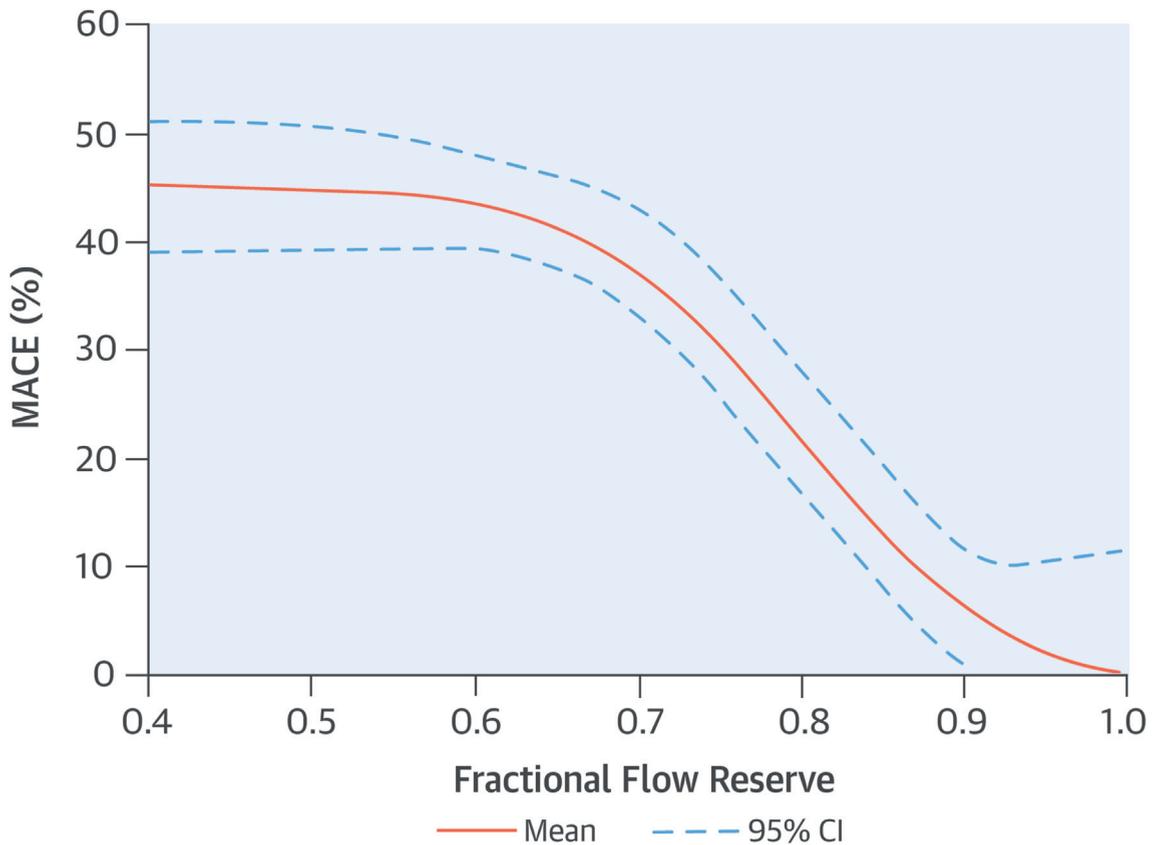
for the FFR quartile (Q) (Q1: 1.00 to 0.87; Q2: 0.86 to 0.78; Q3: 0.77 to 0.64; Q4:  $\leq 0.63$ ), for % diameter stenosis and American College of Cardiology/American Heart Association lesion type. The 0.05 stratum was chosen as it is beyond the threshold of test-retest repeatability of FFR (i.e., a standard deviation of 0.02) and it represents a clinically meaningful FFR variation. In the calculation of the HR for urgent and nonurgent revascularization the occurrence of death was censored. Multivariable adjustment was performed for baseline clinical and angiographic features associated with MACE ( $p \leq 0.15$ ) as described in the results and tables. We constructed Kaplan-Meier curves for the primary endpoint of MACE, and of its individual endpoints at 2 years of follow-up. The equality of the Kaplan-Meier curves was analyzed with the log-rank test. MACE rates at 2 years were calculated with the Kaplan-Meier method. In an exploratory analysis, we also constructed a Kaplan-Meier curve and calculated the hazard ratio for lesion type in stenotic vessels with an FFR above 0.80. A 2-sided  $p$  value  $< 0.05$  was considered statistically significant. All analyses were performed with the SPSS software and GraphPad Prism 4 (GraphPad Software, Inc., San Diego, California).

## RESULTS

**PATIENTS AND CORONARY ARTERIES.** Six hundred and seven patients were included in this analysis (Figure 1). Baseline characteristics of the patients are reported in Table 1 and Online Table 1. Overall, the patients had common risk factors for coronary artery disease, with up to two-thirds of them presenting with multivessel disease (429 of 607). There were no significant differences between patients with or without MACE, with the exception of CCS angina class  $\geq 3$  that was more frequent in those patients experiencing an event during follow-up.

Angiographic characteristics of the 1,029 stenotic vessels included are reported in Table 1. Overall, the stenosis was commonly located in the left anterior descending coronary artery (in about 50% of the cases). A majority of the lesions were in the intermediate range of 50% to 69% diameter stenosis, and of moderate complexity (Online Table 2). There were no significant differences in terms of vessel location between those stenoses with or without an event at follow-up. Coronary arteries responsible for an event during follow-up had angiographically more significant and complex stenoses. FFR values were mostly distributed in the range between 0.70 and 0.90 (Figure 2). Coronary stenoses with an event during follow-up had lower FFR values (median: 0.68

**CENTRAL ILLUSTRATION FFR and Major Adverse Cardiovascular Events**



Barbato, E. et al. *J Am Coll Cardiol.* 2016;68(21):2247-55.

Correlation between fractional flow reserve (FFR) values and vessel-related major adverse cardiovascular events (MACE) at 2 years (odds ratio: 0.009; 95% confidence interval: 0.003 to 0.024;  $p < 0.001$ ). The risk of MACE at 2 years can be calculated after measuring FFR for that given stenotic coronary artery from the following equation:  $MACE (\%) = -0.009602 + 0.459202 / [1 + 10^{(0.7995 - FFR \text{ value}) \times -7.004}]$ .

[IQR: 0.54 to 0.77] vs. 0.80 [IQR: 0.70 to 0.88];  $p < 0.001$ ) as compared to stenoses without an event.

**CLINICAL ENDPOINTS.** Clinical follow-up was available in all patients with a mean duration of  $23 \pm 2$  months. MT at 2 years was available in 582 patients (96%) and was not different between patients with or without MACE (Online Table 3).

The cumulative incidence of MACE decreased with increasing FFR values (Figure 3). This increase in MACE for each 0.05 FFR unit remained statistically significant (HR: 0.87; 95% CI: 0.83 to 0.91;  $p < 0.001$ ) after adjusting for potential confounders. This significant association between FFR values and MACE was nonlinear (Central Illustration), steeply increasing from FFR values of 0.80 to 0.60, and plateauing for FFR values below 0.60.

The cumulative incidence of MACE significantly increased with increasing FFR quartiles (Table 2, Figure 4, Online Figure 1). This was mostly driven by a significant increase in the cumulative incidence of urgent and nonurgent revascularization with increasing FFR quartiles. A borderline nonsignificant association was observed between CV death or vessel-related MI and FFR quartiles. Multivariable Cox regression analysis (Table 3) confirmed a significant association between FFR values and MACE at 2 years.

The cumulative incidence of MACE was significantly increased also with increasing % diameter stenosis severity and increasing stenosis complexity as expressed by the lesion type (Online Figure 2). Nevertheless, only lesion complexity remained significant after adjusting for potential confounders (Table 3). In

**TABLE 2** Rates of MACE, Death or MI, and Urgent and Nonurgent Revascularization at 2 Years for Each FFR Quartile

Quartile	n (%)	HR (95% CI)	p Value
<b>MACE</b>			
Q1 (0.87-1.00)	14 (5.4)	Ref.	—
Q2 (0.78-0.86)	50 (19.2)	3.44 (1.90-6.23)	<0.001
Q3 (0.64-0.77)	91 (35.0)	6.71 (3.82-11.78)	<0.001
Q4 ( $\leq$ 0.63)	105 (40.4)	9.84 (5.63-17.20)	<0.001
<b>Death or MI</b>			
Q1 (0.87-1.00)	6 (14.0)	Ref.	—
Q2 (0.78-0.86)	8 (18.6)	1.20 (0.41-3.45)	0.74
Q3 (0.64-0.77)	17 (39.5)	2.52 (0.99-6.39)	0.05
Q4 ( $\leq$ 0.63)	12 (27.9)	2.04 (0.76-5.43)	0.15
<b>Urgent revascularization</b>			
Q1 (0.87-1.00)	2 (2.9)	Ref.	—
Q2 (0.78-0.86)	8 (11.4)	3.61 (0.77-16.99)	0.10
Q3 (0.64-0.77)	31 (44.3)	14.29 (3.42-59.73)	<0.001
Q4 ( $\leq$ 0.63)	29 (41.4)	15.56 (3.71-65.20)	<0.001
<b>Nonurgent revascularization</b>			
Q1 (0.87-1.00)	7 (4.2)	Ref.	—
Q2 (0.78-0.86)	36 (21.4)	4.89 (2.17-10.98)	<0.001
Q3 (0.64-0.77)	56 (33.3)	7.67 (3.49-16.82)	<0.001
Q4 ( $\leq$ 0.63)	69 (41.1)	11.90 (5.46-25.90)	<0.001

Death or MI is the composite of cardiovascular death or vessel-related MI. For 17 lesions in patients without MACE, and 12 lesions in patients with MACE, fractional flow reserve (FFR) was unavailable.

Q = quartile; other abbreviations as in Table 1.

an exploratory analysis of stenoses with FFR >0.80, the cumulative incidence of MACE significantly increased with increasing stenosis complexity (Online Figure 3), although this association was not statistically significant after adjusting for potential confounders (HR: 1.39; 95% CI: 0.91 to 2.06; p = 0.21).

## DISCUSSION

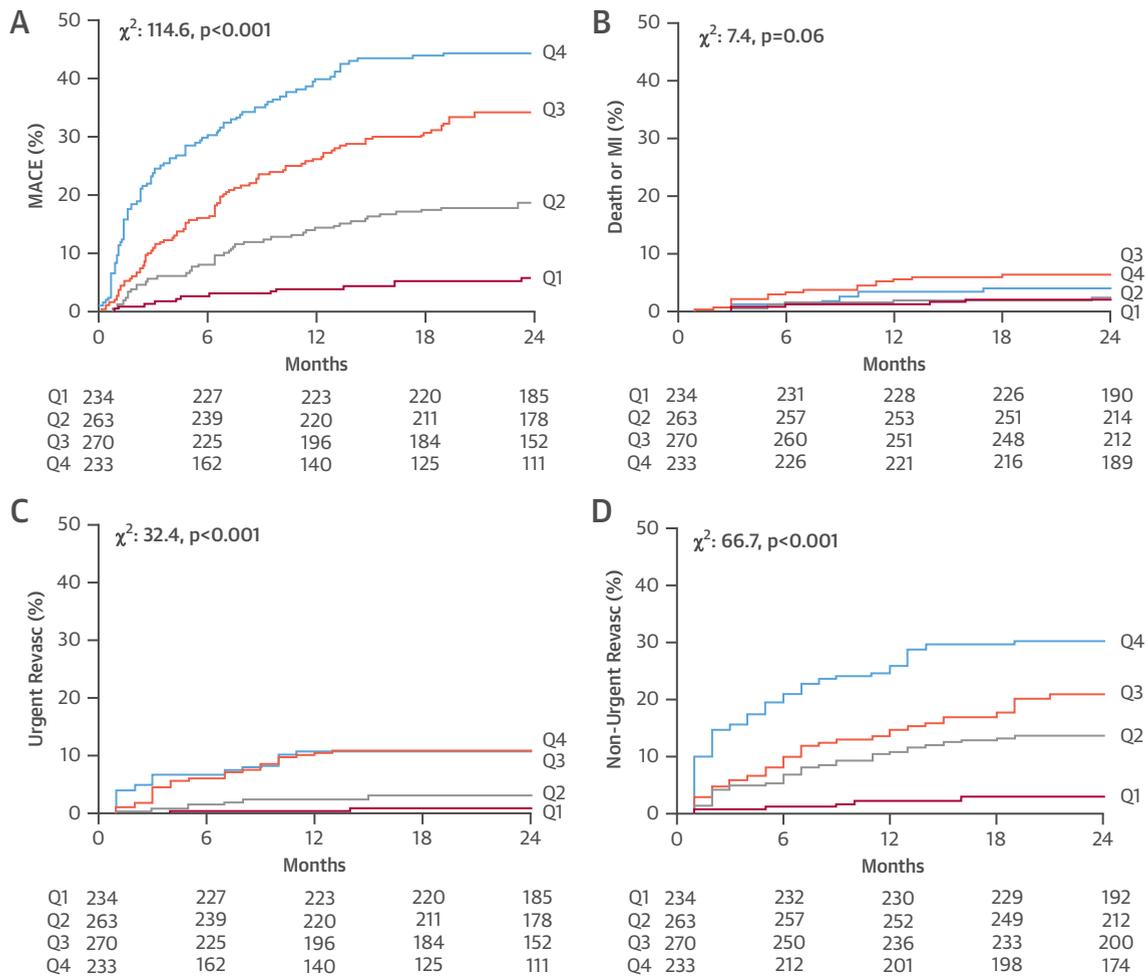
The present study prospectively investigated the vessel-level clinical outcome of stable patients in whom the hemodynamic severity of all angiographically visible stenoses had been assessed by FFR and in whom no mechanical revascularization was performed. The study therefore describes the “natural history” of coronary artery disease in a patient population with stenoses ranging over the whole spectrum of hemodynamic severity, not only stenoses with an FFR >0.80. The data show a significant, independent, and nonlinear association between the functional severity of coronary stenoses as assessed by FFR and the risk of MACE up to 2 years. This increased risk of MACE was mainly driven by urgent and nonurgent TVR, even though a borderline nonsignificant increased rate of CV death or target vessel-related MI was observed. Compared with metrics of angiographic severity and complexity of

coronary artery disease, the functional severity of the coronary stenoses as expressed by FFR quartiles better discriminated the risk and represented the most powerful and independent predictor of MACE at 2 years of follow-up.

**FFR AS A SURROGATE FOR MYOCARDIAL ISCHEMIA.** Myocardial ischemia is the most powerful prognostic factor in patients with coronary artery disease. In patients with documented coronary atherosclerosis, the absence of myocardial ischemia is associated with an excellent long-term clinical outcome (10), while its presence is associated with increased CV events (11,12). Importantly, relieving the ischemic substrate by revascularization improves the unfavorable prognosis of these patients. The benefit of revascularization over MT is particularly clear when the extent of reversible ischemia exceeds 10% (13-16). Because FFR has been uniquely validated against a composite of multiple, noninvasive functional tests, both before and after revascularization, it is considered an invasive surrogate of reversible myocardial ischemia (2-4). By analogy to studies guided by noninvasive evaluation of myocardial ischemia, the absence of coronary stenoses with an abnormal FFR is associated with very favorable long-term clinical outcome in a variety of clinical and anatomic settings (5,6,17-20). On the contrary, in patients with abnormal FFR, a worse clinical outcome has been reported when these patients are managed without revascularization (5,7,8). Revascularization strategies specifically targeting coronary stenoses with abnormal FFR have been associated with a significant improvement in clinical outcome (6-8,19-20).

**DEPTH VERSUS EXTENT OF ISCHEMIA AS PROGNOSTIC FACTORS IN PATIENTS WITH CORONARY ARTERY DISEASE.** Our study provides novel data in support of the prognostic value of FFR at the coronary lesion level. In particular, the lower the FFR value, the higher the risk of MACE at 2 years. The actual value of FFR overrules the prognostic value of angiographic stenosis severity by visual estimate, by taking into account not only the stenotic segment but also the total atherosclerotic burden of the vessel and its impact on regional myocardial perfusion. The lower the FFR value, the more severe, or deeper, the ischemia will be for a same level of stress. This concept of depth of ischemia further extends and complements the concept of extent of ischemia as derived from myocardial perfusion scintigraphy. Hachamovitch et al. (14,15) demonstrated that, in patients without prior revascularization and without extensive scar, the percent of ischemic myocardium correlated with long-term all-cause mortality in the

**FIGURE 4** Cumulative Endpoints up to 24 Months as per FFR Quartiles



(A) Cumulative incidence of major adverse cardiovascular events (MACE) per increasing fractional flow reserve (FFR) quartiles (from quartile [Q] 1 [higher FFR values] to Q4 [lower FFR values]). (B) Cumulative incidence of cardiovascular death (Death) or vessel-related myocardial infarction (MI) per increasing FFR quartiles. (C) Cumulative incidence of urgent revascularizations (Revasc) per increasing FFR quartiles. (D) Cumulative incidence of nonurgent revascularizations. FFR quartiles are as follows: Q1-FFR: 0.87 to 1.00; Q2-FFR: 0.78 to 0.86; Q3-FFR: 0.64 to 0.77; Q4-FFR:  $\leq 0.63$ . The equality among the Kaplan-Meier curves was assessed with the log-rank test.

absence of early revascularization. Yet unlike myocardial perfusion scintigraphy that focuses on the extent of reversible ischemia affecting 1 or more myocardial regions, FFR reflects the depth of inducible ischemia in 1 specific myocardial region subtended by that given stenotic vessel.

**NONLINEARITY OF THE RELATIONSHIP BETWEEN FFR AND MACE.** The present findings corroborate in a prospective cohort a recent meta-analysis supporting a continuous and independent relationship between FFR's numerical value and subsequent

outcomes (9). In the present prospective analysis we found a nonlinear relationship between FFR and MACE. As shown in Figure 3 and in the Central Illustration, FFR values between 0.91 and 1.00 portended a significantly lower risk of MACE than FFR values between 0.81 and 0.90. This risk of MACE steeply increases between FFR values of 0.80 to 0.60 and plateaus for FFR values below 0.60. The brisk increase in the risk of MACE when FFR falls lower than 0.80, confirms the appropriateness of the choice of this value as a threshold triggering revascularization (21). The lack of a further increase in MACE with

<b>TABLE 3 Multivariable Predictors of MACE</b>		
	<b>Adjusted HR (95% CI)</b>	<b>p Value</b>
FFR (quartiles)	1.74 (1.49-2.03)	<0.001
Lesion complexity (AHA/ACC classification)	1.17 (1.03-1.34)	0.014
CCS angina class $\geq$ III	1.15 (1.02-1.29)	0.019
Vessel location	1.23 (0.96-1.58)	0.102
%DS (strata)	1.18 (0.96-1.44)	0.120
Diabetes	1.08 (0.82-1.43)	0.581

HRs are adjusted for all variables in [Table 1 and 2](#) associated with MACE ( $p \leq 0.15$ ). HR reflects the increased risk of MACE for increasing FFR quartile, lesion complexity (from type A to C, American College of Cardiology/American Heart Association [ACC/AHA] classification), and %DS strata (from <50% to >90%) or in case of LMCA/LAD location (vs. LCX/RCA location), and diabetes.  
DS = diameter stenosis; other abbreviations as in [Tables 1 and 2](#).

FFR values below 0.60 is likely due to the presence of well-collateralized vascular territories with a relatively low likelihood of adverse events. Moreover, the low prevalence of lesions with such reduced FFR values in patients with stable angina may induce a selection bias toward the inclusion of tight but fibrotic stenoses, less prone to give rise to lesion progression.

**MULTIVARIABLE ANALYSIS AND CONFOUNDING FACTORS.** The association of FFR with the risk of MACE remained significant even after accounting for potential clinical and angiographic confounders. These data confirm, and further extend over a wide range of FFR values, the recent findings from Depta et al. (22) reporting on a strong association between FFR and the risk of deferred lesion intervention in stenotic vessels with FFR above the ischemic threshold. In addition, FFR is the strongest predictive factor when compared to metrics describing the angiographic complexity of coronary atherosclerotic disease (i.e., American College of Cardiology/American Heart Association lesion type). In fact, baseline confounders largely influence the association between the angiographic stenosis severity and MACE. Likewise, coronary lesions potentially deferred in a routine clinical setting in patients with stable angina (i.e., with FFR above 0.80), with higher degree of complexity, show an increased risk of MACE ([Online Figure 3](#)) that is not significant when adjusting for potential baseline confounders.

FFR's accounting for the impact that the total vascular atherosclerotic burden exerts on the subtended myocardium (severity of ischemia) and for the mechanical stress exerted on the plaque (vulnerability), provides further insight on previous findings from the PROSPECT (Providing Regional Observations

to Study Predictors of Events in the Coronary Tree) trial (1). In the latter study, among the strongest predictors of subsequent CV events in the nonculprit lesions were 2 typical markers of coronary atherosclerotic burden, namely plaque burden and minimal lumen area.

**STUDY LIMITATIONS.** This analysis bears the same limitations as the main FAME-2 trial (7,8). In particular, although the randomization was concealed, it is possible that the physicians' awareness of the actual FFR value influenced decisions regarding revascularization during follow-up. Yet the fact that all the patients had angiographically significant coronary artery disease and that randomization was performed before FFR measurement, suggests that patients' awareness of having an unstented coronary blockage is unlikely to explain the higher event rates among patients with low FFR values. Second, we excluded from our analysis chronic total occlusions, as an FFR value of 0.50 was arbitrarily assigned to these stenotic vessels. Nevertheless, we observed a high proportion of lesions with an FFR value of 0.50. We hypothesize that an arbitrary value of 0.50 was assigned by local investigators to vessels that were tightly stenotic, tortuous or simply difficult to assess with the pressure guidewire. Third, coronary stenosis severity was not assessed by an independent angiographic core-lab but on the basis of the operator's best visual estimation. Fourth, the FAME-2 trial only included lesions in the proximal portion or mid-portion of the major epicardial vessels, therefore these findings may not apply to lesions of side branches or more distal portions of the major vessels. Finally, in the present study we do not have data on the extent of the ischemic territory. It is likely that combining extent and severity of ischemia would improve the characterization of the stenoses and their relationship with outcome.

## CONCLUSIONS

In a patient population treated with MT alone, FFR shows an independent, nonlinear, and inverse risk continuum of MACE over the entire range of lesion severity. These findings indicate that, in addition to the regional extent of myocardial ischemia, the actual severity (or depth) of ischemia determines the lesion-level clinical outcome at 2 years.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** In patients with stable ischemic heart disease managed with medical therapy without revascularization, lesion-specific outcomes are related to the severity of coronary artery stenosis as assessed by measurement of FFR.

**TRANSLATIONAL OUTLOOK:** Future studies should compare clinical outcomes of patients managed medically with those in whom selective coronary revascularization is on the basis of combined assessments of myocardial ischemia and lesion-specific measurements of FFR.

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**KEY WORDS** clinical outcome, fractional flow reserve, stable angina, vessel related

**APPENDIX** For supplemental tables and figures, please see the online version of this article.