Fractional Flow Reserve–Guided Deferred Versus Complete Revascularization in Patients With Diabetes Mellitus

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To assess the safety and efficacy of deferred versus complete revascularization using a fractional flow reserve (FFR)–guided strategy in patients with diabetes mellitus (DM), we analyzed all DM patients who underwent FFR-guided revascularization from January 1, 2010, to December 12, 2013. Patients were divided into 2 groups: those with ≥1 remaining FFR-negative (>0.80) medically treated lesions [FFR(−)MT] and those with only FFR-positive lesions (≤0.80) who underwent complete revascularization [FFR(+)CR] and were followed until July 1, 2015. The primary end point was the incidence of major adverse cardiovascular events (MACE), a composite of death, myocardial infarction (MI), target lesion (FFR assessed) revascularization, and rehospitalization for acute coronary syndrome. A total of 294 patients, 205 (69.7%) versus 89 (30.3%) in FFR(−)MT and FFR(+)CR, respectively, were analyzed. At a mean follow-up of 32.6 ± 18.1 months, FFR(−)MT was associated with higher MACE rate 44.0% versus 26.6% (log-rank p = 0.02, Cox regression –adjusted hazard ratio [HR] 2.01, 95% confidence interval [CI] 1.21 to 3.33, p <0.01), and driven by both safety and efficacy end points: death/MI (HR 2.02, 95% CI 1.06 to 3.86, p = 0.03), rehospitalization for acute coronary syndrome (HR 2.06, 95% CI 1.03 to 4.10, p = 0.04), and target lesion revascularization (HR 3.38, 95% CI 1.19 to 9.64, p = 0.02). Previous MI was a strong effect modifier within the FFR(−)MT group (HR 1.98, 95% CI 1.26 to 3.13, p <0.01), whereas this was not the case in the FFR(+)CR group (HR 0.66, 95% CI 0.27 to 1.62, p = 0.37). Significant interaction for MACE was present between FFR groups and previous MI (p = 0.03). In conclusion, in patients with DM, particularly those with previous MI, deferred revascularization is associated with poor medium-term outcomes. Combining FFR with imaging techniques may be required to guide our treatment strategy in these patients with high-risk, fast-progressing atherosclerosis. **(Am J Cardiol 2016;118:1293–1299)**

Fractional flow reserve (FFR) is presently the guideline-recommended invasive ischemic assessment of intermediate coronary lesions.[1] However, despite proved superiority in primarily stable angina patients, an FFR-guided revascularization strategy has been extrapolated to high-risk patient subgroups, without robust clinical evidence.[2–4] Incomplete revascularization is associated with worse outcomes compared with complete revascularization, particularly in patients with diabetes mellitus (DM) and multivessel disease.[5] Based on the Fractional flow reserve versus Angiography for Multivessel Evaluation (FAME I, II) and DEFER studies, the outcome of residual coronary lesions that are hemodynamically nonsignificant is excellent and not improved by revascularization.[2–4] However, the central premise of deferred revascularization centers on the assumption that these lesions, which are FFR >0.80, will remain quiescent over the short to medium term. Unfortunately, DM is associated with greater atherosclerotic burden and accelerated and therapy-refractive atherosclerosis, and thus, the longevity of an FFR >0.80 is unknown in a DM-only population.[6,7] To date, a direct comparison of complete versus deferred revascularization in patients with DM using FFR has not been described. Therefore, to study the impact of deferred versus complete revascularization based on an FFR-guided strategy in all-comer patients with DM, and in particular, to study the longevity of a negative FFR in patients with DM, we retrospectively analyzed the outcomes of patients with DM in our center, where FFR-guided revascularization represents the standard of care.

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See page 1298 for disclosure information.

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Methods

From a total of 3,379 patients who underwent FFR-guided revascularization from January 1, 2010, to December 31, 2013, we identified all consecutive patients with DM and followed these patients until July 2015. All patients had a previous diagnosis of DM, defined by patient history and classified by treatment with diet, exercise, oral antidiabetic medication, or insulin.

Baseline demographics were obtained by means of the electronic patient record, in addition to data relating to the FFR measurement and baseline angiography. Follow-up events were obtained from the electronic patient record based on subsequent clinical review, by telephone contact with primary care physicians and referring hospitals or direct contact with patients where required. Follow-up was complete in all FFR-assessed patients.

FFR assessment was performed systematically in all patients with intermediate coronary lesions ranging from 40% to 80% diameter stenosis, where no previous noninvasive test of ischemia was performed or when these were inconclusive. FFR was not performed for culprit lesions in MI, lesions with Thrombolysis In Myocardial Infarction flow <3, or when the operator deemed a lesion to be clearly of hemodynamic significance.

FFR was performed using a standard coronary pressure wire (PressureWire Certus; St. Jude Medical, St Paul, Minnesota; or Combowire; Volcano Corporation, Rancho Cordova, California). Both baseline FFR and maximum hyperemic FFR values were noted for each lesion. After steady-state hyperemia was achieved, the FFR was calculated as the ratio of mean distal intracoronary pressure measured by the pressure wire and the mean arterial pressure measured through the coronary guiding catheter. A cutoff value of ≤0.80 was taken to imply a functionally significant coronary stenosis and the patient underwent revascularization as appropriate. A lesion with an FFR value >0.80 was adjudicated as a functionally nonsignificant leading to deferred revascularization and further medical treatment.

Visual assessment of reference vessel diameter, diameter stenosis, American Heart Association lesion type, and the presence of calcification and diffuse disease were noted for all lesions by 2 independent interventional cardiologists. Both reviewers were blinded to the clinical outcomes. A third interventional cardiologist was used in cases where discordance arose. In addition, the Syntax Score (SS) was calculated retrospectively, based on the index (time of FFR-measurement) coronary angiogram, by scoring all lesions >1.5 mm with at least 50% diameter stenosis using the previously described algorithm.[8] For those patients with previous coronary artery bypass graft (CABG), no SS was calculated.

To assess the safety and efficacy of deferred versus complete revascularization using an FFR-guided strategy in patients with DM and to assess the longevity of a negative FFR in patients with DM, 2 groups were formed, according to the presence or absence of any remaining FFR-negative lesions (>0.80). The first group comprised patients in whom ≥1 FFR-negative lesion (>0.80) remained and were further treated medically [FFR(−)MT], whereas the second group included patients with only FFR-positive lesions (≤0.80), which underwent complete angiographic and functional revascularization [FFR(+)CR]. The local institutional review board approved this study and waived the requirement for written consent to an institutional registry.

The primary end point was the incidence of major adverse cardiovascular events (MACE) defined as a composite of death, myocardial infarction (MI), target lesion revascularization (TLR), or rehospitalization for acute coronary syndrome (ACS). A composite of death or MI, in addition to rehospitalization for ACS, represented the safety end points, whereas the efficacy end point was represented by TLR. Data relating to mortality were obtained from the Dutch national civilians register. Target lesion was defined as the lesion(s) in which the FFR was performed, with TLR referring to revascularization in that lesion(s) whether treated by index revascularization or by medical therapy. MI and periprocedural MI were defined according to the established guidelines. Recent MI was defined as occurring <6 months before the FFR assessment. Rehospitalization for ACS refers to urgent presentation to the Emergency Department for MI or unstable angina pectoris requiring an unscheduled hospitalization. Complete revascularization was defined as the absence of any remaining lesions with an FFR >0.80 and any remaining coronary lesions >50% diameter stenosis in a viable myocardial territory, as determined by the operator.

Continuous variables are summarized as mean ± SD. Discrete variables are summarized as frequency (group percentage). Group comparisons were tested using Student's *t* test or Mann−Whitney *U* test for continuous variables and Pearson's chi-square test for discrete data. Kaplan-Meier (KM) estimates were used to estimate survival curves and event rates, and the log-rank test was used to establish differences between groups. Cox proportional hazards multiple regression models were used to estimate differences in time to event between the 2 groups expressed as hazard ratios (HRs) with 95% confidence intervals, adjusted for several patient characteristics. In the exploratory model, gender, age, renal insufficiency, previous MI, previous PCI, type of DM, levels of HbA1c, smoking, reference vessel diameter, diameter stenosis, the presence of calcific and diffuse disease, FFR value, multivessel disease, and left ventricular ejection fraction were analyzed. Formal interaction testing was performed to determine whether the presence of identified effect modifiers influenced the relative risk for the occurrence of MACE in both groups. A p value <0.05 was considered significant. All analyses were conducted using SPSS 23 (SPSS Inc., Chicago, IL).

Results

From a total of 3,379 patients who underwent FFR-guided revascularization, we identified 294 consecutive patients with DM who had FFR measurement in 385 intermediate coronary lesions (Figure 1). A total of 205 patients with at least 1 remaining FFR >0.80 lesion formed the FFR(−)MT group, and 89 patients were included in the FFR(+)CR group, having had complete revascularization of all lesions. The mean length of follow-up was

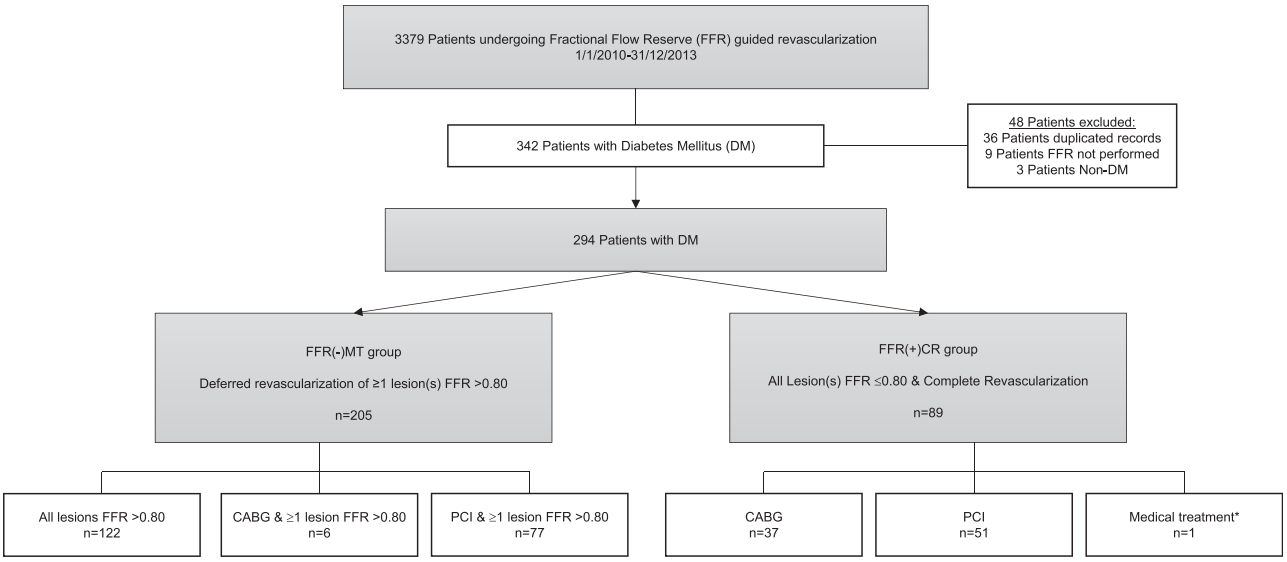


Figure 1. Study flowchart. *One patient in the FFR(+)CR group did not receive revascularization due to technically unsuccessful PCI.

Table 1
Baseline clinical characteristics

	FFR(-)MT (n=205)	FFR(+)CR (n=89)	p-value
Age (years)	69.7 ± 9.6	68.0 ± 10.2	0.23
Men	125 (61%)	67 (75%)	0.02
Diabetes mellitus	205 (100%)	89 (100%)	NA
Insulin-treated	87 (42%)	36 (40%)	0.75
Left ventricle ejection fraction	51.8 ± 10.2	49.6 ± 11.2	0.16
Multi-vessel coronary artery disease	115 (56%)	38 (43%)	0.04
Family history of coronary artery disease	61 (30%)	40.4 (36%)	0.07
Hypertension	197 (96%)	85 (96%)	0.76
Hypercholesterolemia	198 (97%)	85 (97%)	>0.99
Current smoker	41 (20%)	30 (34%)	0.01
Renal insufficiency	30 (15%)	15 (17%)	0.63
HbA1c	53.7 ± 10.5	52.8 ± 10.3	0.59
Prior myocardial infarction	93 (45%)	45 (51%)	0.41
Remote myocardial infarction	47 (23%)	20 (23%)	0.93
Recent myocardial infarction	46 (22%)	25 (28%)	0.30
Prior percutaneous coronary intervention	82 (40%)	46 (52%)	0.06
Prior coronary artery bypass graft	29 (14%)	15 (17%)	0.55

Renal Insufficiency was defined as an estimated glomerular filtration rate, eGFR<60 mL/min.

Table 2
Baseline angiographic, fractional flow reserve (FFR) and lesion characteristics

	FFR(-)MT (n=205)	FFR(+)CR (n=89)	p-value
Clinical syndrome at time of FFR performance:			
Acute coronary syndrome	73 (36%)	33 (37%)	0.81
Non-acute coronary syndrome*	132 (64%)	56 (63%)	0.81
Mean Syntax Score	10.84 ± 6.96	17.34 ± 12.44	<0.01
Low scores (0-22)	165 (81%)	54 (61%)	<0.01
Intermediate scores (23-32)	7 (3%)	7 (8%)	0.13
High scores (≥33)	4 (2%)	13 (15%)	<0.01
Unclassified, prior coronary artery bypass graft	29 (14%)	15 (17%)	0.55
FFR performed in one lesion	143 (70%)	76 (85%)	0.01
FFR performed in two lesions	49 (24%)	10 (11%)	0.01
FFR performed in three lesions	13 (6%)	3 (3%)	0.41
Mean FFR result	0.86 ± 0.06	0.73 ± 0.06	<0.01
Lesion characteristics: lesion level			
Number of lesions assessed	280	105	
AHA/ACC lesion type classification:			
Type A	33 (12%)	6 (6%)	0.04
Type B1	150 (54%)	33 (31%)	<0.01
Type B2	79 (28%)	57 (54%)	<0.01
Type C	18 (6%)	9 (9%)	0.68
Calcified lesion	57 (20%)	51 (49%)	<0.01
Diffuse disease	77 (28%)	51 (49%)	<0.01
Reference vessel diameter (mm)†	2.94 ± 0.43	2.96 ± 0.42	0.58
Diameter stenosis (%)†	60.46 ±8.48	65.96 ± 9.09	<0.01

* Includes stable angina and patients undergoing staged FFR of non-culprit lesions following ACS >1 month previously.
† Visual assessment.

32.6 ± 18.1 months (±SD). Baseline clinical and angiographic characteristics are listed in Tables 1 and 2, respectively. The average age of patients was 69.2 ± 9.8 years, which was similar in both groups. Overall, baseline characteristics were well matched in both groups; however, there were more male patients (75.3% vs 61%, p = 0.02) and more current smokers (33.7% vs 20%, p = 0.01) in the FFR(+)CR group. Patients in the FFR(−)MT group had a lower mean SS compared with the FFR(+)CR group (10.84 ± 6.96 vs 17.34 ± 12.44, p = 0.001).

In the FFR(−)MT group, 122 patients had all lesions (157 lesions) assessed as FFR negative. A total of 83 patients had index revascularization (27 patients with a lesion assessed by FFR as ≤0.80 and 54 patients with non-FFR-guided revascularization of another lesions) in addition to deferred revascularization based on an

Table 3
Clinical outcome results

	FFR(-)MT (n=205)	FFR(+)CR (n=89)	FFR(-)MT KM Estimate (n=205)	FFR(+)CR KM Estimate (n=89)	Adjusted HR (95% CI)	Adjusted p-value
Major adverse cardiac event	76 (37%)	20 (23%)	44.0%	26.6%	2.01 (1.21-3.33)	<0.01
Mortality	36 (18%)	11 (12%)	23.8%	14.8%	1.78 (0.88-3.60)	0.11
Myocardial infarction	13 (6%)	3 (3%)	7.2%	3.5%	1.81 (0.51-6.38)	0.36
Death or myocardial infarction	46 (22%)	13 (15%)	28.6%	16.9%	2.02 (1.06-3.86)	0.03
Rehospitalization for acute coronary syndrome	44 (22%)	10 (11%)	24.8%	12.2%	2.06 (1.03-4.10)	0.04
Target lesion revascularization	29 (14%)	4 (5%)	17.6%	8.2%	3.38 (1.19-9.64)	0.02

Event-rates shown are absolute event rates. K-M denotes Kaplan-Meier event rate estimates.

FFR >0.80 of at least one other lesion. This treatment included 77 patients who underwent PCI and 6 patients in whom CABG was performed. In the FFR(−)MT group, all lesions <0.80 were revascularized. In the FFR(+)CR group, 88 patients (98.8%) (37 patients by CABG and 51 patients by PCI) underwent complete revascularization at index of 104 of 105 FFR ≤0.80 lesions, with 1 patient (1 lesion) not receiving index revascularization due to technically unsuccessful PCI (Figure 1).

The results of the clinical outcomes are listed in Table 3 and Figure 2. The primary end point was observed more frequently in the FFR(−)MT group (76 [KM event rate = 44.0%] vs 20 [KM event rate = 26.6%]), unadjusted p = 0.03, and after adjustment by multivariate Cox regression (HR 2.01, 95% confidence interval [CI] 1.21 to 3.33, p <0.01; Table 3, Figure 2). Both safety end points death and/or MI and rehospitalization for ACS were significantly higher in the FFR(−)MT group (Table 3, Figure 2). Similarly, the efficacy end point, TLR, was also higher in the FFR(−)MT group (Table 3, Figure 2).

The Cox regression multivariate analysis (Table 4) did not identify previous MI as a predictor of MACE; however, previous MI had a strong effect within the FFR(−)MT group (HR 1.98, 95% CI 1.26 to 3.13, p <0.01), whereas this was not the case in the FFR(+)CR group (HR 0.66, 95% CI 0.27 to 1.62, p = 0.37). Indeed, a significant interaction for MACE was observed between FFR groups and previous MI (p = 0.03), indicating that the MACE events were predominantly clustered in the subgroup of patients in the FFR(−)MT group with previous MI, whereas FFR(−)MT patients without a previous MI had similar MACE rates as FFR(+)CR patients (Figure 3).

Discussion

The major finding of this study is that in patients with DM who underwent an FFR-guided revascularization strategy, the presence of ≥1 remaining FFR-negative lesion(s) is associated with a significantly increased risk of MACE compared with those with DM who underwent complete index revascularization, despite the latter group having more advanced disease at baseline. These results are in contrast with previous reports, which indicated that deferred revascularization based on an FFR >0.80 is associated with a low risk of future MACE.[2–4] This elevated MACE rate is driven by both safety end points, death and/or MI and rehospitalization for ACS, and the efficacy end point of TLR.

To date, several studies have examined FFR-guided revascularization, with powerful reassurance that deferred revascularization in nonischemic lesions (FFR >0.80) is safe and associated with excellent outcomes; however, specific outcomes in DM are unknown.[2–4,9] The present study is the first to assess the impact of a deferred versus complete revascularization using FFR in a DM-only population, and so the findings cannot be directly compared with previous studies. Patients with DM have a higher burden of coronary atherosclerosis compared with those without DM.[6] Furthermore, atherosclerotic disease in diabetic patients is strongly associated with a tendency toward negative vessel remodeling and faster coronary atherosclerosis progression.[10] In the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study and the subsequent subgroup analysis, patients with DM had a twofold increase in nonculprit lesion MACE rates at 3 years, originating from lesions that were angiographically mild (diameter stenosis; median 36.2% interquartile range [31.1 to 44.2]) and thus likely to be nonischemic.[11,12] Similarly, in the the Diabetes and Sirolimus-Eluting Stent (DIABETES) trial, at 2 years, approximately 10% of patients required revascularization in a vessel or segment remote from that previously treated.[13] Both these studies highlight the more rapid atherosclerosis seen in patients with DM, including mild angiographic lesions.

Our results may also provide an explanation for the superior clinical outcomes of CABG compared with PCI in a DM population, as shown in the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial.[14] Interestingly, the superior outcomes of CABG in this trial, unlike the Synergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) trial, were independent of the Syntax score, a finding that possibly reflects the better protection provided by grafting, not only for index lesions but also from atherosclerosis progression elsewhere in grafted coronary segments, which is not possible with PCI.[14,15] Given that 41.6% of patients in the FFR(+)CR group underwent CABG, this may explain the lower rates of revascularization that occurred in this group.

Another important finding of this study is the significant interaction for MACE observed between FFR groups and previous MI, suggesting that the higher MACE events were clustered mainly in patients with DM with a previous MI carrying FFR(−)MT lesions, whereas those without previous MI had much more benign outcomes and similar to the

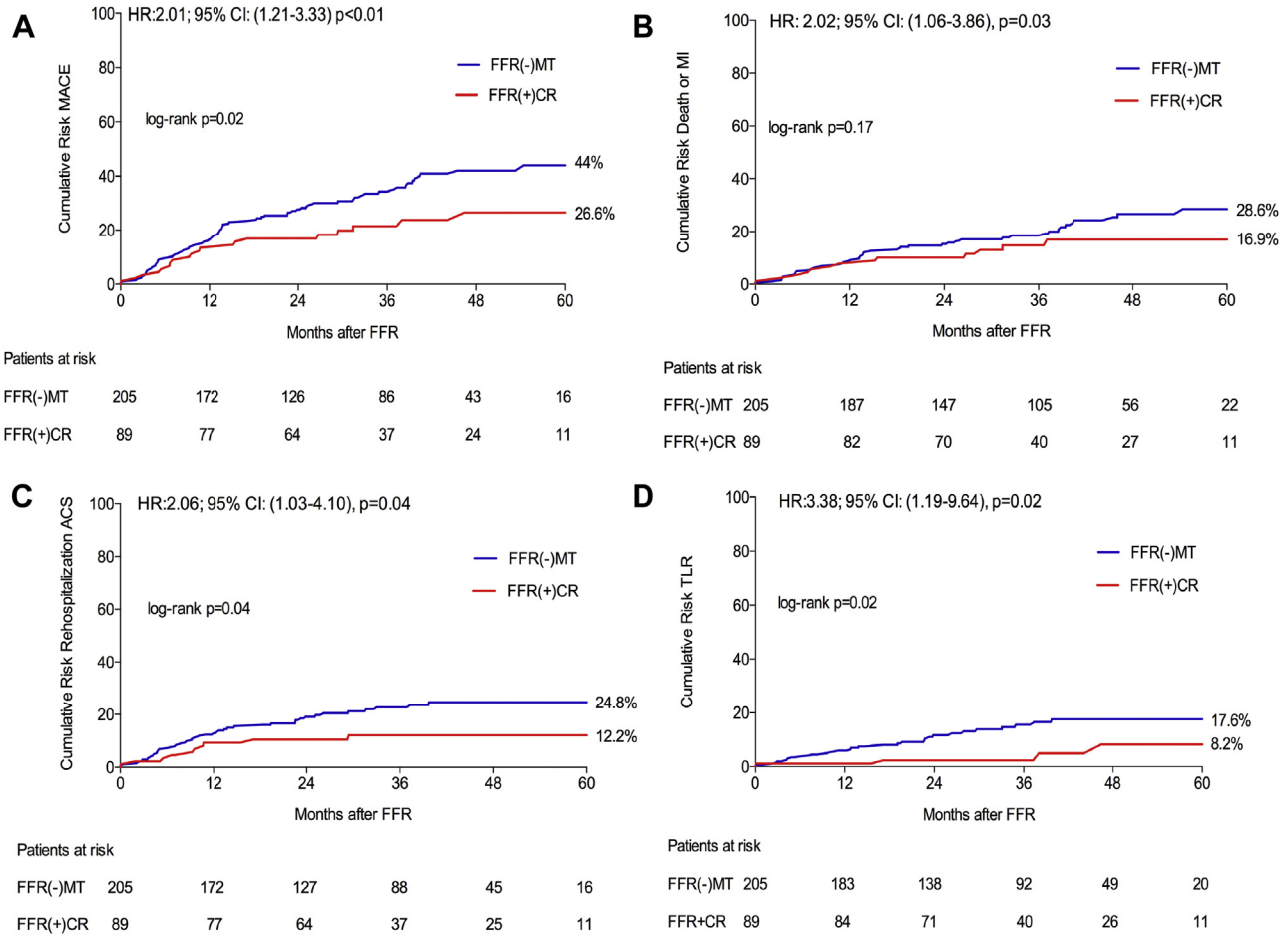


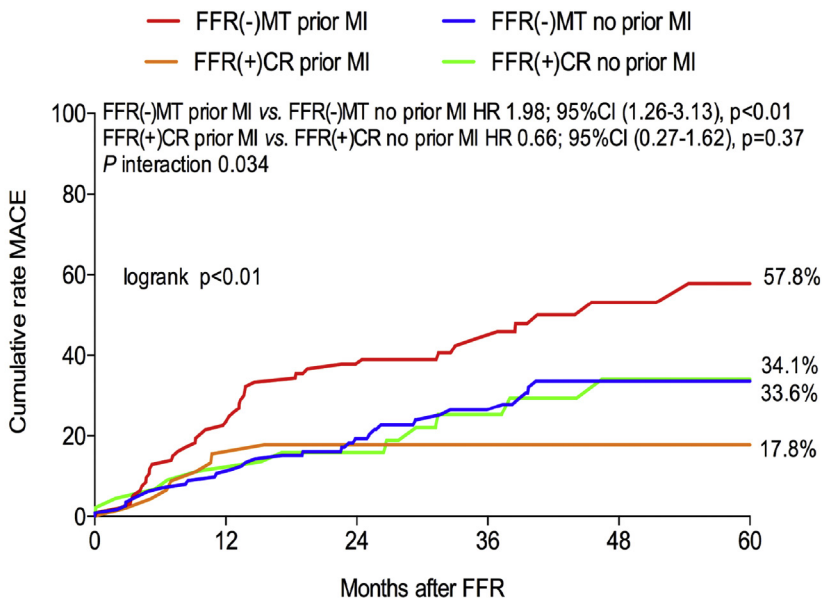
Figure 2. Time-to-event estimates for *(A)* MACE, *(B)* mortality or myocardial infarction, *(C)* rehospitalization for acute coronary syndrome, and *(D)* TLR according to FFR(−)MT and FFR(+)CR groups.

Table 4
Multivariate predictors for major adverse cardiac events

	HR (95% CI)	p-value
FFR(-)MT *vs.* FFR(+)CR	2.01 (1.21-3.33)	<0.01
Age (per 1-year increase)	1.03 (1.01-1.05)	0.02
Multi-vessel coronary artery disease	0.79 (0.52-1.19)	0.25
Prior myocardial infarction	1.14 (0.70-1.84)	0.61
Prior percutaneous coronary intervention	1.78 (1.09-2.92)	0.02
Current smoker	1.44 (0.85-2.42)	0.18
Diabetes mellitus insulin dependent	1.68 (1.12-2.53)	0.01

FFR(+)CR group. This finding supports the previous knowledge that incomplete revascularization after ACS is strongly associated with MACE as shown in a subanalysis from the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) Trial, by Rosner et al.[16] Furthermore, a recently published study by Masrani et al[17] has shown that medically treated FFR-negative lesions in patients with ACS are associated with a significantly higher rate of adverse cardiac events compared with medically treated FFR-negative lesions in those without ACS, a finding which was also observed in patients with previous MI in our study but similarly not seen in those without MI in our analysis. One possible explanation for the worse outcomes in DM with deferred revascularization, including those patients with previous ACS, may center on the greater burden of vulnerable plaque and ongoing inflammation in these patients. Intravascular imaging studies have shown that patients with DM have a larger lipid index and higher prevalence of thin-cap fibroatheroma with macrophage infiltration, especially in those with poorer glycemic control.[18] Additionally, a recent subanalysis of the PROSPECT study has shown that patients with versus without DM presenting with ACS have a higher nonculprit MACE, and when associated with a thin-cap fibroatheroma, there is a fivefold increased MACE rate at 3 years.[19]

Therefore, it seems reasonable that in patients with fast-progressing atherosclerosis, such as those with DM and/or ACS, combining FFR-ischemia detection, which remains the cornerstone of our treatment strategy choice, with other intravascular imaging techniques, capable of identifying high-risk plaque characteristics, may further refine our strategy and improve outcomes in these patients. In particular, 2 intravascular imaging techniques, optical coherence tomography and near infrared spectroscopy, may provide better accuracy than intravascular ultrasound for the detection of vulnerable plaque.[20,21] Indeed, this hypothesis is being investigated in 2 ongoing large-scale natural history



Patients at risk

FFR(-)MT prior MI	93	72	52	32	13	5
FFR(-)MT no prior MI	112	100	74	54	30	11
FFR(+)CR prior MI	45	38	33	18	11	6
FFR(+)CR no prior MI	44	39	31	19	13	5

Figure 3. Time-to-event estimates for MACE in FFR(−)MT and FFR(+)CR groups according to the presence or absence of previous MI.

studies: PROSPECT II and specifically in patients with DM in the COMBINE registry.[22,23] Finally, given the high rates of MACE observed in our study, patients with DM who underwent deferred revascularization should undergo stringent and intensive modification of risk factors as intravascular imaging studies have suggested that the slowing of atheroma volume may be achieved as risk factors achieve treatment targets.[24,25]

Our study has several potential limitations. Cox proportional hazards multiple regression models were used to correct for the baseline characteristic differences resulting from lack of randomization; nonetheless, these methods cannot control for unmeasured confounders. However, considering that the baseline characteristics were rather more favorable in the FFR(−)MT group, this further strengthens our findings. The duration of DM status is unknown for our patient population. Previous studies have shown that the duration of DM is associated with more abundant plaque burden and also more rapid disease progression, as such we cannot exclude the possibility that patients in the FFR(−)MT group may have had a longer duration of DM.[26] However, considering that HbA1c was similar in both groups, and the significantly lower Syntax Score in the FFR(−)MT group, suggests that this possibility is unlikely. As was the case in the FAME II study, neither patients nor clinicians were blinded to the FFR result; therefore, in those patients with ongoing symptoms, knowledge of a previous borderline FFR measurement may have influenced the subsequent rates of TLR or rehospitalization for ACS; however, considering the retrospective nature of this study, this was unavoidable.[4] Medication compliance was not captured in our database, representing another limitation of this analysis. Finally, patients included in our study, because of its nature, represent all-comer patients with DM and, therefore, may be at higher risk than those with DM who have been enrolled in previous randomized trials, and this may have impact on the high MACE rate observed. Given that all patients with DM who underwent an FFR-guided revascularization strategy during the study period were included, we believe that rather than being a true limitation, this is representative of real-world outcomes of an FFR-guided revascularization strategy in such patients.

Disclosures

All authors report no relevant relations to the content of this article.

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