

Comparison of Major Adverse Cardiac Events Between Instantaneous Wave-Free Ratio and Fractional Flow Reserve–Guided Strategy in Patients With or Without Type 2 Diabetes

A Secondary Analysis of a Randomized Clinical Trial

DEFINE-FLAIR Trial Investigators

[+ Supplemental content](#)

IMPORTANCE Invasive physiologic indices such as fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) are used in clinical practice. Nevertheless, comparative prognostic outcomes of iFR-guided and FFR-guided treatment in patients with type 2 diabetes have not yet been fully investigated.

OBJECTIVE To compare 1-year clinical outcomes of iFR-guided or FFR-guided treatment in patients with and without diabetes in the Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularization (DEFINE-FLAIR) trial.

DESIGN, SETTING, AND PARTICIPANTS The DEFINE-FLAIR trial is a multicenter, international, randomized, double-blinded trial that randomly assigned 2492 patients in a 1:1 ratio to undergo either iFR-guided or FFR-guided coronary revascularization. Patients were eligible for trial inclusion if they had intermediate coronary artery disease (40%-70% diameter stenosis) in at least 1 native coronary artery. Data were analyzed between January 2014 and December 2015.

INTERVENTIONS According to the study protocol, iFR of 0.89 or less and FFR of 0.80 or less were used as criteria for revascularization. When iFR or FFR was higher than the prespecified threshold, revascularization was deferred.

MAIN OUTCOMES AND MEASURES The primary end point was major adverse cardiac events (MACE), defined as the composite of all-cause death, nonfatal myocardial infarction, or unplanned revascularization at 1 year. The incidence of MACE was compared according to the presence of diabetes in iFR-guided and FFR-guided groups.

RESULTS Among the total trial population (2492 patients), 758 patients (30.4%) had diabetes. Mean age of the patients was 66 years, 76% were men (1868 of 2465), and 80% of patients presented with stable angina (1983 of 2465). In the nondiabetes population (68.5%; 1707 patients), iFR guidance was associated with a significantly higher rate of deferral of revascularization than the FFR-guided group (56.5% [n = 477 of 844] vs 46.6% [n = 402 of 863]; $P < .001$). However, it was not different between the 2 groups in the diabetes population (42.1% [n = 161 of 382] vs 47.1% [n = 177 of 376]; $P = .15$). At 1 year, the diabetes population showed a significantly higher rate of MACE than the nondiabetes population (8.6% vs 5.6%; adjusted hazard ratio [HR], 1.88; 95% CI, 1.28-2.64; $P < .001$). However, there was no significant difference in MACE rates between iFR-guided and FFR-guided groups in both the diabetes (10.0% vs 7.2%; adjusted HR, 1.33; 95% CI, 0.78-2.25; $P = .30$) and nondiabetes population (4.7% vs 6.4%; HR, 0.83; 95% CI, 0.51-1.35; $P = .45$) (interaction $P = .25$).

CONCLUSIONS AND RELEVANCE The diabetes population showed significantly higher risk of MACE than the nondiabetes population, even with the iFR-guided or FFR-guided treatment. The iFR-guided and FFR-guided treatment showed comparable risk of MACE and provided equal safety in selecting revascularization target among patients with diabetes.

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The presence of myocardial ischemia is the prerequisite for the benefit of percutaneous coronary intervention (PCI).^{1,2} Fractional flow reserve (FFR) has been regarded as a standard invasive method to evaluate the functional significance of epicardial coronary artery stenosis.^{3,4} In 2012, instantaneous wave-free ratio (iFR), a resting physiologic index that does not require hyperemia, was introduced and is also used in clinical practice. Two large-scale randomized clinical trials showed noninferiority of iFR-guided strategy compared with FFR-guided strategy in terms of 1-year clinical outcomes.^{5,6}

Type 2 diabetes is the third most common comorbidity in patients with cardiovascular disease undergoing PCI for ischemic heart disease.⁷ Even after successful PCI using current-generation drug-eluting stents, diabetes is still an independent predictor of major adverse events.⁸ Furthermore, previous studies showed that impaired endothelial function, microvascular dysfunction, and depressed coronary flow reserve occur even before the development of significant epicardial coronary stenosis in patients with diabetes.⁹⁻¹¹ Therefore, resting and hyperemic pressure-derived physiologic indices might perform differently and have different prognostic implication in patients with diabetes. In this regard, this study compared the clinical outcomes of iFR-guided and FFR-guided strategy in patients with and without diabetes.

Methods

Study Design and Patient Population

This study was a post hoc analysis of the Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation (DEFINE-FLAIR) trial, which was a multicenter, international, randomized, double-blinded trial that explored noninferiority of iFR-guided strategy for 1-year clinical outcomes compared with FFR-guided strategy.⁶ The study protocol and main results were published previously.⁶ Patients were eligible for trial inclusion if they had intermediate coronary artery disease (40%-70% diameter stenosis on visual assessment) in at least 1 native coronary artery. Patients with significant left main stenosis (>50%), tandem stenoses separated by more than 10 mm that would require separate pressure guide wire interrogation or PCI, chronic total occlusions, restenotic lesions, hemodynamic instability at the time of PCI, heavily calcified or tortuous vessels, within 48 hours of primary PCI for ST-segment elevation myocardial infarction, acute coronary syndrome with more than 1 target vessel, previous coronary artery bypass graft surgery (CABG), significant hepatic or lung disease and/or malignant disease, severe valvular heart disease, and contraindication to adenosine administration were excluded. For this study, 27 patients with unknown diabetes status were additionally excluded from the total study population (N = 2492), resulting in 2465 patients being eligible for the analysis (Figure 1). The study protocol was approved by the institutional review board or ethics committee at each participating center, and all patients provided written informed consent.

Key Points

Question What are the comparative prognostic outcomes of instantaneous wave-free ratio (iFR) vs fractional flow reserve (FFR)-guided treatment in patients with type 2 diabetes?

Findings In this substudy of the DEFINE-FLAIR randomized clinical trial, 1-year clinical outcomes of iFR-guided and FFR-guided treatment were compared in patients with and without diabetes. At 1 year, there was no significant difference in major adverse cardiac event rates between iFR-guided and FFR-guided groups in both populations with and without diabetes without significant interaction.

Meaning In treatment of patients with diabetes with coronary artery disease, iFR-guided and FFR-guided treatment showed comparable risk of major adverse cardiac events and provided equal safety in selecting revascularization target among patients with diabetes.

Procedure

After randomization into either the iFR-guided or FFR-guided groups, physiologic measurements were obtained in a routine manner with the use of a coronary-pressure guide wire (Verrata; Philips Volcano). Before iFR or FFR measurement, intracoronary nitrate was administered to control vasomotor tone. After iFR or FFR measurement, according to allocation group, prespecified treatment thresholds of iFR (≤ 0.89) or FFR (≤ 0.80) were used as revascularization threshold. When iFR or FFR for a given stenosis was equal to or lower than the prespecified threshold, the stenosis was revascularized using a drug-eluting stent or a bioresorbable vascular scaffold or by CABG. When iFR or FFR was higher than the prespecified threshold, revascularization was deferred. For patients allocated into the FFR-guided group, hyperemia was induced by intravenous or intracoronary adenosine or other agents. When PCI was attempted, revascularization was performed in accordance with standard clinical practice, with pharmacologic therapy left to the discretion of the treating physician.

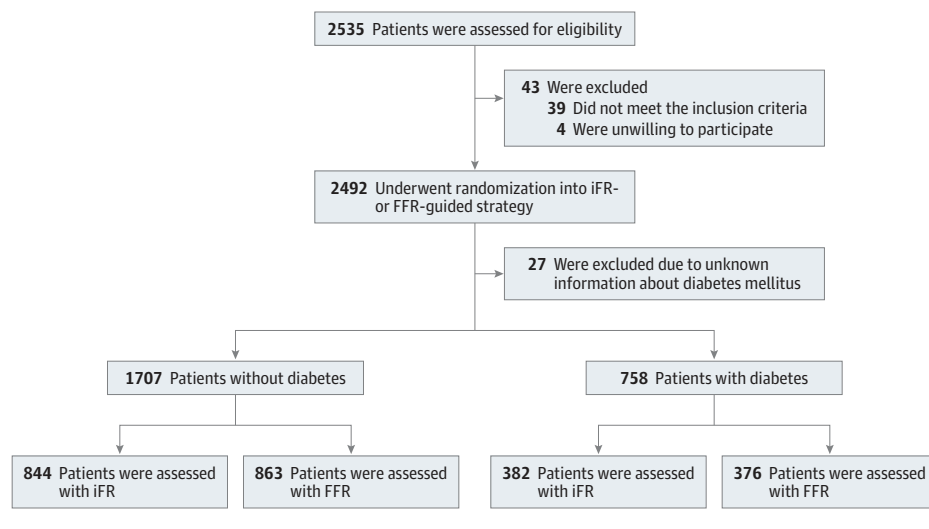
Study End Points

The primary end point of the trial was the 1-year risk of major adverse cardiac events (MACE), which were a composite of death, nonfatal myocardial infarction (MI), or unplanned revascularization. Death was considered to be from cardiovascular causes unless an unequivocal noncardiovascular cause was established. Myocardial infarction was classified as either spontaneous or periprocedural. Revascularization was considered to be unplanned when it was not the index procedure and was not identified at the time of the index procedure as a staged procedure to occur within 60 days. Detailed end point definitions were previously published.⁶ End point events were independently adjudicated by a committee of international experts who were not part of the steering committee and were unaware of patient identity and their group assignment.

Statistical Analysis

Categorical variables were presented as numbers and relative frequencies (percentages), and continuous variables were

Figure 1. Study Flow



This study was a post hoc analysis of the Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation (DEFINE-FLAIR) trial. From the total trial population (2492 patients), 2465 patients (98.9% of trial population) were included for the analysis. FFR indicates fractional flow reserve; iFR, instantaneous wave-free ratio.

presented as means and standard deviations or median with interquartile range (quartile 1 to quartile 3) according to their distribution. The time-to-event analysis was conducted with the use of the Kaplan-Meier method, and Cox proportional hazards regression models were used to calculate hazard ratio (HR) and 95% confidence interval. The validity of the proportional hazards assumption was tested with Schoenfeld residuals, and Cox proportional hazard models for all clinical outcomes satisfied the proportional hazards assumption. Data of patients who withdrew from the study before 1 year follow-up was reached and who were event-free at their last visit were censored at the time of withdrawal for the time-to-event analysis.⁶ As a primary analysis, multivariable adjusted analysis with incorporation of covariates was performed. The covariates with clinical relevance or a univariate association with outcome ($P < .10$) were entered into multivariable Cox models. Variables selected for inclusion were carefully chosen, given the number of events available, to ensure parsimony of the final models. The included covariates were age, sex, clinical presentation, CCS class for grading of angina pectoris, hypertension, hyperlipidemia, previous MI, and previous PCI. All probability values were 2-sided, and P values less than .05 were considered statistically significant.

Results

Characteristics of Patients and Lesions Between Populations With and Without Diabetes

eTables 1 and 2 in the [Supplement](#) show clinical and procedural characteristics of the trial population according to the presence of diabetes. Mean age of the patients was 66 years, 76% were men (1868 of 2465), and 80% of patients presented with stable angina (1983 of 2465). Among the total population, 758 patients (30.4%) had diabetes, 1707 patients (68.5%) did not, and 27 patients with unknown diabetes status were excluded from the analysis (Figure 1). Among the 758 patients with diabetes, 188 patients

(24.8%) were insulin-dependent. Compared with the nondiabetes population, patients with diabetes showed a higher prevalence of hypertension and hypercholesterolemia. Regarding procedural characteristics, patients with diabetes showed a higher number of functionally significant lesions, resulting in a higher proportion of revascularized patients than in the nondiabetes population.

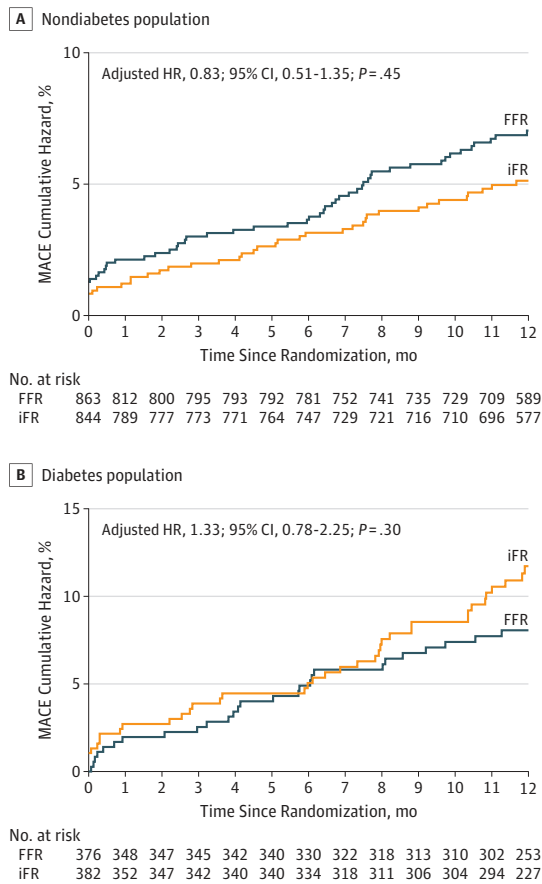
Characteristics of Patients and Lesions Between iFR-Guided and FFR-Guided Strategy Groups

eTables 3 and 4 in the [Supplement](#) show clinical and procedural characteristics between iFR-guided and FFR-guided strategy groups according to the presence of diabetes. When clinical characteristics were compared between the 2 groups, there were no significant differences in both the nondiabetes and diabetes populations (eTables 3 in the [Supplement](#)). Among the nondiabetes population, the iFR-guided group showed a lower number of functionally significant lesions per patient and a lower prevalence of patients with at least 1 functionally significant lesion, resulting in a higher proportion of deferred patients than in the FFR-guided group (56.5% [$n = 477$ of 844] vs 46.6% [$n = 402$ of 863]; $P < .001$). Conversely, there was no significant difference in number of functionally significant lesions per patient, proportion of patients with at least 1 functionally significant lesion, or deferred patients between the 2 groups among the diabetes population (42.1% [$n = 161$ of 382] vs 47.1% [$n = 177$ of 376]; $P = .15$) (eTable 4 in the [Supplement](#)).

Clinical Outcomes in Patients With and Without Diabetes

At 1 year, the diabetes population showed significantly higher risk of MACE (8.6% vs 5.6%; adjusted HR, 1.84; 95% CI, 1.28-2.64; $P < .001$), mainly driven by higher risk of nonfatal MI and unplanned revascularization than the nondiabetes population (eFigure 1 and eTable 5 in the [Supplement](#)). When stratified according to the presence of diabetes, both iFR-guided and FFR-guided groups showed comparable risk of MACE in both the nondiabetes (adjusted HR, 0.83; 95% CI, 0.51-1.35;

Figure 2. Comparison of Major Adverse Cardiac Events (MACE) Between Instantaneous Wave-Free Ratio (iFR)-Guided and Fractional Flow Reserve (FFR)-Guided Strategy According to Type 2 Diabetes



Kaplan-Meier curves are shown for the comparison of 1-year rates of MACE between iFR-guided and FFR-guided strategy groups in the nondiabetes population (A) or diabetes population (B). HR indicates hazard ratio.

$P = .45$) and diabetes populations (adjusted HR, 1.33; 95% CI, 0.78-2.25; $P = .25$) without significant interaction (Figure 2 and Table 1). There was no significant interaction regarding risk of death from any cause, cardiovascular death, and unplanned revascularization between treatment strategy and the presence of diabetes. Among the diabetes population, the iFR-guided group showed a higher incidence of nonfatal MI than the FFR-guided group (HR, 2.61; 95% CI, 0.99-6.87; $P = .05$) with significant interaction (interaction P value = .04) (eFigure 2 in the Supplement). However, the difference in the risk of nonfatal MI between iFR and FFR was mainly observed in revascularized patients (eTable 6 in the Supplement). When nonfatal MI was separated into spontaneous or periprocedural MI, the significant interaction was mainly driven by a higher incidence of target vessel MI in the iFR group than the FFR group among the diabetes population (interaction P value of target vessel MI = .03). However, there was no skewed distribution of non-target vessel MI or periprocedural MI between the 2 groups, regardless of the presence of diabetes. These results were consistent in unadjusted analy-

sis (eTable 7 in the Supplement). In addition, when the risk of MACE was compared between iFR-guided and FFR-guided groups according to non-insulin-dependent or insulin-dependent diabetes, there were no significant differences in the risk of MACE between the 2 groups, regardless of insulin dependency (non-insulin-dependent diabetes: adjusted HR, 1.00; 95% CI, 0.49-2.04; $P > .99$; insulin-dependent diabetes: adjusted HR, 1.85; 95% CI, 0.77-4.40; $P = .17$).

Among the total population, revascularization was deferred in 878 patients (51.5%) and 338 patients (44.6%) in patients with and without diabetes, respectively. In the deferred diabetes population, the risk of MACE was not statistically different between the iFR-guided and FFR-guided groups (6.8% vs 5.1%; adjusted HR, 0.98; 95% CI, 0.38-2.55; $P = .58$), and the comparable risk of MACE between the 2 groups was also similar in the deferred nondiabetes population (3.1% vs 4.5%; adjusted HR, 0.83; 95% CI, 0.37-1.85; $P = .64$) without significant interaction ($P = .58$) (Figure 3 and Table 2). These results were consistent in unadjusted analysis (eTable 8 in the Supplement).

Discussion

This study analyzed 1-year clinical outcomes after physiologic indices-guided treatment, according to the presence of diabetes, and the main findings were as follows. First, patients with diabetes showed an almost 2-fold higher risk of MACE than the nondiabetes population after invasive physiologic index-guided treatment. Second, although iFR guidance resulted in more deferral of revascularization among the nondiabetes population, iFR-guided and FFR-guided strategies resulted in similar rates of deferral among the diabetes and nondiabetes populations, iFR-guided and FFR-guided groups showed comparable risk of MACE, regardless of the presence of diabetes.

It is well known that patients with diabetes undergoing PCI have worse prognosis than patients without diabetes. In this study, even with the meticulous use of ischemia-directed PCI, patients with diabetes showed about a 2-fold higher risk of MACE compared with the nondiabetes population, regardless of treatment strategy. The significantly higher risk of MACE in the diabetes population was mainly driven by a higher incidence of nonfatal MI and unplanned revascularization. These results are in line with previous studies that evaluated all-comers undergoing PCI using second-generation drug-eluting stent and support the importance of secondary prevention and meticulous management of comorbidities in patients with diabetes.^{8,12}

In patients with diabetes, there has been concern for underestimation of ischemia with FFR owing to the relatively higher prevalence of endothelial dysfunction, depressed hyperemic myocardial blood flow (MBF), and microvascular dysfunction.⁹⁻¹¹ In an earlier study using dipyridamol-positron emission tomography, hyperemic MBF and myocardial flow reserve were significantly lower in patients with diabetes, while there was no difference in resting MBF between

Table 1. Multivariable-Adjusted Clinical Outcomes at 1 Year Between iFR and FFR in Patients With and Without Type 2 Diabetes

Outcome	Nondiabetes			P Value	Diabetes			P Value	P Value for Interaction
	No. (%)		Adjusted HR (95% CI) ^a		No. (%)		Adjusted HR (95% CI)		
	iFR (n = 844)	FFR (n = 863)			iFR (n = 382)	FFR (n = 376)			
Primary end point: MACE ^b	40 (4.7)	55 (6.4)	0.83 (0.51-1.35)	.45	38 (10.0)	27 (7.2)	1.33 (0.78-2.25)	.30	.25
Cardiac death, MI, or unplanned revascularization	34 (4.0)	47 (5.5)	0.81 (0.47-1.38)	.43	31 (8.1)	26 (6.9)	1.15 (0.66-2.01)	.61	.44
Death									
Any cause	12 (1.4)	10 (1.2)	1.09 (0.42-2.85)	.86	10 (2.6)	3 (0.8)	2.60 (0.68-10.0)	.16	.31
Cardiovascular causes	5 (0.6)	2 (0.2)	1.27 (0.20-7.96)	.80	2 (0.5)	2 (0.5)	0.93 (0.13-6.75)	.95	.79
Noncardiovascular causes	7 (0.8)	8 (0.9)	1.00 (0.32-3.14)	>.99	8 (2.1)	1 (0.3)	6.39 (0.74-54.8)	.09	.16
Nonfatal myocardial infarction	13 (1.5)	21 (2.4)	0.56 (0.21-1.54)	.26	18 (4.7)	7 (1.9)	2.61 (0.99-6.87)	.05	.04
Spontaneous MI									
Target vessel MI	3 (0.4)	12 (1.4)	0.32 (0.09-1.17)	.08	6 (1.6)	2 (0.5)	3.26 (0.64-16.53)	.15	.03
Non-target vessel MI	2 (0.2)	2 (0.2)	NA	NA	7 (1.8)	5 (1.3)	1.68 (0.46-6.07)	.43	.21
Periprocedural MI	8 (1.0)	7 (0.8)	1.94 (0.07-54.81)	.70	5 (1.3)	0	NA	NA	.38
Unplanned revascularization	22 (2.6)	38 (4.4)	0.78 (0.44-1.38)	.40	24 (6.3)	24 (6.4)	1.11 (0.62-2.00)	.72	.49

Abbreviations: CCS, Canadian Cardiovascular Society; FFR, fractional flow reserve; HR, hazard ratio; iFR, instantaneous wave-free ratio; MACE, major adverse cardiac event; MI, myocardial infarction; NA, not applicable; PCI, percutaneous coronary intervention.

^a The included covariates in the multivariable-adjusted model were age, sex,

clinical presentation, CCS class for grading of angina pectoris, hypertension, hyperlipidemia, previous MI, and previous PCI.

^b MACE was defined as a composite of death from any cause, nonfatal myocardial infarction, or unplanned revascularization.

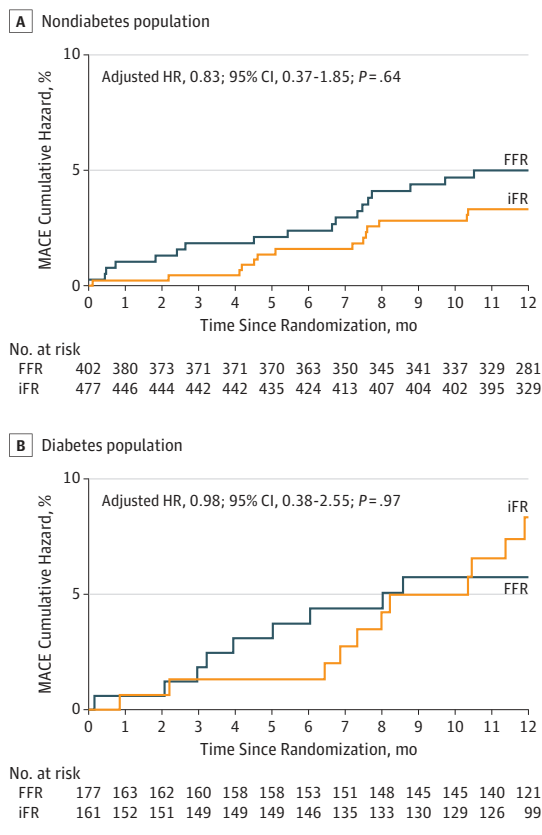
asymptomatic non-insulin-dependent patients with diabetes and an age-matched healthy control group.^{9,10} Because the absolute MBF is a major determinant of the transstenotic pressure gradient,¹³ decreased hyperemic MBF theoretically causes underestimation of stenosis severity using hyperemic pressure-derived indices in patients with diabetes, even with a similar degree of stenosis compared with patients without diabetes. Nevertheless, the results from the previous studies support the benefit of an FFR-guided strategy, even in patients with diabetes.¹⁴⁻¹⁹ For the diagnostic performance of FFR using thallium-201 single-photon emission computed tomography as a reference test, the best cutoff value of FFR and its diagnostic performance were not different between patients with and without diabetes.¹⁴ In another study evaluating FFR value according to stenosis severity between patients with and without diabetes, there was no significant difference in the FFR value.^{16,17} In addition, 2 large-scale prospective registries that evaluated the prognosis of patients undergoing FFR-guided treatment, including more than 2000 patients with diabetes, showed favorable outcomes for those patients.^{19,20}

Because iFR is measured during a resting state without hyperemia induction, it would be expected to be less affected by microvascular dysfunction compared with a hyperemic physiologic index, where blunting of adenosine-induced hyperemia could potentially reduce the sensitivity of FFR. Considering the previous study results, which showed the presence of diabetes was significantly associated with the discordant results between iFR and FFR,²¹ those 2 indices might have different prognostic implications in patients with diabetes. However, to our knowledge, there has been no report that focused on the prognostic role of an iFR-guided strategy in patients with diabetes.

In our study, the FFR-guided group showed a higher number of functionally significant lesions than in the iFR-guided group among the nondiabetes population. This result is in line with a study by Lee et al,¹³ which showed that FFR was more sensitive to anatomical and hemodynamic stenosis severity than iFR. However, there were no significant differences in the number of functionally significant lesions, number of patients with at least 1 functionally significant lesion, and the proportion of revascularized patients between the 2 groups among the diabetes population. This was mainly owing to the relative increase in revascularization rate in the iFR group among the diabetes population. This might be explained by higher disease severity or plaque burden throughout the target vessels in patients with diabetes or by the other factors that might cause underestimation of epicardial lesion severity by FFR, such as diffuse atherosclerotic narrowing, concomitant microvascular disease, or blunted response to hyperemic stimuli in the diabetes population. However, because this trial did not systematically assess intravascular imaging studies, further study is needed to clarify this issue. Nevertheless, considering the comparable risk of MACE between iFR-guided and FFR-guided groups among the diabetes population, the different response of iFR and FFR for the severity of epicardial coronary stenosis might have limited effect on patient prognosis. In addition, these results support the clinical relevance of both an iFR-guided and FFR-guided strategy, even in patients with diabetes.

It is interesting to note that there was significant interaction in the risk of nonfatal MI according to the presence of diabetes. This was caused by the opposite direction of HR between the nondiabetes and diabetes populations, especially for nonfatal target vessel MI. However, this result

Figure 3. Deferred Population Outcome Between Instantaneous Wave-Free Ratio (iFR)-Guided and Fractional Flow Reserve (FFR)-Guided Strategy, According to Type 2 Diabetes



Kaplan-Meier curves are shown for the comparison of 1-year major adverse cardiac event (MACE), defined as a composite of death from any cause, nonfatal myocardial infarction, or unplanned revascularization, rates of deferred population between iFR and FFR-guided strategy groups in the nondiabetes population (A) or diabetes population (B). HR indicates hazard ratio.

should be interpreted with caution owing to limited number of events and sample size. In addition, the incidence of unplanned revascularization and cardiovascular death was almost the same between the 2 guided strategy groups among the diabetes population. Furthermore, the excess risk of nonfatal MI in the iFR group among the diabetes population was statistically borderline (adjusted HR, 2.61; 95% CI, 0.99-6.87; P = .05) and the difference was mainly observed in revascularized patients. Because this study was a post hoc analysis that was not designed to detect the possible difference in risk of nonfatal MI between the 2 groups, larger data sets are needed for the confirmation of this finding.

It should be noted that angiography-only guided PCI in patients with diabetes with multivessel disease has failed to show benefit vs CABG.²² However, evidence from the Synergy Between PCI With Taxus and Cardiac Surgery II (SYNTAX II) study²³ implies that ischemia-directed PCI might have similar clinical outcomes with CABG in patients with multivessel disease and equipoise risk between PCI and CABG. Because anatomic residual disease did not show prognostic implications after ischemia-directed PCI,²⁴ iFR-guided or FFR-guided treatment should be emphasized more in patients with diabetes.

Limitations

This study has several limitations. First, this study was an exploratory post hoc analysis of the DEFINE-FLAIR trial. Therefore, this post hoc analysis was not powered enough to detect the potential differences in the risk of clinical events between iFR and FFR groups. However, this study evaluated the largest number of patients with diabetes evaluated by iFR. Second, detailed data on diabetes status and treatment were not available. Third, because the DEFINE-FLAIR trial adopted exclusive allocation into either the iFR-guided or FFR-guided group, the incidence of discordance between the 2 indices according to the presence of diabetes and its

Table 2. Multivariable-Adjusted Clinical Outcomes at 1 Year Between iFR and FFR in Deferred Patients With and Without Type 2 Diabetes

Outcome	Nondiabetes				Diabetes				P Value for Interaction
	iFR, No. (%) (n = 477)	FFR, No. (%) (n = 402)	Adjusted HR (95% CI) ^a	P Value	iFR, No. (%) (n = 161)	FFR, No. (%) (n = 177)	Adjusted HR (95% CI)	P Value	
Primary end point: MACE ^b	15 (3.1)	18 (4.5)	0.83 (0.37-1.85)	.64	11 (6.8)	9 (5.1)	0.98 (0.38-2.55)	.97	.58
Cardiac death, MI, or unplanned revascularization	12 (2.5)	15 (3.7)	0.77 (0.32-1.87)	.56	9 (5.6)	8 (4.5)	1.03 (0.38-2.83)	.95	.54
Death									
Any cause	5 (1.1)	3 (0.8)	1.30 (0.20-8.39)	.78	2 (1.2)	1 (0.6)	NA	NA	.83
Cardiovascular causes	2 (0.4)	0	NA	NA	0	0	NA	NA	NA
Noncardiovascular causes	3 (0.6)	3 (0.8)	0.87 (0.11-7.12)	.90	2 (1.2)	1 (0.6)	NA	NA	.86
Nonfatal myocardial infarction	0	7 (1.7)	NA	NA	4 (2.5)	2 (1.1)	2.63 (0.35-19.99)	.35	NA
Spontaneous MI									
Target vessel MI	0	5 (1.2)	NA	NA	2 (1.2)	1 (0.6)	1.66 (0.05-53.81)	.78	NA
Non-target vessel MI	0	1 (0.3)	NA	NA	2 (1.2)	1 (0.6)	2.81 (0.15-51.65)	.49	NA
Periprocedural MI	0	1 (0.3)	NA	NA	0	0	NA	NA	NA
Unplanned revascularization	10 (2.1)	14 (3.5)	0.71 (0.29-1.78)	.47	9 (5.6)	8 (4.5)	1.02 (0.37-2.80)	.97	.47

Abbreviations: FFR, fractional flow reserve; HR, hazard ratio; iFR, instantaneous wave-free ratio; MACE, major adverse cardiac event; MI, myocardial infarction; NA, not applicable; PCI, percutaneous coronary intervention.

^a The included covariates in the multivariable-adjusted model were age, sex,

clinical presentation, CCS class for grading of angina pectoris, hypertension, hyperlipidemia, previous MI, and previous PCI.

^b MACE was defined as a composite of death from any cause, nonfatal myocardial infarction, or unplanned revascularization.

prognostic implications could not be evaluated. Fourth, invasive physiologic indices for evaluation of microvascular dysfunction were not available. Fifth, because total disease burden or microvascular assessment was not systematically performed in this study, mechanistic explanations for difference in deferral rates in patients with diabetes could not be clearly explained. Therefore, the possibility of play-of-chance findings from a post hoc analysis cannot be completely excluded.

Conclusions

The diabetes population showed significantly higher risk of MACE than the nondiabetes population, even with iFR-guided or FFR-guided treatment strategy. The iFR-guided and FFR-guided treatments showed comparable risk of MACE and provided equal safety in selecting revascularization target among patients with diabetes.

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