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Safety of the Deferral of Coronary Revascularization on the Basis of Instantaneous Wave-Free Ratio and Fractional Flow Reserve Measurements in Stable Coronary Artery Disease and Acute Coronary Syndromes

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CME/MOC Objective for This Article: At the end of the activity the reader should be able to: 1) understand the differences of currently available physiologic indices; 2) recognize the safety of deferred patients with physiology-guided decision-making; and 3) compare the results in the present study to previous trials.

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ABSTRACT

OBJECTIVES The aim of this study was to investigate the clinical outcomes of patients deferred from coronary revascularization on the basis of instantaneous wave-free ratio (iFR) or fractional flow reserve (FFR) measurements in stable angina pectoris (SAP) and acute coronary syndromes (ACS).

BACKGROUND Assessment of coronary stenosis severity with pressure guidewires is recommended to determine the need for myocardial revascularization.

METHODS The safety of deferral of coronary revascularization in the pooled per-protocol population (n = 4,486) of the DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation) and iFR-SWEDEHEART (Instantaneous Wave-Free Ratio Versus Fractional Flow Reserve in Patients With Stable Angina Pectoris or Acute Coronary Syndrome) randomized clinical trials was investigated. Patients were stratified according to revascularization decision making on the basis of iFR or FFR and to clinical presentation (SAP or ACS). The primary endpoint was major adverse cardiac events (MACE), defined as the composite of all-cause death, nonfatal myocardial infarction, or unplanned revascularization at 1 year.

RESULTS Coronary revascularization was deferred in 2,130 patients. Deferral was performed in 1,117 patients (50%) in the iFR group and 1,013 patients (45%) in the FFR group ($p < 0.01$). At 1 year, the MACE rate in the deferred population was similar between the iFR and FFR groups (4.12% vs. 4.05%; fully adjusted hazard ratio: 1.13; 95% confidence interval: 0.72 to 1.79; $p = 0.60$). A clinical presentation with ACS was associated with a higher MACE rate compared with SAP in deferred patients (5.91% vs. 3.64% in ACS and SAP, respectively; fully adjusted hazard ratio: 0.61 in favor of SAP; 95% confidence interval: 0.38 to 0.99; $p = 0.04$).

CONCLUSIONS Overall, deferral of revascularization is equally safe with both iFR and FFR, with a low MACE rate of about 4%. Lesions were more frequently deferred when iFR was used to assess physiological significance. In deferred patients presenting with ACS, the event rate was significantly increased compared with SAP at 1 year.

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Physiology-guided coronary revascularization is currently recommended in clinical practice guidelines on the grounds of ample evidence supporting its clinical value (1). Compared with angiography alone, decision making using fractional flow reserve (FFR) improves patient outcomes and procedural cost efficiencies (2). These benefits are due largely to deferral of myocardial revascularization in hemodynamically nonsignificant stenosis (3–5). The 15-year follow-up of the DEFER (Deferral vs. Performance of Percutaneous Coronary Intervention of Functionally Non-Significant Coronary Stenosis) trial, the pivotal study assessing the safety of FFR-based revascularization deferral, has shown favorable very long term outcomes (4). However, the results of that study are difficult to translate into current clinical practice because of the small sample size, the use of a different FFR cutoff (0.75), and major developments in percutaneous coronary intervention (PCI) and medical therapy in the intervening 17 years (3).

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Recently, 2 large randomized clinical trials, DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation) and iFR-SWEDEHEART (Instantaneous Wave-Free Ratio Versus Fractional Flow Reserve in Patients With Stable Angina Pectoris or Acute Coronary Syndrome), compared the clinical outcomes of 4,529 patients with coronary stenoses undergoing either FFR-based or instantaneous wave-free ratio (iFR)-based revascularization, the latter a novel adenosine-free index of stenosis severity (6,7). The combined dataset of both studies provides a unique opportunity to revisit the safety of physiology-guided deferral of revascularization in contemporary clinical practice, with the added value of depicting the predominant clinical use of FFR, which is interrogation of stenoses with intermediate angiographic severity (8–10).

In this study, we investigated the 1-year clinical outcomes of patients who were included in the per-protocol populations of the DEFINE-FLAIR and iFR-SWEDEHEART randomized trials. As both trials included patients with stable angina pectoris (SAP) and acute coronary syndromes (ACS), the safety of revascularization deferral in both clinical scenarios could be compared. This may shed light on conflicting reports regarding the comparable safety of revascularization deferral in patients in stable condition and in those presenting with ACS (11–15).

METHODS

STUDY DESIGN. The DEFINE-FLAIR and iFR-SWEDEHEART trial designs have been previously reported (6,7). In brief, both are multicenter, prospective, randomized trials comparing clinical outcomes and cost-effectiveness of iFR- and FFR-based decision making in physiologically guided coronary revascularization. Eligible patients were randomly assigned to undergo revascularization decision making guided by either iFR or FFR. Patients enrolled in iFR-SWEDEHEART were included in the SCAAR (Swedish Coronary Angiography and Angioplasty Registry), which was used to obtain immediate and continuous feedback on processes and quality-of-care measures (Online Appendix). Whereas iFR-SWEDEHEART had an open-label design, DEFINE-FLAIR was a double-blind trial with patients and follow-up teams blinded to the use of iFR or FFR. Both trials confirmed their primary hypothesis, that iFR was noninferior to FFR for major adverse cardiac events (MACE) at 1 year in patients undergoing physiologically guided revascularization decision making.

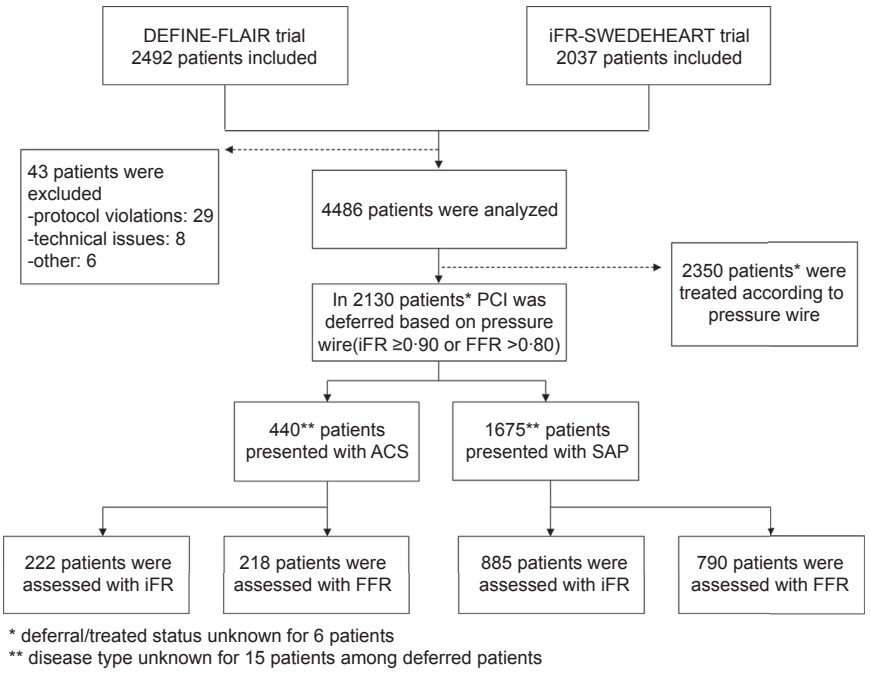
STUDY POPULATION. Our study combined and analyzed the merged populations of the DEFINE-FLAIR and iFR-SWEDEHEART randomized clinical trials. These patients had an indication for physiological assessment of at least 1 coronary lesion in which the functional severity was questionable (40% to 80% stenosis by visual assessment). This study included patients with SAP and ACS (unstable angina pectoris, non-ST-segment elevation myocardial infarction [MI], and ST-segment elevation MI). In patients with SAP, any lesion could be assessed. In patients with ACS, physiological interrogation was performed only in the nonculprit artery once the culprit vessel was revascularized. In the case of ST-segment elevation MI, nonculprit vessels were evaluated >48 h after primary PCI. Inclusion and exclusion criteria are listed in the Online Appendix. In both trials, all participants provided written informed consent before enrollment.

PROCEDURE. Physiological measurements were performed in the usual manner using the same coronary pressure guidewire (Verrata, Philips Volcano, San Diego, California). Before measurement, intracoronary nitrates were administered to control vasomotor tone. Pre-specified treatment thresholds were 0.89 for iFR and 0.80 for FFR. Stenoses were revascularized with either PCI or coronary artery bypass grafting. When iFR or FFR exceeded these prespecified thresholds, treatment was deferred. Pressure drift was assessed using the pressure ratio at the catheter tip after each physiological measurement.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)
CI = confidence interval
FFR = fractional flow reserve
HR = hazard ratio
iFR = instantaneous wave-free ratio
MACE = major adverse cardiac event(s)
MI = myocardial infarction
PCI = percutaneous coronary intervention
SAP = stable angina pectoris

FIGURE 1 Flowchart of the Study



A combined total of 4,529 participants were enrolled in the DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation) and iFR-SWEDEHEART (Instantaneous Wave-Free Ratio Versus Fractional Flow Reserve in Patients With Stable Angina Pectoris or Acute Coronary Syndrome) randomized clinical trials. ACS = acute coronary syndrome(s); FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; PCI = percutaneous coronary intervention; SAP = stable angina pectoris.

If the pressure ratio exceeded ±0.02, physiological measurements were repeated. For patients assigned to FFR, hyperemia was obtained with intravenous or intracoronary hyperemic agents as previously described (6,7). When multivessel revascularization was required, investigators could stage procedures within 60 days of the index measurement. Revascularization was performed according to standard clinical practice, with pharmacological therapy left to the discretion of the treating physician.

ENDPOINTS. The primary safety endpoint of the study was the composite of MACE, defined as all-cause death, nonfatal MI, or unplanned revascularization within 12 months of the index procedure. Secondary endpoints were the individual components of MACE. In both DEFINE-FLAIR and iFR-SWEDEHEART, death and MI were adjudicated with anonymized source documentation by independent clinical event adjudication committees, whose members were unaware of the group assignments. A consensus decision was made on the basis of the pre-specified endpoint definitions. Unplanned revascularization events and secondary angiographic outcomes were adjudicated by the clinical event adjudication committee in DEFINE-FLAIR and by an independent experienced observer who was unaware of the group assignments in iFR-SWEDEHEART.

STATISTICAL ANALYSIS. The objective of this study was to compare event rates between physiological techniques (iFR vs. FFR) in patients for whom revascularization was deferred on the grounds of physiological measurements. Additionally, we investigated whether clinical presentation (SAP vs. ACS) influenced event rates and subsequently if this was modified by which physiological technique was used to guide decision making.

For MACE and its components, a time-to-event analysis was performed in the per-protocol population by Cox survival modeling. Participants who withdrew from the study before reaching 1 year of follow-up and who were event free at their last visit were censored at their time of last visit. Testing of the validity of the proportional hazards assumption was done using Schoenfeld residuals. There were no signs of violations of proportional hazards assumption.

TABLE 1 Baseline Characteristics of the Deferred Population

	iFR (n = 1,117)	FFR (n = 1,013)	p Value
Age (yrs)	66.1 ± 10.7	66.6 ± 9.9	0.55
Male	72.0 (804)	68.0 (689)	0.05
Body mass index (kg/m^2)	27.5 ± 4.7	27.5 ± 5.0	0.51
Diabetes mellitus	21.8 (243)	24.8 (251)	0.19
Hypertension	71.1 (794)	71.7 (726)	0.32
Hyperlipidemia	68.5 (765)	66.3 (672)	0.52
Current smoker	19.0 (212)	17.8 (180)	
Previous MI	30.1 (336)	30.4 (308)	0.09
Previous PCI	42.6 (476)	43.4 (440)	0.57
CCS angina class			<0.01
I	26.8 (299)	22.5 (228)	
II	32.8 (366)	27.9 (283)	
III	4.8 (54)	7.8 (79)	
IV	1.8 (20)	2.3 (23)	
Clinical presentation			0.36
Acute coronary syndrome	19.9 (222)	21.5 (218)	
Stable angina pectoris	79.2 (885)	78.0 (790)	
No information	0.9 (10)	0.5 (5)	

Values are mean ± SD or % (n).

CCS = Canadian Cardiovascular Society; FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Results are reported using hazard ratios (HRs), 95% 2-sided confidence intervals (CIs), and cumulative hazard curves. Analyses were performed in an unadjusted manner as well as adjusted for the following baseline characteristics that were chosen a priori for their known associations with cardiovascular events: age, sex, body mass index, clinical presentation, Canadian Cardiovascular Society class for grading of angina pectoris, diabetes, hypertension, hyperlipidemia, smoking status, previous MI, and previous PCI. Fully adjusted results are presented in the text and both unadjusted and fully adjusted in the tables.

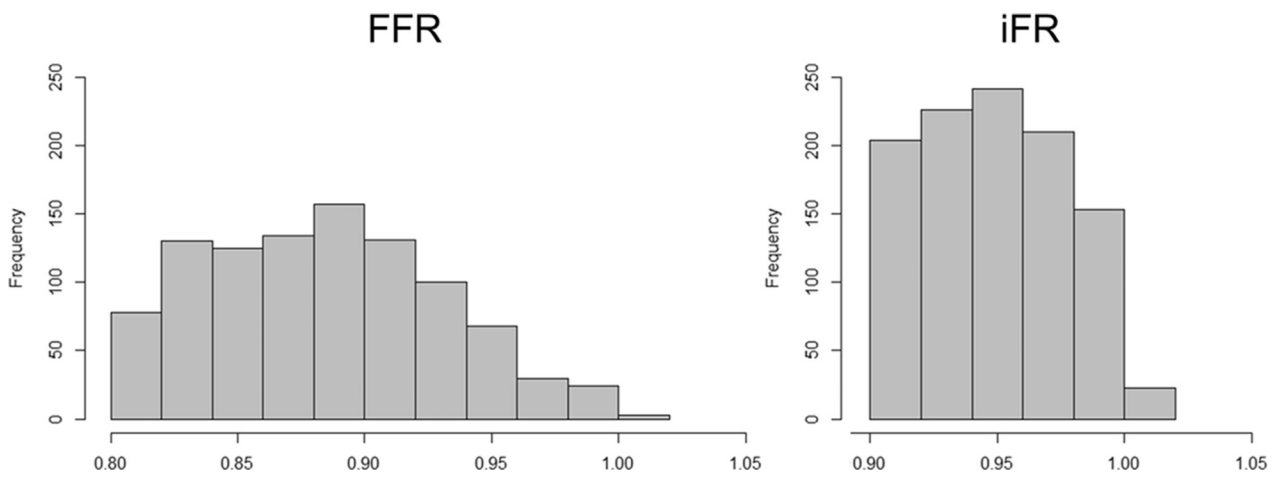
RESULTS

STUDY POPULATION. A combined total of 4,529 participants were enrolled in both trials; 2,261 were assigned to the iFR group and 2,268 to the FFR group (Figure 1). Data for 43 patients were excluded from the analyses because of unacceptable side effects associated with adenosine, technical issues, incorrect group assignment, or other reasons; data for the remaining 4,486 patients were included in the analyses.

BASELINE CHARACTERISTICS. In the overall study population, the mean age was 66.3 years, 26.6% of patients had diabetes mellitus, 72.2% had SAP, and 31.0% had history of MI. No differences were found in baseline characteristics between the iFR and FFR groups (Online Table 1).

Coronary revascularization was deferred in 2,130 patients. Deferral was performed in 1,117 patients (50%) in the iFR group and 1,013 patients (45%) in the FFR group ($p < 0.01$). The baseline characteristics of patients deferred by iFR and FFR methods are displayed in Table 1. The iFR group included a higher proportion of male patients than the FFR group (72.0% vs. 68.0%; $p = 0.05$). Canadian Cardiovascular Society grading of angina pectoris was significantly higher in the iFR group (26.8% in class I and 32.8% in

FIGURE 2 Distribution of Physiological Values



Histograms of FFR **(left)** and iFR **(right)** values in the deferred pooled patient population of the DEFINE-FLAIR and iFR-SWEDEHEART randomized clinical trials. Abbreviations as in Figure 1.

TABLE 2 Procedural Characteristics of the Deferred Population

	iFR (n = 1,117)	FFR (n = 1,013)	p Value
Site of access			0.60
Radial	76.2 (851)	75.2 (762)	
Procedure time (min)			0.02
Median	30	34	
Interquartile range	20–45	24–48	
Total number of vessels evaluated	1,478	1,317	
Mean iFR/FFR value	0.95 ± 0.03	0.89 ± 0.05	

Values are % (n) or mean ± SD, unless otherwise indicated.
Abbreviations as in Table 1.

class II) than in the FFR group (22.5% in class I and 27.9% in class II) ($p < 0.01$ for the difference between groups). The remaining baseline characteristics were otherwise well balanced between the iFR- and FFR-deferred groups.

When the deferred population was stratified according to clinical presentation, overall less lesions were deferred in ACS compared with clinical presentation with SAP (36% vs. 50%; $p < 0.001$). In SAP, more lesions were deferred with iFR than FFR (55% vs. 48%; $p < 0.001$). In ACS, deferral rates were similar for both iFR and FFR guidance (36% vs. 36%; $p = 0.91$).

PROCEDURAL CHARACTERISTICS. In the deferred population, mean iFR was 0.95 ± 0.03 and mean FFR was 0.89 ± 0.05. The distribution of iFR and FFR values is displayed in Figure 2. The procedural characteristics for the deferred populations are displayed in Table 2. The numbers of physiological evaluations per patient were 1.32 ± 0.67 for iFR and 1.30 ± 0.62 for FFR ($p = 0.67$). Total procedure time was significantly shorter in the iFR group (median 30 min; interquartile range: 20 to 45 min) than in the FFR group (median 34 min; interquartile range: 24 to 48 min) ($p = 0.02$).

TABLE 3 Time-to-Event Analysis for Major Adverse Cardiac Events and Their Components According to Clinical Presentation (Stable Angina Pectoris Versus Acute Coronary Syndromes) in Deferred Patients

			SAP vs. ACS		
	SAP (n = 1,675)	ACS (n = 440)	Unadjusted HR (95% CI)	Fully Adjusted HR (95% CI)	p Value
MACE	3.64 (61)	5.91 (26)	0.62 (0.39–0.99)	0.61 (0.38–0.99)	0.04
All-cause death	0.66 (11)	1.36 (6)	0.50 (0.19–1.36)	0.44 (0.16–1.23)	0.12
Cardiovascular death	0.18 (3)	0.45 (2)	0.41 (0.07–2.45)	0.21 (0.02–1.71)	0.14
Noncardiovascular death	0.48 (8)	0.91 (4)	0.55 (0.16–1.82)	0.46 (0.13–1.59)	0.22
Myocardial infarction	0.90 (15)	2.50 (11)	0.34 (0.16–0.76)	0.36 (0.16–0.79)	0.01
Unplanned revascularization	2.87 (48)	3.64 (16)	0.81 (0.46–1.43)	0.83 (0.46–1.49)	0.53

Values are % (n), unless otherwise indicated.
ACS = acute coronary syndrome(s); CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac event(s); SAP = stable angina pectoris.

PRIMARY ENDPOINT AND COMPONENTS. There was no censoring before 12 months in iFR-SWEDEHEART; 150 patients (6.1% of 2,467) in DEFINE-FLAIR voluntarily withdrew from the study before 12 months and were censored at the time of their last visit. In the overall study population, at 1 year, the primary endpoint had occurred in 145 of 2,240 patients (6.47%) in the iFR group and in 144 of 2,246 (6.41%) in the FFR group (unadjusted HR: 1.03; 95% CI: 0.81 to 1.31; $p = 0.81$) (Online Figure 1). No significant differences were noted in terms of the components of the primary endpoint in both study arms (Online Table 2). The number of deaths from any cause at 12 months did not differ significantly between the iFR group (36 deaths, including 15 from cardiovascular causes) and the FFR group (25 deaths, including 10 from cardiovascular causes) ($p = 0.14$). The rates of nonfatal MI and unplanned revascularization did not differ significantly between the 2 groups.

When stratified according to clinical presentation, the overall MACE rate in patients with ACS (7.7%) was higher than in patients with SAP (6.0%) (fully adjusted HR: 0.72 in favor of SAP; 95% CI: 0.55 to 0.93; $p = 0.01$) (Online Table 3). In the deferred population, this difference was driven mainly by a higher 1-year MACE rate among the deferred patients with ACS (26 of 440 [5.9%]) compared with deferred patients with SAP (61 of 1,675 [3.6%]) (fully adjusted HR: 0.61 in favor of SAP; 95% CI: 0.38 to 0.99; $p = 0.04$) (Table 3).

In the deferred population, at 1 year, the primary endpoint occurred in 46 of 1,117 patients (4.12%) in the iFR group and in 41 of 1,013 patients (4.05%) in the FFR group (fully adjusted HR: 1.13; 95% CI: 0.72 to 1.79; $p = 0.60$) (Figure 3). The HRs for the individual components of MACE for iFR- versus FFR-guided deferral are displayed in Table 4. Unplanned revascularization was the biggest contributor numerically to the total MACE rate for both iFR- and FFR-deferred groups (2.78% and 3.26%, respectively; $p = 0.63$). There were no significant differences in the components of MACE between the 2 physiological techniques.

Within the deferred group, the MACE rate was more influenced by clinical presentation in patients evaluated with FFR (unadjusted HR: 0.52 in favor of SAP; 95% CI: 0.27 to 1.00; $p < 0.05$) than in those evaluated with iFR (unadjusted HR: 0.74 in favor of SAP; 95% CI: 0.38 to 1.43; $p = 0.37$) (Table 5), with a statistically nonsignificant interaction (Figure 4). The effect of clinical presentation on MI rate was more

marked in the FFR group (unadjusted HR: 0.28 in favor of SAP; 95% CI: 0.09 to 0.88) than in the iFR group (unadjusted HR: 0.42 in favor of SAP; 95% CI: 0.14 to 1.27), but the interaction was not statistically significant.

DISCUSSION

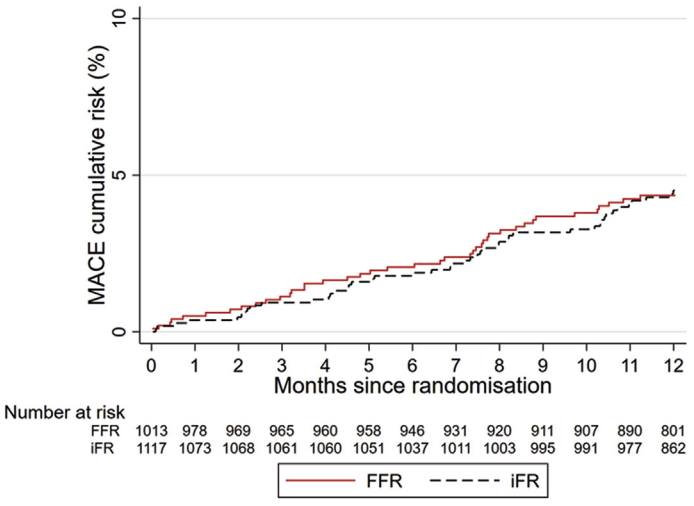
The present study demonstrates that the revascularization of intermediate stenoses in patients with SAP can be safely deferred on the grounds of iFR or FFR measurements. In patients with ACS, deferral was associated with more cardiovascular events at follow-up, compared to patients with SAP.

DEFERRAL OF REVASCULARIZATION: A KEY ASPECT OF PHYSIOLOGY-GUIDED REVASCULARIZATION. Physiology-guided revascularization is the current main application of coronary physiology in the catheterization laboratory. It aims to improve patient outcomes by restricting revascularization to stenoses that cause myocardial ischemia (2,16). Because coronary angiography is an inadequate diagnostic tool for estimating functional stenosis severity, particularly in intermediate stenoses (17), the predominant role of intracoronary physiology is to serve as a gatekeeper to revascularization in intermediate stenoses (18).

The pivotal DEFER trial, in which 92 of the 325 patients included were randomized to PCI deferral, consolidated the concept that FFR-based postponement of revascularization is safe (3). However, translation of the trial to contemporary clinical practice is hampered not only by the fact that the 0.75 FFR cutoff in the study has been abandoned from treatment guidelines but also primarily by the evolution of treatment over the past 20 years: balloon angioplasty as a stand-alone therapy has virtually been abandoned, drug-eluting stents have been developed, and more potent antiplatelet agents and other medical therapies have become available. Furthermore, subsequent randomized studies such as the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) trial, although performed in the stent era, were conducted in study populations that do not align with guidelines for the recommended use of coronary physiology to guide decision making. Mean FFR in FAME was 0.71, while FFR in DEFINE-FLAIR and iFR-SWEDEHEART studies was close to the 0.80 cutoff, which is in agreement with all other contemporary registries and trials (8–10).

In the FAME trial, 513 lesions were deferred in 509 patients. At 2 years, 1.8% of patients had presented with MI, and 10.4% required repeat revascularization (19). In the FAME II trial, 166 registry patients (those with FFR >0.80) were followed up. At 2 years, 9% of patients had reached the primary endpoint. Looking at the components of the primary endpoint, the mortality rate was 1.2%, the MI rate 5.4%, and the urgent revascularization rate 5.4% (16). Ahn et al. (20) enrolled 5,846 patients in a prospective multicenter study from 2009 to 2015 who had revascularization guided by FFR (6,468 deferred lesions, 2,165 treated lesions). In this study, the risk for cardiac events in deferred lesions, at a median

FIGURE 3 Cumulative Risk for Primary Endpoint (Major Adverse Cardiac Events) by Physiological Technique in the Deferred Population



Shown is the cumulative risk for the composite of death from any cause, nonfatal myocardial infarction, or unplanned revascularization at 1 year. MACE = major adverse cardiac event(s); other abbreviations as in Figure 1.

TABLE 4 Outcomes in the Overall Deferred Population According to Instantaneous Wave-Free Ratio or Fractional Flow Reserve

	iFR (n = 1,117)	FFR (n = 1,013)	iFR vs. FFR: Unadjusted HR (95% CI)	iFR vs. FFR: Fully Adjusted HR (95% CI)	p Value
MACE	4.12 (46)	4.05 (41)	1.05 (0.69–1.60)	1.13 (0.72–1.79)	0.60
All-cause death	0.98 (11)	0.59 (6)	1.68 (0.62–4.55)	2.21 (0.68–7.13)	0.19
Cardiovascular death	0.36 (4)	0.10 (1)	3.66 (0.41–32.76)	2.53 (0.23–28.32)	0.45
Noncardiovascular death	0.63 (7)	0.49 (5)	1.29 (0.41–4.05)	2.04 (0.51–8.13)	0.31
Myocardial infarction	1.16 (13)	1.28 (13)	0.99 (0.45–2.18)	1.00 (0.44–2.28)	1.00
Unplanned revascularization	2.78 (31)	3.26 (33)	0.86 (0.53–1.40)	0.88 (0.52–1.49)	0.63

Values are % (n), unless otherwise indicated.
Abbreviations as in Tables 1 and 3.

TABLE 5 Outcomes in the Overall Deferred Population According to Clinical Presentation (Stable Angina Pectoris Versus Acute Coronary Syndrome) and Effect Modification by Physiological Technique

	SAP (n = 1,675)	ACS (n = 440)	SAP vs. ACS Unadjusted HR (95% CI)	p Value	Interaction p Value
MACE	3.64 (61)	5.91 (26)	0.62 (0.39–0.99)	0.04	
FFR	3.42 (27)	6.42 (14)	0.52 (0.27–1.00)		0.46
iFR	3.84 (34)	5.41 (12)	0.74 (0.38–1.42)		
All-cause death	0.66 (11)	1.36 (6)	0.50 (0.19–1.36)	0.17	
FFR	0.51 (4)	0.92 (2)	0.57 (0.10–3.13)		0.83
iFR	0.79 (7)	1.80 (4)	0.46 (0.13–1.57)		
Cardiovascular death	0.18 (3)	0.45 (2)	0.41 (0.07–2.45)	0.33	
FFR	0.00 (0)	0.46 (1)			
iFR	0.34 (3)	0.45 (1)	0.78 (0.08–7.52)		
Noncardiovascular death	0.48 (8)	0.91 (4)	0.55 (0.16–1.82)	0.32	
FFR	0.51 (4)	0.46 (1)	1.14 (0.13–10.24)		0.38
iFR	0.45 (4)	1.35 (3)	0.35 (0.08–1.56)		
Myocardial infarction	0.90 (15)	2.50 (11)	0.34 (0.16–0.76)	0.01	
FFR	0.89 (7)	2.75 (6)	0.28 (0.09–0.88)		0.64
iFR	0.90 (8)	2.25 (5)	0.42 (0.14–1.27)		
Urgent revascularization	2.87 (48)	3.64 (16)	0.81 (0.46–1.43)	0.47	
FFR	2.78 (22)	5.05 (11)	0.56 (0.27–1.16)		0.15
iFR	2.94 (26)	2.25 (5)	1.36 (0.52–3.53)		

Values are % (n), unless otherwise indicated.
Abbreviations as in Tables 1 and 3.

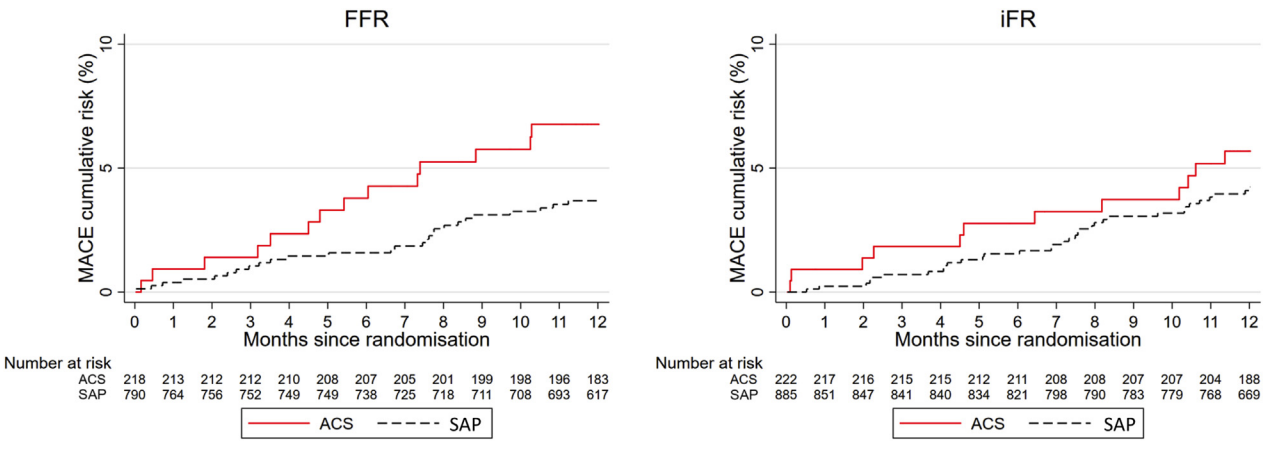
follow-up of 1.9 years, was linearly associated with FFR values. When FFR was >0.70, the higher the FFR value, the lower the incidence of cardiac events. However, contemporary evidence supporting the safety of FFR-based revascularization deferral is based largely on registry data, not randomized clinical trials comparing outcomes in patients with ACS compared with those with SAP.

DEFERRAL OF REVASCULARIZATION WITH EITHER FFR OR iFR. The recently published DEFINE-FLAIR and iFR-SWEDEHEART trials demonstrated that iFR is noninferior to FFR in terms of clinical outcomes associated with ischemia-driven revascularization (6,7). These trials provide the first opportunity to assess the validity of PCI deferral with a pressure-derived index of stenosis severity other than FFR. Of note, both studies consistently demonstrated that fewer stenoses were deemed hemodynamically significant when iFR was used. As this implies a higher rate of PCI deferral when iFR is used as a diagnostic tool, comparing the outcomes of patients who had iFR or FFR determined PCI deferral is an objective of the utmost clinical importance.

Overall, iFR and FFR are equally safe in deferring revascularization, with event rates in our study of 4.12% and 4.05%, respectively (fully adjusted HR: 1.13; 95% CI: 0.72 to 1.79; p = 0.60). These event rates, at 1-year follow-up, are virtually one-half of those reported for deferred patients in the DEFER trial (8%) (3), reflecting the evolution of interventional and medical therapy.

DEFERRAL OF REVASCULARIZATION IN PATIENTS WITH ACS. The evidence supporting the safety of deferral of PCI in patients with ACS on the basis of

FIGURE 4 Cumulative Risk for Primary Endpoint (Major Adverse Cardiac Events) by Clinical Presentation in Patients Assessed With Fractional Flow Reserve and Instantaneous Wave-Free Ratio in the Deferred Population



Shown is the cumulative risk for the composite of death from any cause, nonfatal myocardial infarction, or unplanned revascularization at 1 year, stratified according to clinical presentation with either stable angina pectoris (SAP) or acute coronary syndrome (ACS). Data for fractional flow reserve (FFR) **(left)** and instantaneous wave-free ratio (iFR) **(right)** are displayed.

pressure-derived measurements is limited. The conclusions of the DEFER trial, based on patients with SAP, are therefore not applicable in contemporary clinical practice, in which ACS is a very common indication for PCI. A substudy of the FAME trial documented a higher prevalence of 2-year MACE in 150 patients with ACS who had physiology-guided PCI performed (21.3%), compared with 359 patients with SAP included in the trial (16.4%); importantly, that study did not report separately the outcomes of deferred patients according to clinical presentation (21). Recent randomized trials addressing the safety of FFR-guided revascularization of nonculprit stenoses in patients with ACS and multivessel disease (11,12) have focused only on the ACS subset, not comparing the long-term outcomes with patients with SAP when revascularization is deferred on the basis of FFR (2,16). Furthermore, these trials included small numbers of patients presenting with non-ST-segment elevation MI, therefore contributing to the paucity of data on this important topic. A further limitation is that much evidence in this population comes from observational data rather than randomized clinical trials.

The present analysis confirms that among patients who had revascularization deferred, those presenting with ACS had a higher 1-year MACE rate than those presenting with SAP (5.91% vs. 3.64%; fully adjusted HR: 0.61; 95% CI: 0.38 to 0.99; $p = 0.04$) (**Table 3**). These findings are in agreement with recently reported studies (13,14). Hakeem et al. (14) found that FFR-based deferral of PCI in patients with ACS was associated with a more than 2-fold increase in the combined endpoint of MI or target vessel revascularization at 3.4-year follow-up compared with patients with SAP (23% vs. 11%, respectively, $p < 0.0001$). Masrani Mehta et al. (13) reported similar findings in a retrospective analysis of a series of 674 patients, of whom 334 presented with ACS. At a mean follow-up of 4.5 years, patients with ACS had a significantly higher MACE rate than those with SAP (32% vs. 23%, respectively, $p = 0.02$). Lee et al. (15) reported, as part of a prospective, international registry on FFR use, the long-term outcomes (mean 2.1 years) after FFR-based deferral of revascularization in 1,596 patients, of whom 301 presented with ACS. Deferral of revascularization in nonculprit stenoses in patients with ACS ($n = 409$) was associated with a more than 2-fold increase in MACE compared with deferral of stenoses in patients with SAP (adjusted HR: 2.97; 95% CI: 1.33 to 7.17; $p = 0.026$). Clinical presentation with ACS was identified in a multivariate Cox model as the most powerful independent predictor of MACE after FFR-based intervention deferral (adjusted HR: 2.74; 95% CI: 1.13 to 6.64; $p = 0.026$). In contrast, our findings are not concordant with those obtained in the pooled population of 2 separate registries, including 1,983 patients, of whom 533 presented with ACS (22). At 1-year follow-up, FFR-based deferral was associated with similar MACE rates in patients presenting with ACS and SAP (8.0% vs. 8.5% with ACS and SAP, respectively; $p = 0.83$). Of note, MACE rates in that registry were markedly higher than in our study, particularly in patients with SAP (8.5% vs. 3.6% in our study).

INFLUENCE OF CLINICAL PRESENTATION ON THE SAFETY OF PRESSURE-DERIVED INDEXES OF STENOSIS SEVERITY. Whether the observed higher event rates among patients with ACS are due to their inherent higher risk or to inadequate stenosis assessment with pressure guidewires is unclear. From contemporary trial data (23) patients presenting with ACS have increased cardiovascular risk after stabilization, with respective 1-year rates of MI and death of 5.8% and 2.4%.

In our analysis, we found that MACE in deferred patients with ACS were driven largely by coronary revascularization, although both MI and death also contributed. This might provide indirect support for the concept that in patients with ACS, pressure-based indexes do not consistently identify the stenoses for which revascularization can be safely deferred. Furthermore, other studies have reported repeat revascularization as an important contributor to MACE in patients presenting with ACS who had revascularization deferred on the grounds of FFR interrogation (13–15). As we did not assess the characteristics of the atheromatous plaques in nonculprit vessels in patients with ACS, an increased risk attributable to vulnerable lesions in these patients cannot be ruled out. Such risk might be amplified by the presence of systemic inflammation, which has been documented in patients with ACS (24).

The excess of risk for physiology-based stenosis deferral in patients with ACS may reflect the substantially different physiological conditions found in these patients from those in patients with SAP. Although FFR has been extensively validated as a clinical tool in patients with SAP, its value in patients with ACS is less well described. Microcirculatory vasodilation during hyperemia can be transiently blunted in the acute phase of ACS, affecting also

myocardial territories remote to those subtended by nonculprit stenoses (25). We explored whether iFR or FFR resulted in better long-term outcomes of stenosis deferral in patients with ACS. However, the negative outcome associated with ACS presentation on 1-year outcomes after revascularization deferral was not significantly influenced by the use of either iFR or FFR, even when the individual components of MACE were analyzed separately. Numerically, we observed higher rates of MACE in the ACS compared with SAP cohort among patients deferred with FFR. This difference in rates was less pronounced in patients deferred with iFR.

STUDY LIMITATIONS. This was a nonrandomized subset of 2 prospective randomized trials, but the results have been fully adjusted for baseline clinical characteristics. Both iFR and FFR are continuous variables, which were reported and acted in a dichotomous manner (i.e., treat or do not treat if below or above a threshold), and therefore relevant clinical information is omitted from the decision-making process. In DEFINE-FLAIR, both the patients and the treating physicians remained blinded to group assignments, whereas in iFR-SWEDEHEART, both were aware of the group assignment.

CONCLUSIONS

Overall, deferral of revascularization is equally safe with both iFR and FFR, with a low MACE rate of approximately 4%. Lesions were more frequently deferred when iFR was used to assess physiological stenosis significance. Deferral of patients with ACS is associated with a significant increase in event rates at 1 year compared with patients with SAP.

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PERSPECTIVES

WHAT IS KNOWN? DEFINE-FLAIR and iFR-SWEDEHEART are the largest coronary physiology clinical outcome trials ever conducted. Within the trials, overall MACE rates at 1 year were similar for both iFR- and FFR-guided populations. However, the clinical outcomes of patients who had coronary revascularization deferred on the basis of iFR or FFR measurements, and the influence of clinical presentation (SAP and ACS) on outcomes, are unknown.

WHAT IS NEW? Despite a higher rate of deferral with iFR, clinical outcomes for both iFR- and FFR-deferred populations were similar at 1 year. This indicates that deferral of coronary revascularization by either iFR or FFR methods is equally safe. However, deferral of patients with ACS was associated with a significant increase in event rates at 1 year compared with patients with SAP.

WHAT IS NEXT? Reporting of longer term clinical outcomes from the DEFINE-FLAIR and iFR-SWEDEHEART trials are awaited. Furthermore, analyses of key substudy populations of clinical interest are ongoing.

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APPENDIX For inclusion and exclusion criteria, supplemental tables, and a supplemental figure, please see the online version of this paper.

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