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Long-Term Prognosis of Deferred Acute Coronary Syndrome Lesions Based on Nonischemic Fractional Flow Reserve

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ABSTRACT

BACKGROUND Deferring percutaneous coronary intervention in nonischemic lesions by fractional flow reserve (FFR) is associated with excellent long-term prognosis in patients with stable ischemic heart disease (SIHD). Although FFR is increasingly used for clinical decision making in acute coronary syndrome (ACS) patients with intermediate lesions, its effect on long-term prognosis has not been well established.

OBJECTIVES This study investigated the clinical and prognostic utility of FFR in ACS patients with percutaneous coronary intervention deferred on the basis of nonischemic FFR.

METHODS We studied 206 consecutive ACS patients with 262 intermediate lesions and 370 patients with SIHD (528 lesions) in whom revascularization was deferred on the basis of a nonischemic FFR (>0.75). The primary outcome measure was a composite of myocardial infarction and target vessel failure (major adverse cardiovascular events [MACE]).

RESULTS In the entire cohort, the long-term (3.4 ± 1.6 years) MACE rate was higher in the ACS group than in the SIHD group (23% vs. 11%, $p < 0.0001$). After propensity score matching (200 patients/group), MACE remained significantly higher (ACS 25% vs. SIHD 12%; $p < 0.0001$). On Cox proportional hazards analysis for MACE, ACS had a hazard ratio of 2.8 (95% confidence interval: 1.9 to 4.0; $p < 0.0001$). In both the matched and unmatched cohorts, across all FFR categories, ACS patients had a significantly higher annualized myocardial infarction/target vessel revascularization rate compared with SIHD ($p < 0.05$). Receiver-operating characteristic analysis identified FFR cutoffs (best predictive accuracy for MACE) of <0.84 for ACS (MACE 21% vs. 36%; $p = 0.007$) and <0.81 for SIHD (MACE 17% vs. 9%; $p = 0.01$).

CONCLUSIONS Deferring percutaneous coronary intervention on the basis of nonischemic FFR in patients with an initial presentation of ACS is associated with significantly worse outcomes than SIHD. Caution is warranted in using FFR values derived from patients with SIHD for clinical decision making in ACS patients. (J Am Coll Cardiol 2016;68:1181–91)

On the basis of a large body of evidence, fractional flow reserve (FFR) evaluation for intermediate coronary stenosis has become the standard of care for clinical decision making in stable ischemic heart disease (SIHD) (1). The DEFER trial demonstrated that FFR-based deferral of nonischemic (defined as FFR >0.75) intermediate lesions is safe and effective compared with an angiography-only guided strategy. The durability of such an approach is sustained through 15 years, without a late catch-up phenomenon, such that patients in the deferred arm had identical survival

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CFTC = corrected TIMI (Thrombolysis In Myocardial Infarction) frame count

CI = confidence interval

CMR = cardiac magnetic resonance

FFR = fractional flow reserve

HR = hazard ratio

IC = intracoronary

IV = intravenous

MACE = major adverse cardiovascular event

MI = myocardial infarction

MLA = minimal luminal area

NSTEMI = non-ST-segment elevation myocardial infarction

OCT = optical coherence tomography

PCI = percutaneous coronary intervention

SIHD = stable ischemic heart disease

STEMI = ST-segment elevation myocardial infarction

TLR = target lesion revascularization

TVF = target vessel failure

TVR = target vessel revascularization

UA = unstable angina

VA = Veterans Administration

compared with a percutaneous coronary intervention (PCI) strategy, whereas the risk of myocardial infarction (MI) was significantly higher in the PCI group than in the deferred group (10% vs. 2.2%; p = 0.03) (2).

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Although the DEFER trial included only SIHD patients, these findings have begun to be extrapolated to patients with acute coronary syndromes (ACS). Whether FFR is actually useful for predicting long-term outcomes with intermediate lesions in ACS patients is uncertain. Furthermore, there is some concern that it may not be possible to achieve maximal hyperemia (an essential prerequisite of FFR measurement) in ACS patients (due to microvascular dysfunction) (3–7). Recent studies have, however, suggested that FFR may be usable in most ACS settings. With the exception of the immediate period after ST-segment elevation myocardial infarction (STEMI), FFR evaluation has been shown to accurately identify ischemic and nonischemic lesions in non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA) patients (5–7). Several studies, including a recent randomized trial, have suggested that FFR-guided evaluation of ACS patients may reduce the rates of coronary revascularization without compromising short-term safety (6,7). These studies are limited, however, by small patient numbers, low-risk populations, and/or short-term follow-up, and they have yielded mixed results.

In the current study, we investigated the clinical and prognostic utility of FFR in ACS patients with PCI deferred on the basis of nonischemic FFR in a large contemporaneous real-world population.

METHODS

This was a retrospective analysis of consecutive patients with clinical diagnosis of NSTEMI and UA who were "deferred" from PCI on the basis of a nonischemic FFR (>0.75) at our institution between March 1, 2009 and October 30, 2014. This study enrolled ACS patients who were relatively stable, without signs of hemodynamic or electric instability. All patients had TIMI (Thrombolysis In Myocardial Infarction) flow grade 3. ACS patients included those with NSTEMI (combination of clinical presentation, positive biomarkers with or without electrocardiographic changes). UA patients had recent onset angina (<3 weeks) or accelerating/rest angina with electrocardiographic changes, but without evidence of positive biomarkers. We used a contemporaneously evaluated group of deferred SIHD patients as the comparator group. The Central Arkansas Veterans Administration (VA) Health System's institutional review board approved the study.

FFR MEASUREMENT. FFR was measured using non-side-hole guide catheters with a 0.014-inch wire (Volcano, San Diego, California; or St Jude, St. Paul, Minnesota). The wire was advanced distal to the lesion once therapeutic anticoagulation was achieved. After intracoronary (IC) nitroglycerin administration, the baseline gradient was recorded. FFR was then measured under maximal hyperemia with either intravenous (IV) (140 μg/kg/min) or IC (at least 60 μg) adenosine. The median dose of IC adenosine in our cohort was 130 μg (interquartile range: 120, 216 μg).

DATA COLLECTION AND ENDPOINTS. Sources of data. The Veterans Health System has a uniform, fully electronic national record system called CPRS (Computerized Patient Record System). It provides networked, robust, and timely retrieval of remote-site patient data. All medical records, including outpatient phone contacts, are stored in CPRS. Hospital stays outside the VA are either recorded in VA physician notes or scanned and stored electronically in the VA system. The initial patient visit (at the time of PCI) was used to record demographic data, cardiovascular symptoms, and baseline cardiac risk factors.

The primary endpoint was a composite of MI and target vessel failure (TVF). TVF was defined as a subsequent MI or target lesion revascularization/target vessel revascularization (TVR) from the index FFR vessel. MI was defined as a clinical syndrome of ischemic symptoms and a rise in serum troponin >99th percentile of the reference lab value or IC thrombus in the target vessel with or without new ischemic ST-segment and T-wave changes. TVR was defined as subsequent revascularization of the index vessel by either PCI or bypass grafting of the target vessel. The secondary endpoint was cardiac death, defined as death due to any cardiac cause, including fatal MI, sudden death with or without documented arrhythmia without known cause, or congestive heart failure. Three independent reviewers (blinded to the angiographic/FFR and demographic data) adjudicated the cause of death through chart review, death certificate, and physicians' records. Conflicts were

TABLE 1 Baseline Characteristics

		Before Matching			After Matching		
	Entire Group (N = 576)	SIHD (n = 370)	ACS (n = 206)	p Value	SIHD (n = 200)	ACS (n = 200)	p Value
Age, yrs	66 ± 8	64.7 ± 8.7	66.6 ± 8	0.01	65 ± 8	64.6 ± 8	0.58
Male	554 (96.0)	358 (97.0)	197 (95.0)	0.256	190 (95.0)	190 (95.0)	>0.99
Diabetes	282 (49.0)	175 (47.0)	106 (51.0)	0.384	96 (48.0)	102 (51.0)	0.54
CKD	137 (23.7)	94 (25.0)	43 (21.0)	0.204	38 (19.0)	39 (19.5)	0.89
Smoking	278 (48.0)	183 (49.4)	95 (46.0)	0.44	102 (51.0)	93 (46.5)	0.42
Previous MI/revascularization	363 (63.0)	202 (55.0)	161 (78.0)	0.0001	153 (77.0)	154 (77.0)	0.90
PVD/CVA	122 (21.0)	70 (19.0)	52 (25.0)	0.083	48 (24.0)	52 (26.0)	0.64
Multivessel disease	351 (61.0)	216 (58.0)	135 (65.0)	0.115	134 (67.0)	130 (65.0)	0.67
LVEF, %	50.7 ± 12	51 ± 11	50 ± 12	0.43	51 ± 11	50 ± 12	0.61

Values are mean ± SD or n (%).

ACS = acute coronary syndrome; CKD = chronic kidney disease; CVA = cerebrovascular accident; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PVD = peripheral vascular disease; SIHD = stable ischemic heart disease.

resolved by global consensus or by the senior investigator. In case of more than 1 event, only the first event was counted for Kaplan-Meier analysis.

STATISTICAL ANALYSIS. Adjustment for baseline confounders. To account for significant differences in the distribution of key baseline characteristics between the groups, we used propensity scoring to assemble a cohort in which the 2 groups were well balanced (8,9). The score was computed by a logistic regression model using mode of presentation (ACS vs. SIHD) as the outcome variable and the following predictor variables: age; sex; presence of diabetes mellitus or chronic kidney disease; history of MI or revascularization; peripheral vascular disease or stroke (cerebrovascular accident); IV adenosine use; and presence of multivessel disease. One-to-one propensity-score nearest-neighbor matching without replacement was applied with a caliper of 0.20 to generate the 2 study groups. The overall balance test (9) showed that the data were balanced ($p = 0.99$); the C-statistic for the model was 0.67. The Hosmer-Lemeshow goodness-of-fit test was used to check the accuracy of the model ($p = 0.70$). In addition, predictor variables were tested before and after matching to ensure a balanced distribution (no significant difference between the 2 study groups after matching).

STATISTICS. Patient groups (ACS and SIHD) were compared using the unpaired Student *t* test for continuous variables and the chi-square test for categorical or dichotomous variables. Unadjusted annual event rates were calculated by first estimating overall event rates through calculation of Kaplan-Meier curves, then dividing the event rate by the mean follow-up time for each of the groups.

Baseline characteristics and clinical outcomes were analyzed using patient-based analysis. Lesion characteristics, including FFR values, PCI characteristics, and hemodynamics, were analyzed using lesion bases analysis. In the presence of multiple coronary stenoses, the first lesion (thought to be the likely "culprit") was used for clinical outcome analyses for all outcomes, including survival and Cox proportional hazards analysis.

Receiver-operating characteristic curve analysis was performed to assess the optimal FFR cutoff value for predicting MI/TVF in ACS and SIHD patients. Multivariate models were constructed using Cox proportional hazards analysis for MI/TVF prediction (ENTER method, inclusion criteria $p < 0.05$; exclusion criteria $p > 0.10$). The number of covariates entered into the model was restricted to maintain ≥10 events per degree of freedom. The proportional hazards assumption was tested graphically with Cox-adjusted log (minus [survival]) curves (parallel) and statistically using time interaction tests in SPSS Statistics (version 13, IBM Corp., Armonk, New York). All significant covariates met the proportionality assumption. The level of statistical significance was set a priori at 0.05, and a 2-sided probability value was used for the analyses. Statistics were performed using MedCalc statistical software (version 15.2.1, MedCalc Software, Ostend, Belgium) and SPSS Statistics.

RESULTS

PATIENT CHARACTERISTICS. The study group include 206 ACS patients with 262 lesions and 370 patients with SIHD (528 lesions). In the ACS group, 39

TABLE 2 Medications at Deferral

		Before Matching			After Matching		
	Total Cohort (N = 576)	SIHD (n = 370)	ACS (n = 206)	p Value	SIHD (n = 200)	ACS (n = 200)	p Value
Aspirin	513 (89.0)	325 (88.0)	188 (91.0)	0.20	183 (91.5)	183 (91.5)	0.85
ADP inhibitor	145 (25.0)	73 (20.0)	72 (35.0)	0.001	57 (28.5)	71 (35.5)	0.16
Beta-blocker	428 (74.0)	262 (71.0)	166 (80.0)	0.01	151 (75.5)	161 (80.5)	0.27
ACE inhibitor	338 (58.6)	207 (56.0)	131 (63.0)	0.09	110 (55.0)	127 (63.5)	0.12
Nitrates	200 (35.0)	107 (29.0)	93 (45.0)	0.001	68 (34.0)	87 (43.5)	0.06
Statin	457 (79.0)	281 (76.0)	176 (85.0)	0.03	160 (80.0)	171 (85.5)	0.18
Insulin	115 (20.0)	68 (18.0)	47 (23.0)	0.2	42 (21.0)	45 (22.5)	0.8

Values are n (%).
ACE = angiotensin-converting enzyme; ADP = adenosine diphosphate; other abbreviations as in Table 1.

patients (55 lesions) had NSTEMI and 167 patients (207 lesions) had UA. Baseline characteristics of the study population are shown in Table 1. The median TIMI risk score was 4 (interquartile range: 4 to 5) for the NSTEMI patients and the median angina Canadian Cardiovascular Society class was II among SIHD patients. Before matching, patients in the SIHD group were older (66.6 ± 8.0 years vs. 64.7 ± 8.7 years; $p = 0.01$), and ACS patients were more likely to have had previous MI or revascularization (77% vs. 54.8%; $p < 0.001$). Groups were well balanced with respect to medications on discharge, except that ACS patients were more likely to be on dual antiplatelet therapy and nitrates (Table 2). Medication variables were not included in the propensity score matching because they were expected to be different between groups.

PROCEDURAL AND HEMODYNAMIC CHARACTERISTICS. Angiographic and hemodynamic characteristics are presented in Table 3. Before matching, patients with ACS had a small, but statistically significant higher luminal diameter stenosis compared with SIHD patients (51.8 ± 14.7% vs. 49.5 ± 12.9%; $p = 0.01$) and a greater use of IV adenosine (56% vs. 40%; $p < 0.001$). After matching, there was no difference in baseline angiographic and hemodynamic variables (Table 3). FFR was similar in both groups (ACS 0.87 ± 0.05 vs. SIHD 0.87 ± 0.04; $p = 0.48$). Similarly the distribution of FFR categories was identical between the ACS and SIHD groups (Figure 1).

CLINICAL OUTCOMES. Cumulative events during a follow-up period of 3.4 ± 1.6 years are shown in Table 4. ACS patients had significantly higher rates of MI/TVF than did SIHD patients. Similarly, the rates of MI, TVR, and TLR were higher in ACS than in SIHD patients. The rates of cardiac death were similar. Similar trends were observed in the propensity-matched cohort (Table 4).

PRIMARY OUTCOME. Figures 2A and 2B show Kaplan-Meier survival analysis for the primary endpoint of MI/TVF in the entire cohort and in matched patients, respectively. ACS patients had a significantly higher rate of MI/TVR than did SIHD patients (23% vs. 11%; log-rank $p < 0.0001$) in the entire cohort, as well as the matched cohort (25% vs. 12%; log rank $p < 0.0001$). Furthermore, patients with NSTEMI had the highest event rates (42%), followed by UA (19%), and then SIHD (10%) (Central Illustration).

PRIMARY OUTCOME AND FFR CATEGORIES. Figure 3 shows the annualized event rates between the 2 groups among the different FFR categories. For all FFR categories, ACS patients had a significantly higher annualized MI/TVR rate compared with SIHD ($p < 0.05$) in both the matched and unmatched cohorts. Additionally, ACS patients had a 2-fold higher rate of MI/TVF in the low/borderline category compared with higher categories, such that the event rate was 12.8%/year and 10%/year for the categories of 0.75 to 0.80 and 0.81 to 0.85 compared with 6.2%/year for FFR >0.90. The event rate for SIHD patients remained consistent across the different categories without such a trend.

TABLE 3 Baseline Angiographic and Hemodynamic Characteristics

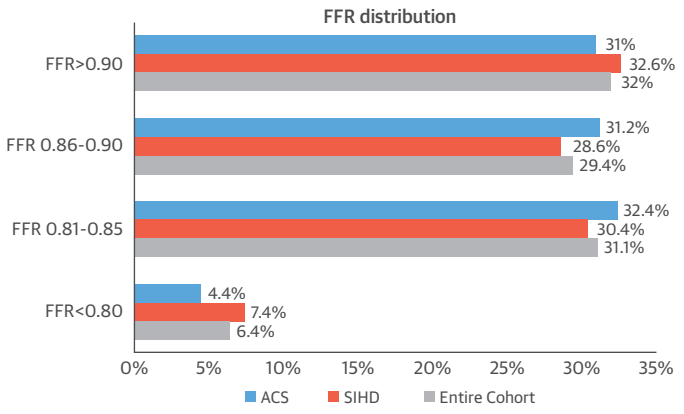
		Before Matching			After Matching		
	Entire Group (N = 796)	SIHD (n = 528)	ACS (n = 268)	p Value	SIHD (n = 286)	ACS (n = 258)	p Value
Stenosis severity	50.3 ± 13.6	49.5 ± 12.9	51.8 ± 14.7	0.01	50 ± 12.7	51.7 ± 14.6	0.15
Baseline Pd/Pa	0.96 ± 0.03	0.96 ± 0.03	0.96 ± 0.06	0.66	0.96 ± 0.03	0.96 ± 0.06	0.41
FFR	0.87 ± 0.05	0.87 ± 0.05	0.87 ± 0.04	0.68	0.87 ± 0.05	0.87 ± 0.04	0.48
LAD	276 (34.6)	195 (37.0)	81 (30.2)	0.06	102 (35.6)	76 (29.4)	0.14
IV adenosine	365 (45.8)	213 (40.0)	151 (56.3)	<0.001	153 (53.4)	142 (55.0)	0.77
Diffuse disease	238 (29.8)	165 (31.5)	73 (27.2)	0.24	80 (28.0)	72 (28.0)	0.92

Values are mean ± SD or n (%).
FFR = fractional flow reserve; IV = intravenous; LAD = left anterior descending artery; Pa = aortic pressure; Pd = distal pressure (across the stenotic lesion); other abbreviations as in Table 1.

OPTIMAL FFR THRESHOLD FOR PREDICTION OF PRIMARY ENDPOINT. Using receiver-operating characteristic curve analysis with MI/TVF as the classification variable, an FFR cutoff ≤0.84 was found to have the best predictive accuracy in the ACS population (MI/TVR 11.4%/year vs. 6.8%/year; p = 0.04). FFR cutoff <0.81 had the best predictive accuracy in SIHD patients (MI/TVR 6%/year vs. 0.6%/year; p = 0.009) (Central Illustration).

MULTIVARIATE ANALYSIS. On Cox proportional hazards analysis in the matched population, ACS (hazard ratio [HR]: 3.03; 95% confidence interval [CI]: 1.82 to 5.04), and multivessel disease (HR: 2.66; 95% CI: 1.33 to 5.31) were independent predictors of MI/TVF (Table 5). In the entire cohort, ACS, previous MI/revascularization, multivessel disease, and FFR were independent predictors of MI/TVF. Among ACS patients, FFR ≤0.84 was independently predictive of MI/TVF (HR: 2.62; 95% CI: 1.4 to 4.9; p < 0.01).

FIGURE 1 Distribution of FFR Categories in the ACS and SIHD Groups



There was no difference in the distribution of fractional flow reserve (FFR) categories between the acute coronary syndrome (ACS) and stable ischemic heart disease (SIHD) groups.

DISCUSSION

The major study finding is that the long-term prognostic value of a nonischemic FFR depends on the index clinical presentation. We have shown in a large contemporaneous cohort of patients, using propensity matching to adjust for baseline covariate confounders, that FFR-guided deferral in ACS patients using the FFR value established for SIHD, is associated with a significantly higher risk of MI, TLR, and TVR compared with SIHD. Index presentation of NSTEMI had the highest risk, with UA being worse than SIHD, but lower risk than NSTEMI. ACS remained an independent predictor of adverse events at extended follow-up. Furthermore, the predictive FFR cutoffs for subsequent events were different in ACS and SIHD patients.

Baseline risk factors were different between the 2 groups, as would be expected with ACS patients, demonstrating a higher burden of atherosclerotic risk factors in ACS patients. Despite propensity matching, the ACS group persisted in having a significantly higher event rate (vs. the SIHD group) that became manifest soon after deferral and remained persistently higher over the entire follow-up period. Compared with SIHD patients, ACS patients had a 3-fold higher risk of subsequent MI/TVF.

RELIABILITY OF FFR MEASUREMENT IN ACS. Despite initial concerns of impaired microvascular function during ACS that might yield a false negative FFR result, recent studies have suggested that FFR may be accurate, with a few important caveats. In 48 patients with recent MI, Samady et al. (10) found that FFR diagnostic accuracy in the infarct-related artery (FFR value ≤0.78) was 92% using single-photon emission computed tomography as the "gold standard." Similarly De Bruyne et al. (11) showed that an FFR ≤0.75 in a culprit vessel ≥6 days after a STEMI was predictive of reversible ischemia on single-photon emission computed tomography imaging.

The FAMOUS NSTEMI (Fractional flow reserve versus angiography in guiding management to optimize outcomes in non-ST-elevation myocardial infarction) CMR (Cardiac Magnetic Resonance) substudy showed excellent diagnostic accuracy of FFR <0.80 (92%) for predicting perfusion defects on CMR (12). It is very important to note, however, that the majority (83 patients [76%]) had stress CMR (the reference standard) *after* angiography/PCI (66 underwent PCI). Furthermore, these were medically stabilized patients who underwent invasive

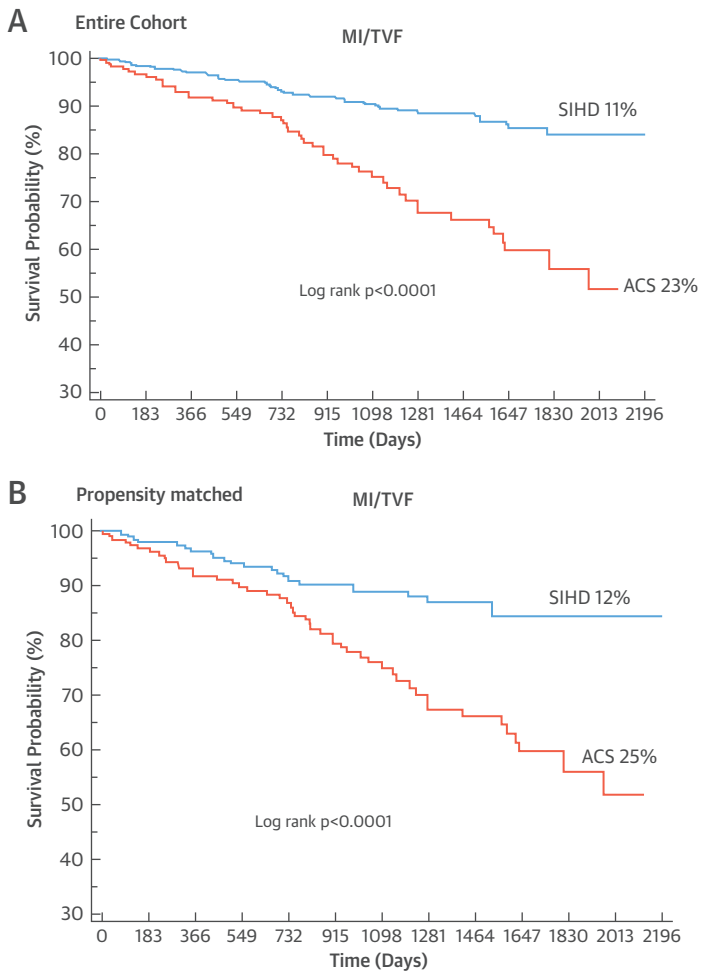
TABLE 4 Cumulative Events at Follow-Up

	Entire Cohort			Matched Cohort		
	SIHD (n = 370)	ACS (n = 206)	p Value	SIHD (n = 200)	ACS (n = 200)	p Value
MI/TVF	40 (11.0)	50 (24.0)	<0.001	24 (12.0)	50 (25.0)	<0.001
Cardiac death	30 (8.0)	9 (4.4)	0.1	12 (6.0)	9 (4.5)	0.5
MI	11 (3.0)	16 (7.8)	0.009	7 (3.5)	16 (8.0)	0.05
TLR	29 (7.8)	36 (17.5)	0.004	19 (9.5)	36 (18.0)	0.01
TVR	14 (4.0)	15 (7.3)	0.08	8 (4.0)	15 (7.5)	0.1

Values are n (%).

TLR = target lesion revascularization; TVF = target vessel failure; TVR = target vessel revascularization; other abbreviations as in Table 1.

FIGURE 2 Annualized MI/TVF Rates on the Basis of FFR Categories in the ACS and SIHD Groups



Freedom from myocardial infarction/target vessel failure (MI/TVF) in **(A)** entire cohort and **(B)** matched patients. Kaplan-Meier curves show significantly higher survival free of MI/TVF in the SIHD patients compared with the ACS group. Abbreviations as in Figure 1.

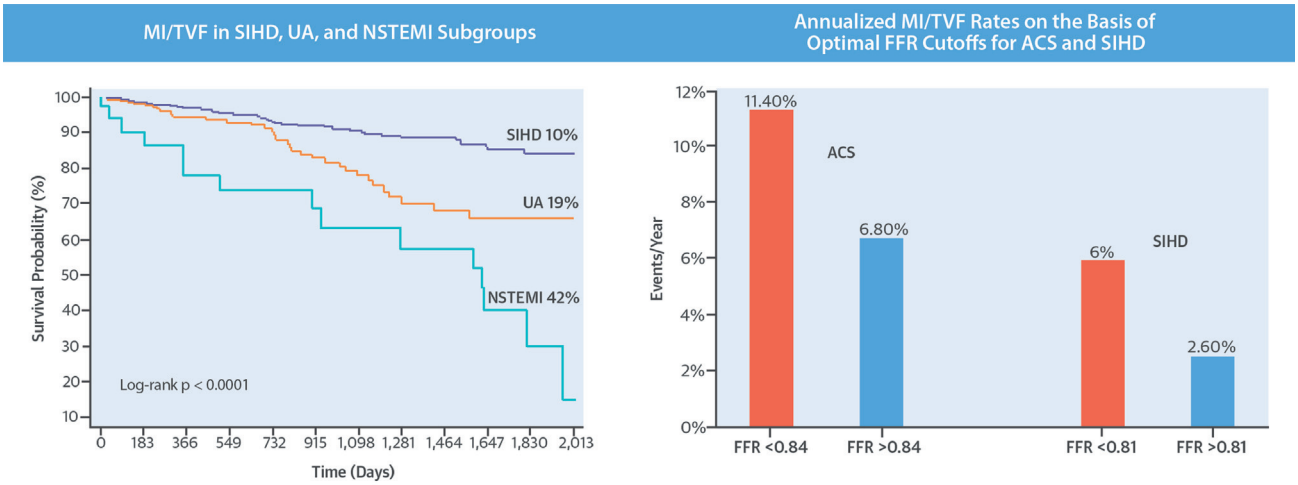
evaluation 4 days after symptom onset, and CMR was performed at an average of 6.6 days after the index procedure (12).

Layland et al. (13) further complemented these observations by measuring the index of microcirculatory resistance and resistive reserve ratio in STEMI, NSTEMI, and SIHD PCI patients, all of whom had ischemic FFR. The study demonstrated that the microcirculatory reserve was preserved in NSTEMI patients, as in SIHD patients, but it was not preserved in STEMI patients (13). That the culprit ACS vessel underwent PCI and had abnormal FFR might suggest preservation of the ability to vasodilate in this patient subgroup (13).

COMPARISON WITH PREVIOUS OUTCOMES STUDIES. Previous studies evaluating outcomes associated with FFR-based deferral in ACS patients are small, with only short-term follow-up. Fischer et al. (14) evaluated the outcomes of deferred patients (35 ACS and 76 SIHD) at 1 year on the basis of FFR >0.75. ACS patients had a trend toward a higher rate of cumulative events (28.5% vs. 17%; $p = 0.21$), with higher rates of TVR and cardiac death (14). In another all-comer ACS population including NSTEMI and STEMI (>24 h post-MI), 201 consecutive patients (FFR ≥0.75) had an event-free survival at 11 months of 90%, with 7.5% of events related to the deferred coronary lesion, including 1 cardiac death and a 2% MI incidence (15). Esen et al. (16) evaluated 162 patients (60% ACS) in whom revascularization was deferred on the basis of nonischemic FFR (>0.75). Major adverse cardiovascular event (MACE) risk was significantly higher in patients with FFR <0.85 compared with those with FFR >0.85 (22% vs. 9%) at 18 ± 10 months of follow-up. Furthermore, 70% of patients with MACE had an initial presentation of ACS. Using the corrected TIMI frame count (CTFC >28) as a marker of microvascular dysfunction, patients with CTFC >28 had a higher event rate compared with those with CTFC <28 (24% vs. 12%). ACS patients had a significantly higher CTFC compared with stable angina patients (16).

In a FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) trial subgroup analysis, the benefit of FFR-guided PCI, compared with angiography alone, was similar for the ACS and SIHD groups. Despite a higher rate of adverse cardiac events in ACS patients, none of the MI during follow-up reportedly occurred in the index lesion. Nevertheless, it is notable that the number of deferred ACS patients in FAME undergoing FFR-guided revascularization was small, with shorter follow-up, and limited the power to show differences among subgroups (17). Similarly, the recent FAMOUS NSTEMI trial was powered to study the impact of an FFR-guided strategy on reducing the number of revascularization procedures in patients with NSTEMI (7). FFR disclosure changed the treatment plan in over 1 in 5 patients, with a reduction in revascularization on a per-patient basis. Although this trial was not powered to detect differences in clinical outcomes, the MACE rate (excluding periprocedural events) was twice as high in the FFR-guided arm versus the angiography-guided arm (5.7% vs. 2.9%; $p = 0.2$) at 1-year follow-up. Furthermore, in the deferred arm, MACE was 7.5% in the FFR group and 0% in the angiography-only group at 12 months. Importantly, 4 of the 10 patients with subsequent MACE

CENTRAL ILLUSTRATION **Outcomes of FFR-Based Deferral in ACS**



Hakeem, A. et al. J Am Coll Cardiol. 2016;68(11):1181–91.

(Left) Non-ST-segment elevation myocardial infarction (NSTEMI) patients had the worst outcomes, followed by unstable angina (UA) patients, compared with stable ischemic heart disease (SIHD) patients (log rank $p < 0.01$). **(Right)** Annualized myocardial infarction/target vessel failure (MI/TVF) rates on the basis of the optimal fractional flow reserve (FFR) cutoff (derived from receiver-operating characteristic analysis as having the best predictive accuracy) in the acute coronary syndrome (ACS) and SIHD groups. In the ACS group, FFR <0.84 had the best predictive accuracy for events, whereas in the SIHD group, an FFR <0.81 ($p < 0.05$ for all comparisons) had the best accuracy.

in the FFR group had an initial treatment plan for PCI in a culprit artery changed to medical therapy on the basis of an FFR >0.80. The fact that late spontaneous MACE occurred more frequently in the FFR- group in this study casts doubt on the wisdom of utilizing FFR to determine PCI deferral in culprit arteries of ACS patients using SIHD patient thresholds (7).

Our findings are in line with another moderately large ACS cohort (n = 334) with long-term follow-up in whom revascularization was deferred on the basis of nonischemic FFR >0.80 (18). At a mean follow-up of 4.5 years, patients with ACS had a significantly higher MACE risk (32% vs. 23%; p = 0.02) compared with SIHD patients. Furthermore, lower FFR (but nonischemic) values were independently predictive of MACE in ACS, but not in SIHD patients (18).

Taken together, these studies suggest that the prognosis of ACS patients in whom revascularization is deferred remains guarded, given a significantly higher risk of subsequent events compared with SIHD patients.

PREDICTIVE FFR THRESHOLD AND EVENTS. We observed a graded association between FFR values and event rates, such that ACS patients within the gray zone (0.75 to 0.80) and borderline zone (0.81 to 0.85) had a several-fold higher event rate compared with higher FFR categories (**Figures 3A and 3B**). No such association was observed for SIHD patients. We have also shown that compared with SIHD patients, in whom the standard cutoff of <0.8 retained its predictive power, ACS patients appeared to have a higher threshold of ≤0.84, on the basis of receiver-operating characteristic analysis. On multivariate analysis, FFR <0.84 had an HR of 2.62 (95% CI: 1.40 to 4.90; $p < 0.01$) for MI/TVF. This value is in agreement with previous studies by Esen et al. (16), showing that patients with FFR <0.85 had a significantly higher event rate than those with FFR >0.85, and Mehta et al. (18), where lower FFR values were predictive of a higher event rate in ACS (HR: 1.08 for every 0.01 decrease in FFR).

POTENTIAL EXPLANATIONS FOR HIGHER RISK WITH DEFERRAL IN ACS PATIENTS. As previously described (3,5,6,10,11,19), timing of FFR measurement in the ACS patient is a fundamentally important issue. Microvascular injury may be temporary, such that initial FFR measurements may be artificially elevated immediately after MI, but the use of antiplatelet and antithrombotic therapy for 3 to 4 days may have a

TABLE 5 Cox Proportional Hazards Model

	HR	95% CI	p Value
Entire cohort			
Age	0.97	0.95–1.00	0.07
DM	0.83	0.54–1.29	0.42
Previous MI or revascularization	1.96	1.07–3.61	**0.03**
ACS	2.64	1.70–4.1	**<0.0001**
FFR	0.007	0.0001–0.64	**0.03**
Multivessel disease	1.62	1.23–2.13	**0.0005**
PVD/CVA	1.38	0.85–2.23	0.19
CKD	0.80	0.44–1.43	0.45
Propensity-matched population			
Age	0.97	0.94–1.00	0.15
Prior MI or revascularization	1.9	0.86–4.25	0.10
CKD	0.81	0.40–1.61	0.55
ACS	3.03	1.82–5.04	**<0.0001**
FFR	0.01	0.0001–1.40	0.06
PVD/CVA	1.15	0.67–1.96	0.60
Multivessel disease	2.66	1.33–5.31	**0.005**

Bold values are statistically significant.

CI = confidence interval; CKD = chronic kidney disease; DM = diabetes mellitus; HR = hazard ratio; other abbreviations as in Tables 1 to 3.

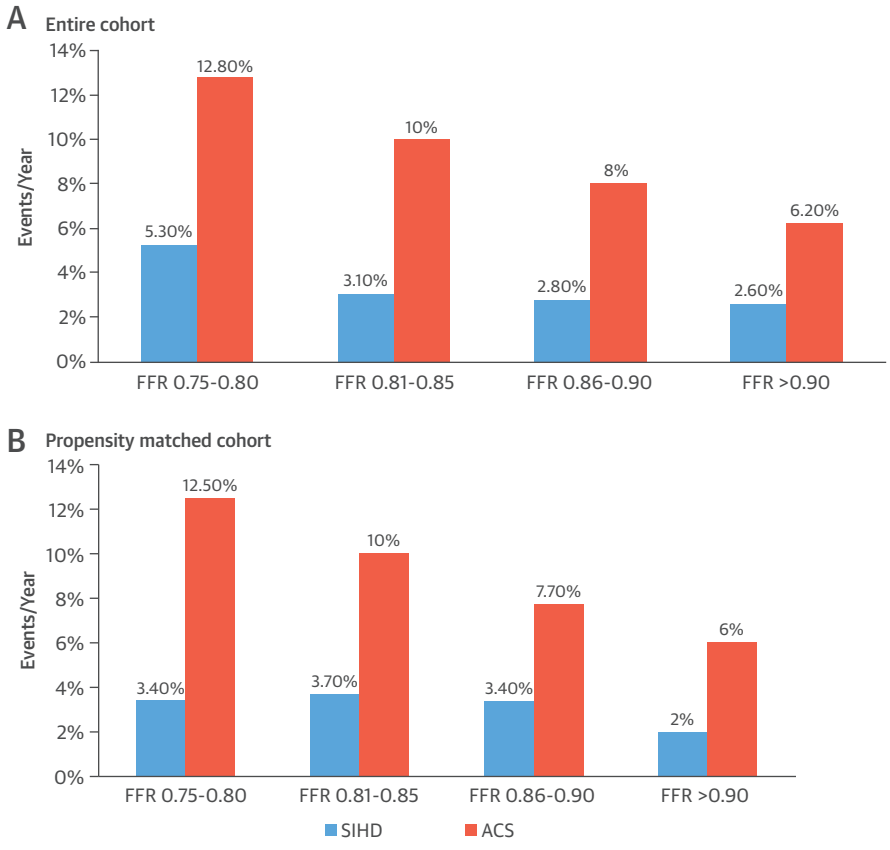
favorable impact on microvascular dysfunction, and FFR may then reflect the true hemodynamic effect (6). The European Society of Cardiology guidelines suggest waiting >5 days to measure FFR in ACS patients (19). Many centers, however, perform invasive evaluation of ACS patients within 48 h of presentation, and measuring FFR early could lead to potentially higher (than truly baseline) FFR values (false negative) and a consequently higher adverse event rate.

Furthermore, the higher risk of subsequent MI and TVF may be explained, in large part, on the pathophysiological basis of ACS versus SIHD. "Plaque instability/vulnerability" appears to be the underlying pathophysiological basis for ACS and compromised flow, its consequence (20). It has been long known that at least two-thirds of lesions responsible for unstable syndromes arise from vessels with <50% stenosis, which would presumably have normal flow prior to plaque instability (20). Importantly, FFR has poor correlation with plaque characteristics. Hence a non-flow-limiting culprit lesion may be "anatomically significant," but "physiologically nonsignificant" (21). Intracoronary imaging has yielded useful information in this regard (21–26). Major predictors of future adverse coronary events in the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study were plaque burden, minimal luminal area (MLA) <4 mm^2, and thin-cap fibroatheroma in angiographically mild stenosis (22). The importance of refining risk prediction in ACS patients on the basis of the underlying pathobiological mechanisms has been further highlighted in recent studies. Bogale et al. (23) evaluated 70 ACS patients with optical coherence tomography (OCT), of whom 26 had intermediate lesions (40% to 70%). OCT of the angiographically intermediate lesions showed a larger MLA than the angiographically severe lesions (MLA 3.3 mm^2 vs. 1.6 mm^2) and less severe percentage of lumen area stenosis (54.2% vs. 70.9%). On the basis of the OCT appearance of unstable plaque characteristics (thrombus, ruptured plaque), 62% of these patients with intermediate lesions underwent PCI (23). In another report, Niccoli et al. (25) evaluated 139 ACS patients undergoing OCT evaluation and found that 59% patients had plaque rupture. Compared with patients with intact fibrous caps, patients with plaque rupture had a significantly higher MACE risk at the 32-month follow-up (39% vs. 14%), leading to the conclusion that ACS patients are a heterogeneous group and identification of plaque rupture on OCT could have clinical implications in affecting long-term prognosis (25).

CLINICAL IMPLICATIONS. Caution is warranted in using FFR for clinical decision making in ACS patients using FFR thresholds developed for SIHD patients given a 3-fold increase in the risk of subsequent MI and TVF compared with SIHD patients. This value takes on added significance when put in the larger context of several thousand patients undergoing FFR-based evaluation of ACS in the United States. We recently showed that there has been an exponential increase in the use of FFR, including an 18- to 23-fold increase in the inpatient use of FFR among ACS patients in the United States, since the publication of the pivotal FAME trial (27).

Hence, ACS patients should undergo a comprehensive evaluation at the time of the index procedure. If an intermediate lesion is considered the culprit in ACS, and FFR is performed and is in the borderline zone (0.75 to 0.85), OCT evaluation may be useful for determination of high-risk lesion characteristics, including thrombus/compromised MLA and plaque rupture. The optimal treatment for these patients is not known and requires further study. However, the conclusion that an FFR above 0.80 in an ACS patient shows a good prognosis is not borne out by our data (as opposed to SIHD patients). Close follow-up, strict adherence to guideline-guided medical therapy, including dual antiplatelet therapy, and low threshold for re-evaluation in the case of

FIGURE 3 Freedom From MI/TVF



(A) Entire cohort. **(B)** Matched cohort. ACS patients had significantly higher MI/TVF rates compared with SIHD patients ($p < 0.05$ for all comparisons). Abbreviations as in Figures 1 and 2.

persistent or recurring symptoms may help to curtail the risk of subsequent events. Further evaluation, using a well-powered randomized trial to evaluate the role of FFR, is warranted to refine risk stratification of this subset.

STUDY LIMITATIONS. The limitations of the present study relate primarily to its being single-center, observational, and retrospective. Using propensity matching, key differences between patients groups were, however, minimized showing results similar to those of the entire cohort. Subjects were predominantly men; thus, application to women must be inferred.

FFR was not used in every ACS patient and was largely undertaken in cases where there was no clear culprit lesion or the culprit lesion was thought to be an intermediate stenosis; this selection may have introduced a bias, although FFR was used as in usual clinical practice. We do not have a comparison of ACS patients who had FFR and underwent PCI with those who did not have a culprit lesion (and did not get an FFR evaluation) and were medically managed.

Only 35% of ACS patients (56% in the NSTEMI cohort) were discharged on dual antiplatelet therapy. This could have contributed to the higher event rate in ACS patients. Given the retrospective nature of the study, we can only hypothesize about the possible reasons for not using dual antiplatelet therapy, including bleeding risk, practice variations among treating physicians, underlying anemia, and other potential contraindications. It is also quite likely that the nonischemic FFR may have somewhat (falsely) reassured the treating physician about the "favorable" prognosis of nonischemic FFR in ACS patients, thus far assumed to parallel that of SIHD patients.

Although the VA is a large, integrated system and all efforts were made to capture patient outcomes, including outside records, it is possible that some events may not have been captured, especially those outside the VA system, leading to some degree of under-reporting.

CONCLUSIONS

Deferring PCI on the basis of nonischemic FFR in patients with an initial presentation of ACS is associated with significantly worse outcomes compared with stable CAD patients. Given the less favorable prognosis, FFR testing should be used with caution in ACS patients who may require additional evaluation, including IC imaging, for clinical decision making.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The diagnostic performance of FFR measurements in patients with ACS may be compromised by microvascular dysfunction.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Although in patients with stable ischemic heart disease deferred revascularization on the basis of nonischemic FFR measurements is generally associated with favorable long-term outcomes, those with ACS faced a 3-fold greater risk of subsequent MI or TVF.

TRANSLATIONAL OUTLOOK: Future studies should evaluate whether combining physiological (FFR) data with anatomic assessments (using OCT or intravascular ultrasound) can more accurately risk stratify patients than FFR alone.

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