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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