Outcomes of Coronary Stenoses Deferred Revascularization for Borderline Versus Nonborderline Fractional Flow Reserve Values

Jeremiah P. Depta, MD, MPHS, Jayendrakumar S. Patel, MD, Eric Novak, MS, Shriti K. Masrani, MD, David Raymer, MD, Gabrielle Facey, Yogesh Patel, MD, Alan Zajarias, MD, John M. Lasala, MD, PhD, Jasvindar Singh, MD, Richard G. Bach, MD, and Howard I. Kurz, MD*

Current evidence supports deferral of revascularization for lesions with fractional flow reserve (FFR) values >0.80. The natural history after deferral of revascularization of lesions with borderline FFR values is unknown. This study evaluated the outcomes of patients after deferred revascularization of coronary stenoses based on a borderline FFR value. We retrospectively studied 720 patients with 881 intermediate-severity coronary stenoses who underwent FFR assessment from October 2002 to July 2010 and were deferred revascularization. Patients were divided into gray zone (0.75 to 0.80), borderline (0.81 to 0.85), and nonborderline (>0.85) FFR groups. Any subsequent percutaneous coronary intervention or coronary artery bypass grafting of a deferred stenosis during follow-up was classified as a deferred lesion intervention (DLI). Patient and/or lesion characteristics and clinical outcomes were compared between the FFR groups using univariate and propensity score–adjusted inverse probability of weighting Cox proportional hazards analyses. During a mean follow-up of 4.5 ± 2.1 years, 157 deferred lesions (18%) underwent DLI by percutaneous coronary intervention (n = 117) or coronary artery bypass grafting (n = 40). No statistically significant differences were observed in clinical outcomes between the gray zone and borderline FFR groups. Lesions with a borderline FFR were associated with a significantly higher risk of DLI compared with lesions with nonborderline FFR values (hazard ratio 1.63, 95% confidence interval 1.14 to 2.33, p = 0.007). Lesions deferred revascularization because of a borderline FFR (0.81 to 0.85) were associated with a higher risk of DLI compared with lesions with a nonborderline FFR (>0.85). Further study is needed to determine the optimal management of coronary stenoses with a borderline FFR value. **(Am J Cardiol 2014;113:1788–1793)**

Fractional flow reserve (FFR) assesses the hemodynamic significance of coronary stenoses, and the threshold of functional significance has been an area of uncertainty.[1,2] Initial validation studies established an FFR value of <0.75 as a highly specific measure that correlated strongly with inducible ischemia.[1,3,4] The FFR cutoff was further extended to 0.80 based on evidence from the Fractional flow reserve versus Angiography for Multivessel Evaluation (FAME) trial.[5] Revascularization of physiological significant stenoses is associated with improved cardiovascular outcomes and symptoms.[6–8] Conversely, stenoses with FFR values >0.80 are not associated with inducible ischemia and previous studies suggest can safely be deferred revascularization as rates of cardiovascular death and myocardial infarction (MI) are low.[5–16] Rates of deferred lesion intervention (DLI), defined as future revascularization by way of percutaneous coronary intervention (PCI) or coronary artery bypass graft of a functionally nonsignificant lesion, have varied among studies.[5–16] Furthermore, some observational studies have suggested that worse clinical outcomes are associated with stenoses deferred revascularization with lower FFR values compared with higher FFR values.[9,10] Variability in the rates of clinical outcomes based on a lesion's FFR value questions the assumption that deferred stenoses are at equal risk for adverse outcomes. The aim of this study was to assess the rate of adverse clinical outcome between lesions with lower (borderline) versus higher (nonborderline) FFR values in a real-world cohort after deferred revascularization based on FFR assessment.

Methods

This study is a retrospective, single-center, observational study approved by the Institutional Review Board. All patients in the study provided informed written consent for the procedure(s). From October 2002 to July 2010, a total of 1,872 patients underwent FFR assessment. Of the 1,872 patients, 742 patients with 906 coronary stenoses were deferred revascularization based on FFR assessment. Of the 742 patients, we excluded 21 patients without any clinical follow-up after FFR assessment and who were unable to be contacted by telephone. We also excluded 1 patient who was deferred revascularization with an FFR value of 0.74. Thus, the final study population included 720 patients with

Division of Cardiology, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri. Manuscript received January 16, 2014; revised manuscript received and accepted March 6, 2014.

This study was supported by Department of Medicine, Division of Medical Education, Mentors in Medicine grant from Washington University School of Medicine, St. Louis, Missouri.

See page 1792 for disclosure information.

*Corresponding author: Tel: (314) 747-4451; fax: (314) 747-1417.

E-mail address: HURZ@dom.wustl.edu (H.I. Kurz).

0002-9149/14/$ - see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.amjcard.2014.03.004

Table 1
Baseline patient-level characteristics of the study population

Variable	FFR		
	0.75−0.80 (n = 61)	0.81−0.85 (n = 254)	>0.85 (n = 405)
Age (yrs)	65.8 ± 12.3	63.5 ± 11.5	65.0 ± 10.8
Men	36 (59)	145 (57)	227 (56)
Diabetes mellitus	30 (49)	95 (37)	145 (36)
History of hypertension	48 (79)	208 (82)	341 (84)
History of hyperlipidemia	47 (77)	207 (82)	329 (81)
Ever smoker	43 (70)*	138 (54)	194 (48)
Previous PCI	32 (52)	107 (42)	195 (48)
Previous coronary bypass	8 (13)	28 (11)	58 (14)
Peripheral arterial disease	10 (16)	25 (10)	46 (11)
Chronic kidney disease	14 (23)*	31 (12)	38 (9)
Heart failure	15 (25)	54 (21)	89 (22)
Stress testing 3 months before FFR	27 (44)	125 (49)	205 (51)
Creatinine level (mg/dl)	1.4 ± 1.5	1.2 ± 1.2	1.1 ± 1.2
Diagnosis at FFR assessment			
AMI	11 (18)	33 (13)	40 (10)
STEMI	1 (2)	2 (1)	4 (1)
NSTEMI	10 (16)	31 (12)	36 (9)
Unstable angina pectoris	26 (43)	98 (39)	156 (39)
Stable angina pectoris	15 (25)	86 (34)	160 (40)
Asymptomatic/atypical chest pain	9 (15)	37 (15)	49 (12)

All remaining comparisons between the FFR 0.75 to 0.80 and 0.81 to 0.85 groups and the FFR 0.81 to 0.85 and >0.85 groups were not statistically significant. Values are shown as absolute number (percentage) or mean ± SD.

NSTEMI = non−ST elevation myocardial infarction; STEMI = ST elevation myocardial infarction.

* $p < 0.05$ compared with FFR 0.81 to 0.85.

881 coronary stenoses deferred revascularization based on FFR.

Patients received aspirin 325 mg and intracoronary (IC) nitroglycerin before FFR assessment. FFR was measured at maximal hyperemia after administration of IC (n = 874 coronary lesions) or intravenous (n = 7 coronary lesions) adenosine. For FFR measurement, an IC adenosine dose was administered to induce maximal hyperemia by successively increasing the IC adenosine dose until no further decrement in the FFR value was observed or to the maximal tolerated dose. During intravenous administration, adenosine (140 to180 μg/kg/min) was infused for approximately 2 minutes to achieve a steady-state adenosine concentration before FFR measurement.

Follow-up was assessed by telephone interview and review of the medical record for every patient included in the study. Patients were followed up from the date of index FFR assessment through March 12, 2013. All follow-up coronary angiograms were reviewed independently by a minimum of 2 investigators. If a patient had follow-up outside our institution, medical records including angiograms were obtained for review. The primary outcome of the study was a composite of cardiovascular death, MI, or DLI. DLI was defined as any PCI performed within 5 mm proximal or distal to or any coronary artery bypass graft placed distal to a lesion deferred revascularization based on the index FFR assessment. Cardiovascular death and MI were defined according to the guidelines set forth by the Academic Research Consortium guidelines.[17]

Coronary stenoses were divided into groups based on FFR values: the gray zone group had FFR values 0.75 to 0.80 (n = 61 patients, 65 lesions); the borderline group had FFR values 0.81 to 0.85 (n = 254 patients, 275 lesions); and the nonborderline group had FFR values >0.85 (n = 405 patients, 541 lesions). Differences between the FFR groups among categorical variables were analyzed by Fisher's exact tests and continuous variables were analyzed by Student *t* tests. Because of 135 patients having multiple coronary stenoses, patient-level characteristics and outcomes were analyzed for each patient according to the FFR group designated by the patient's lowest FFR value.

Outcomes were evaluated both before and after propensity score inverse probability of weighting (IPW). Two separate propensity scores were created to compare the FFR 0.75 to 0.80 with 0.81 to 0.85 groups and the FFR 0.81 to 0.85 with >0.85 groups. The following variables were used to calculate propensity scores: age, male gender, diabetes mellitus, hypertension, hyperlipidemia, current or former smoker, previous coronary artery disease, previous PCI, previous coronary artery bypass graft surgery, peripheral arterial disease, chronic kidney disease, congestive heart failure, acute myocardial infarction (AMI), unstable angina, stable angina, asymptomatic or atypical chest pain, multivessel coronary artery disease (≥2 significant lesions with a percent stenosis ≥50% at the time of FFR assessment), vessel location, bifurcation lesion, ostial lesion, previous PCI of the lesion assessed by FFR, PCI of another stenosis (at the time of FFR assessment), stress testing performed (within the 3 months before FFR assessment), myocardial jeopardy index score for the lesion,[18] creatinine level (mg/dl), aspirin, clopidogrel, warfarin, β blocker, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, statin, calcium channel antagonist, nitrates, mean number of optimal medical therapy (OMT) medications[19] at