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Noninvasive FFR Derived From Coronary CT Angiography

Management and Outcomes in the PROMISE Trial

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ABSTRACT

OBJECTIVES The purpose of this study was to determine whether noninvasive fractional flow reserve derived from computed tomography (FFR_{CT}) predicts coronary revascularization and outcomes and whether its addition improves efficiency of referral to invasive coronary angiography (ICA) after coronary computed tomography angiography (CTA).

BACKGROUND FFR_{CT} may improve the efficiency of an anatomic CTA strategy for stable chest pain.

METHODS This observational cohort study included patients with stable chest pain in the PROMISE (PROspective Multicenter Imaging Study for Evaluation of Chest Pain) trial referred to ICA within 90 days after CTA. FFR_{CT} was measured at a blinded core laboratory, and FFR_{CT} results were unavailable to caregivers. We determined the agreement of FFR_{CT} (positive if ≤0.80) with stenosis on CTA and ICA (positive if ≥50% left main or ≥70% other coronary artery), and predictive value for a composite of coronary revascularization or major adverse cardiac events (death, myocardial infarction, or unstable angina). We retrospectively assessed whether adding FFR_{CT} ≤0.80 as a gatekeeper could improve efficiency of referral to ICA, defined as decreased rate of ICA without ≥50% stenosis and increased ICA leading to revascularization.

RESULTS FFR_{CT} was calculated in 67% (181 of 271) of eligible patients (mean age 62 years; 36% women). FFR_{CT} was discordant with stenosis in 31% (57 of 181) for CTA and 29% (52 of 181) for ICA. Most patients undergoing coronary revascularization had an FFR_{CT} of ≤0.80 (91%; 80 of 88). An FFR_{CT} of ≤0.80 was a significantly better predictor for revascularization or major adverse cardiac events than severe CTA stenosis (HR: 4.3 [95% confidence interval [CI]: 2.4 to 8.9] vs. 2.9 [95% CI: 1.8 to 5.1]; $p = 0.033$). Reserving ICA for patients with an FFR_{CT} of ≤0.80 could decrease ICA without ≥50% stenosis by 44%, and increase the proportion of ICA leading to revascularization by 24%.

CONCLUSIONS In this hypothesis-generating study of patients with stable chest pain referred to ICA from CTA, an FFR_{CT} of ≤0.80 was a better predictor of revascularization or major adverse cardiac events than severe stenosis on CTA. Adding FFR_{CT} may improve efficiency of referral to ICA from CTA alone. (J Am Coll Cardiol Img 2017;10:1350–8)

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More than 4 million Americans with stable chest pain undergo noninvasive diagnostic testing for suspected coronary artery disease (CAD) annually (1). Most have functional testing, which may lead to referral to invasive coronary angiography (ICA) and coronary revascularization. Coronary computed tomography angiography (CTA) has emerged as an alternative whose strength is the accurate exclusion of significant coronary artery stenosis (negative predictive value: 97% to 99%). However, CTA has limited positive predictive value (64% to 86%), and so management of patients with stenosis on CTA is challenging (2,3). Furthermore, anatomic stenosis on CTA and ICA is often discordant with measures of hemodynamic significance such as invasive fractional flow reserve (FFR) (4,5). The importance of the latter to improve clinical outcomes has been demonstrated in randomized comparisons of invasive FFR-guided versus stenosis-guided coronary revascularization (6,7).

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Emerging computational fluid dynamics modeling techniques allow calculation of noninvasive FFR derived from computed tomography (FFR_{CT}) (8). FFR_{CT} correlates well (r = 0.82) with invasive FFR, with a per-patient sensitivity of 86% and specificity of 79% for an invasive FFR of ≤0.80 indicating ischemia (9). PROMISE (PROspective Multicenter Imaging Study for Evaluation of Chest Pain), a pragmatic comparative effectiveness trial of coronary CTA in patients with stable chest pain, provides an opportunity to test the potential impact of adding FFR_{CT} to CTA as a gatekeeper to ICA against observed anatomic CTA-guided care. This PROMISE FFR_{CT} substudy assessed patients referred to ICA from CTA to determine the association of a positive FFR_{CT} of ≤0.80 with coronary revascularization or major adverse cardiovascular events (MACE), to assess the agreement of FFR_{CT} with significant stenosis on CTA and ICA, and to predict whether the addition of FFR_{CT} to the computed tomography (CT)-guided practice patterns observed in PROMISE could improve efficiency of an anatomic CTA strategy.

METHODS

STUDY DESIGN. This retrospective, observational, cohort study was nested in PROMISE, a pragmatic North American multicenter comparative effectiveness trial that randomized patients with stable chest pain and without known CAD to anatomic coronary CTA versus functional testing between July 2010 and September 2013. The PROMISE trial has been described in detail elsewhere (10). For this study, we included the subgroup randomized to CTA who subsequently underwent ICA as part of clinical care in the 90 days after CTA. Demographics and traditional cardiovascular risk factors were documented at enrollment. Institutional review board approval was obtained with waiver of informed consent.

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CTA = computed tomography angiography

FFR = fractional flow reserve

FFR_{CT} = noninvasive fractional flow reserve derived from computed tomography

ICA = invasive coronary angiography

MACE = major adverse cardiovascular event(s)

PCI = percutaneous coronary intervention

COMPUTED TOMOGRAPHY ANGIOGRAPHY. Electrocardiogram-gated CTA had been performed on CT scanners with ≥64 detector rows (10). "Advanced" scanners were defined as each manufacturer's most advanced model available during the trial (General Electric HD 750 [General Electric, Fairfield, Connecticut], Philips Brilliance iCT [Philips, Amsterdam, the Netherlands], Siemens SOMATOM Definition Flash [Siemens, Munich, Germany], Toshiba Aquilion One [Toshiba, Tokyo, Japan]). CTA was interpreted for stenosis by local physicians who made all clinical decisions. Severe stenosis, defined as an anatomic stenosis of ≥50% in the left main or ≥70% in other major epicardial coronary arteries, constituted a per-patient "positive" CTA result.

INVASIVE CORONARY ANGIOGRAPHY. Subjects were referred to ICA by local physicians based on the results of CTA and other clinical characteristics. ICA had been performed according to standard practice (11) and interpreted for stenosis by local physicians who made all clinical decisions, including whether to pursue revascularization. As with CTA, a severe stenosis constituted a per-patient "positive" ICA result.

CORONARY REVASCULARIZATION AND MACE. The primary endpoint was a composite of revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting) or major adverse cardiovascular events (MACE: death, nonfatal myocardial infarction, or hospitalization for unstable angina). All subjects had ≥12 months of follow-up. A blinded independent clinical events committee adjudicated all events.

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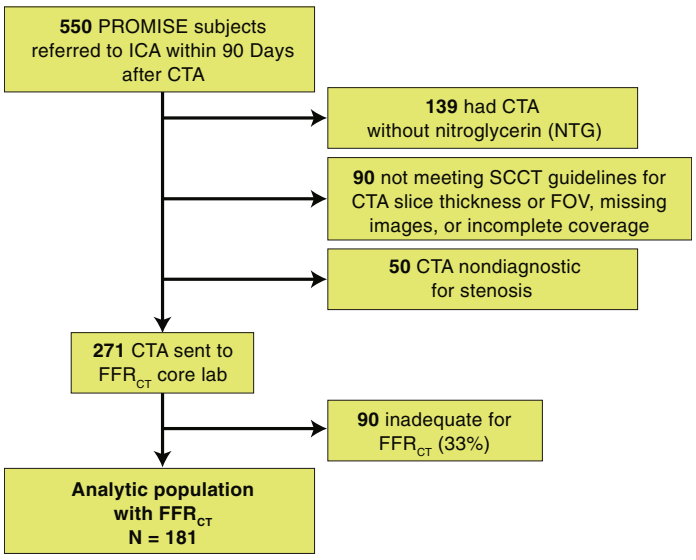
FIGURE 1 Flow Diagram



The analytic population included 181 subjects who had computed tomography angiography (CTA), invasive coronary angiography (ICA), and noninvasive fractional flow reserve derived from computed tomography (FFR_{CT}). FOV = field of view; PROMISE = PROspective Multicenter Imaging Study for Evaluation of Chest Pain; SCCT = Society of Cardiovascular Computed Tomography.

ELIGIBILITY FOR FFR_{CT}. Prospectively established exclusion criteria included CTA performed without nitroglycerin, image reconstructions not compliant with Society of Cardiovascular Computed Tomography guidelines for pixel resolution (field of view >250 mm or slice thickness ≥1 mm) (12), missing images, incomplete coverage of the heart or coronary arteries, or image quality graded nondiagnostic for stenosis by a single cardiac radiologist (MTL) (Figure 1). CTA performed without nitroglycerin was excluded, based on data suggesting that FFR_{CT} has better accuracy against invasive FFR when systemic nitrates are given (13).

COMPUTATION OF FFR_{CT} FROM CTA. The FFR_{CT} implementation used in this study is computationally intensive and currently only available at a single core laboratory (HeartFlow, Redwood City, California) as a "send off" test (8). CTA datasets meeting eligibility criteria were sent to the FFR_{CT} core laboratory. As previously validated in the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps), the FFR_{CT} core laboratory applied a second set of quantitative criteria to determine whether there was adequate image quality for FFR_{CT} analysis based on whether the coronary artery lumen and myocardial boundaries could be defined clearly (9).

FFR_{CT} was calculated blinded to all aspects of clinical care, including CTA interpretation and clinical outcomes. The results of FFR_{CT} were not available to care providers and did not affect clinical management. Techniques for calculation of FFR_{CT} have been detailed (8) and accuracy against invasive FFR validated (9) elsewhere. Briefly, 3-dimensional models of the coronary arterial tree and myocardium were segmented from standard CTA images used for diagnosis in the trial. Computational fluid dynamics techniques modeled coronary arterial flow under simulated maximal hyperemia. FFR_{CT} was calculated as the ratio of mean simulated pressure to aortic pressure at all coronary artery locations measuring ≥1.8 mm. Occluded vessels were assigned a value of 0.5. The lowest per-patient FFR_{CT} value is reported; an FFR_{CT} of ≤0.80 constituted a per-patient "positive" result.

STATISTICAL ANALYSIS. Comparisons of baseline characteristics between the analytic group who had FFR_{CT} versus the excluded group who did not and between those with an FFR_{CT} of ≤0.80 versus an FFR_{CT} of >0.80 were performed with the Wilcoxon 2-sample test/Kruskal-Wallis analysis of variance for continuous variables and chi-square/Fisher exact test for categorical variables. The primary study objective was to determine whether the addition of a positive FFR_{CT} of ≤0.80 was more strongly associated with the composite outcome of coronary revascularization or MACE than an anatomic-only finding of severe stenosis on CTA. Cox proportional hazards models were used to assess the relationship of a positive FFR_{CT} or positive CTA compared with a negative test result for the time to the first clinical event (or censoring) for the composite endpoint (14). Relative risks were expressed as hazard ratios with 95% confidence intervals (CIs) derived from Cox models; hazard ratios for a positive FFR_{CT} versus positive CTA were compared with the chi-square test.

To project whether the addition of FFR_{CT} to the observed anatomic CTA strategy could improve the efficiency of referral to ICA from CTA, we prospectively defined an FFR_{CT}-guided decision rule that reserved ICA for patients with an FFR_{CT} of ≤0.80. The projected numbers of patients having ICA, ICA without ≥50% stenosis, and ICA leading to revascularization were described in comparison with what was observed in the trial. To determine the agreement of FFR_{CT} results with CTA and ICA findings of coronary artery stenosis, angiographic lesion severity per category and respective FFR_{CT} values were plotted in box-and-whisker plots. The proportion of subjects having an FFR_{CT} of ≤0.80 across stenosis

strata on ICA and CTA were compared using the chi-square test. Statistical analysis was performed using SAS version 9.4 and JMP Pro version 12 from the SAS Institute (Cary, North Carolina) with a 2-sided level of significance of 0.05.

RESULTS

STUDY POPULATION. Of the 609 patients who were randomized to the CTA arm of PROMISE and had ICA, 59 (9.7%) either did not have CT as their first diagnostic test, had ICA >90 days after CT, or had a noncontrast CT for calcium score only (no CTA). Of the remaining 550 patients, we excluded 139 (25%) because they did not receive nitroglycerin during CTA; 90 (16%) due to missing images, incomplete coverage of the heart, or CTA image reconstruction with field of view >250 mm or slice thickness ≥1 mm; and 50 (9%) whose CT images were nondiagnostic for the assessment of stenosis (Figure 1). Of the 271 patients (49%) who met prospectively defined inclusion criteria, 90 (33%) were inadequate for FFR_{CT} analysis. Thus, the analytic study population consisted of 181 patients who had complete information on CTA, ICA, and FFR_{CT}.

The average age was 62 years, 36% (66 of 181) were women, and 76% were at intermediate risk for obstructive CAD by the combined Diamond and Forrester and Coronary Artery Surgery Study risk score (Table 1) (15). Compared with those who did not have FFR_{CT} (n = 369), the analytic population who had FFR_{CT} was less likely to be obese (34% vs. 53%; p < 0.001), consistent with the adverse effect of obesity on CT image quality. However, both groups had a similar burden of CAD, incident revascularization, and MACE (Online Table 1). The 181 subjects were enrolled at 69 North American sites (mean 2.6 per site). Coronary CTA datasets were acquired from all 4 major CT vendors (44% [80 of 181] General Electric, 11% [20 of 181] Phillips, 36% [66 of 181] Siemens, and 8% [15 of 181] Toshiba). Advanced CT scanners were used in 17% (31 of 181) of the CTAs evaluated with FFR_{CT} compared with 12% (43 of 369; p for comparison = 0.08) of the CTAs not evaluated with FFR_{CT}.

CTA AND ICA STENOSIS. Most patients had severe (≥70% or ≥50% left main) stenosis on coronary CTA (66%, 120 of 181) and ICA (54%, 97 of 181) (Table 2).

CORONARY REVASCULARIZATION AND MACE. During median follow-up of 29 months (interquartile range: 18.9 to 36.3 months) the primary outcome of a composite of coronary revascularization or MACE occurred in 51% (93 of 181) (Table 2). Overall, 49% (88 of 181) had coronary revascularization, including 75 PCI and 13 coronary artery bypass grafting procedures. MACE occurred in 9% (16 of 181), including 1 death, 2 nonfatal MIs, and 13 hospitalizations for unstable angina.

TABLE 1 Characteristics of PROMISE FFR_{CT} Participants Referred to ICA After CTA, According to FFR_{CT} ≤0.80 or >0.80

	FFR_{CT} ≤0.80 (n = 131)	FFR_{CT} >0.80 (n = 50)	p Value
Age, yrs	61.6 ± 8.1	62.5 ± 9.8	0.79
Female	42 (32)	24 (48)	0.046
Racial/ethnic minority	11 (8.5)	7 (14)	0.28
Cardiac risk factors			
BMI ≥30 kg/m^2	42 (31)	20 (40)	0.27
Hypertension	83 (63)	31 (62)	0.87
Diabetes	25 (19)	7 (14)	0.42
Dyslipidemia	91 (70)	31 (62)	0.34
Family history of premature CAD	58 (45)	26 (52)	0.17
Peripheral arterial disease	2 (1.5)	1 (2.0)	1.0
CAD equivalent	28 (21)	13 (26)	0.51
Metabolic syndrome	39 (30)	13 (26)	0.62
Smoking history	77 (59)	24 (78)	0.17
Combined Diamond and Forrester and CASS			0.066
Low (<25%)	7 (5.3)	6 (12.0)	
Intermediate (25% to 75%)	98 (75)	40 (80)	
High (>75%)	26 (20)	4 (8.0)	
CTA radiation dose, mSv	9.8 ± 6.4	9.8 ± 6.1	0.99

Values are mean ± SD or n (%).

BMI = body mass index; CAD = coronary artery disease; CASS = Coronary Artery Surgery Study; CTA = coronary computed tomography angiography; FFR_{CT} = noninvasive fractional flow reserve derived from CTA; ICA = invasive coronary angiography.

FFR_{CT} MEASUREMENTS. With per-patient FFR_{CT} defined as the lowest FFR_{CT} value for that patient, mean per-patient FFR_{CT} was 0.71 ± 0.13, with 72% (131 of 181) of patients having an FFR_{CT} of ≤0.80. Patients with an FFR_{CT} of ≤0.80 were less likely to be women (32% vs. 48%; p = 0.046), but had otherwise similar demographics and risk factors compared with those with an FFR_{CT} of >0.80 (Table 1). Two representative cases are presented in Figure 2.

AGREEMENT OF FFR_{CT} WITH CTA AND ICA. Compared with the degree of stenosis on CTA (worst per patient), mean FFR_{CT} (lowest per patient) decreased from 0.81 ± 0.09 for mild stenosis (<50%) to 0.77 ± 0.10 for moderate stenosis (50% to 69%) to 0.67 ± 0.13 for severe stenosis (p < 0.001). Similar results were seen for ICA (0.80 ± 0.11, 0.75 ± 0.08, and 0.64 ± 0.12, respectively; p < 0.001) (Figure 3). There was agreement between FFR_{CT} and CTA in 69% of patients (124 of 181), among them 54% (97 of 181) with a positive FFR_{CT} of ≤0.80 who had severe CTA stenosis and 15% (27 of 181) with a negative FFR_{CT} who had less than severe CTA stenosis (Table 2). A similar agreement rate of 71% (129 of 181) was seen between an FFR_{CT}

TABLE 2 Stenosis, Revascularization, and MACE Stratified by FFR_{CT} ≤0.80

	FFR_{CT} ≤0.80 (n = 131)	FFR_{CT} >0.80 (n = 50)	p Value
CTA stenosis			0.002
Mild (<50%)	8 (6)	9 (18)	
Moderate (50% to 69%)	26 (20)	18 (36)	
Severe (≥70% or ≥50% left main)	97 (74)	23 (46)	
Left main	11 (8)	3 (6)	0.76
One vessel	65 (50)	17 (34)	0.004
Two vessel	24 (18)	4 (8)	
Three vessel	8 (6)	2 (4)	
ICA stenosis			<0.001
Mild (<50%)	20 (15)	29 (58)	
Moderate (50% to 69%)	23 (18)	12 (24)	
Severe (≥70% or ≥50% left main)	88 (67)	9 (18)	
Left main	9 (7)	0 (0)	0.065
Single vessel	57 (44)	8 (16)	<0.001
Two vessel	17 (13)	1 (2)	
Three vessel	14 (11)	0 (0)	
Revascularization	80 (61)	8 (16)	<0.001
PCI	67 (51)	8 (16)	
CABG	13 (10)	0 (0)	
MACE	14 (11)	2*(4)	0.24
Death	1 (0.8)	0 (0)	
Nonfatal myocardial infarction	1 (0.8)	1 (2)	
Hospitalization for unstable angina	12 (9)	1 (2)	
Composite of revascularization or MACE	83 (63)	10 (20)	<0.001

Values are n (%). *Both patients with an event and FFR_{CT} >0.80 did not have severe stenosis on ICA and were not revascularized.

CABG = coronary artery bypass grafting; MACE = major adverse cardiovascular event(s); PCI = percutaneous coronary intervention; other abbreviations as in Table 1.

of ≤0.80 and severe ICA stenosis. The disagreement rates with FFR_{CT} were 31% (57 of 181) for CTA and 29% (52 of 181) for ICA.

ASSOCIATION OF FFR_{CT} WITH CORONARY REVASCULARIZATION AND MACE. Patients with an FFR_{CT} of ≤0.80 were significantly more likely to have coronary revascularization (61% [80 of 131] vs. 16% [8 of 50]; hazard ratio (HR): 5.13 [95% confidence interval (CI): 2.63 to 11.53]; p < 0.001) (Table 2). There was a trend toward more patients with an FFR_{CT} of ≤0.80 experiencing a MACE (11% [14 of 131] vs. 4% [2 of 50]; HR: 2.67 [95% CI: 0.75 to 17.02]; p = 0.14). There were 2 MACE events (1 nonfatal myocardial infarction and 1 hospitalization for unstable angina) with an FFR_{CT} of >0.80, both in patients with <70% stenosis on ICA who did not undergo coronary revascularization.

An FFR_{CT} of ≤0.80 was significantly associated with the composite endpoint of MACE or revascularization compared with those with an FFR_{CT} of >0.80 (63% [83 of 131] vs. 20% [10 of 50]; HR: 4.31 [95% CI: 2.35 to 8.88]; p < 0.001). Severe stenosis on CTA was also associated significantly with the composite endpoint compared with lesser stenosis (63% [76 of 120] vs. 28% [17 of 61]; HR: 2.90 [95% CI: 1.76 to 5.10]; p < 0.001). However, an FFR_{CT} of ≤0.80 was significantly better than severe CTA stenosis at predicting the composite endpoint (HR: 4.31 for FFR_{CT} vs. HR: 2.90 for CTA stenosis; p = 0.033). This is notable because the FFR_{CT} results were not available to physicians during the trial while the CTA results guided management.

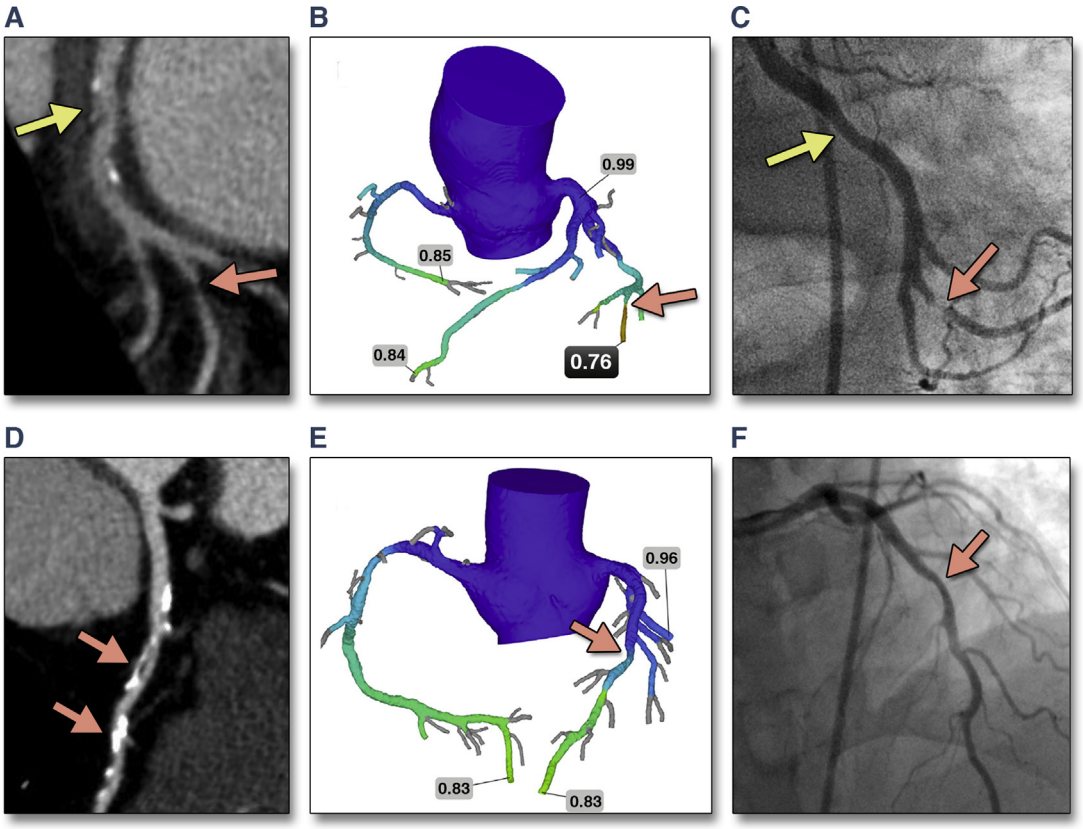
POTENTIAL IMPROVEMENT IN EFFICIENCY OF REFERRAL TO ICA BY ADDING FFR_{CT}. Reserving ICA for patients with a positive FFR_{CT} (≤0.80) could reduce the number of ICA after CTA by 28% (50 of 181), decrease the rate of ICA without ≥50% stenosis by 44% (from 27% [49 of 181] to 15% [20 of 131]), and increase the rate of ICA leading to revascularization by 24% (from 49% [88 of 181] to 61% [80 of 131]). In contrast, this rule would result in 9% fewer (8 of 88) coronary revascularizations (8 PCI, 0 coronary artery bypass grafting); the impact of which cannot be estimated in this study. On ICA, 6 of these patients had PCI of severe single-vessel stenosis (none involving the left main or proximal left anterior descending coronary arteries), and 2 had PCI of moderate (50% to 69%) proximal left anterior descending stenoses. Notably, none of these patients experienced a MACE.

In a sensitivity analysis, we recalculated these figures including the 90 patients whose images were sent to the FFR_{CT} core laboratory but were inadequate for FFR_{CT} analysis. Assuming a worst case that all 90 proceeded to ICA, we estimate a lesser reduction in the rate of ICA by 18% (50 of 271), decrease in the rate of ICA without ≥50% stenosis by 20% (from 31% [84 of 271] to 25% [55 of 221]), and increase in the rate of ICA leading to revascularization by 15% (from 49% [134 of 271] to 57% [126 of 221]).

DISCUSSION

Our study demonstrates the potential impact of adding noninvasively calculated FFR_{CT} to an anatomic CTA strategy for evaluation of stable chest pain. In patients referred to ICA after CTA, we demonstrate that retrospectively obtained FFR_{CT} has a better predictive value for the composite outcome of coronary revascularization or MACE than severe stenosis (≥70%) on CTA. Furthermore, our data suggest that adding information on FFR_{CT} to coronary CTA may improve the efficiency of referral to ICA by lowering the number of invasive angiograms, decreasing the proportion of ICA without ≥50% stenosis, and increasing the rate of subsequent coronary revascularization.

FIGURE 2 **Representative CTA, FFR_{CT}, and ICA**

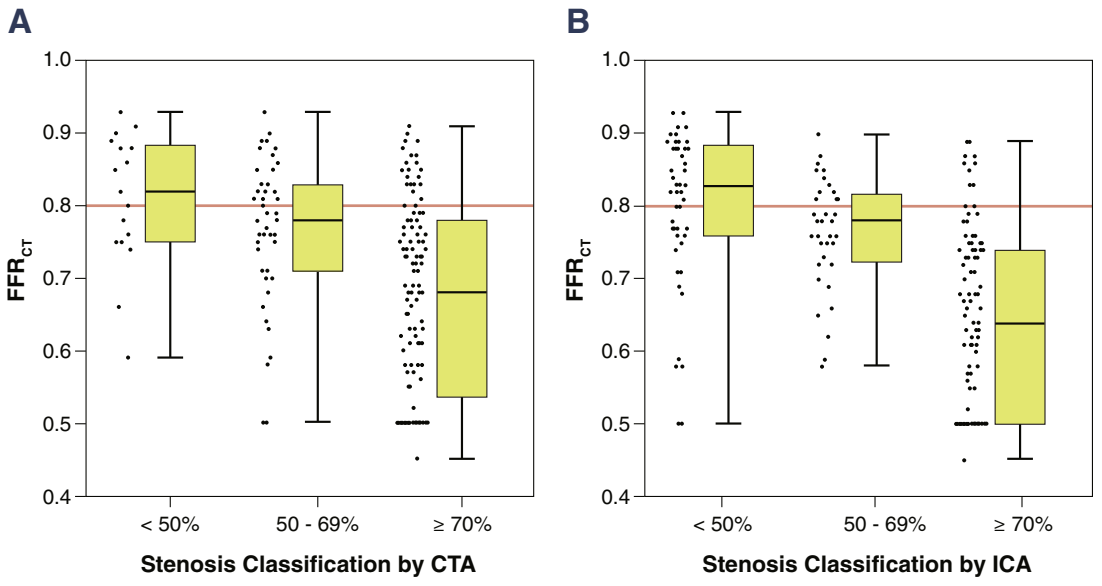


The first patient **(A to C)** was referred to ICA based on **(A)** CTA moderate stenosis in the left circumflex **(yellow arrow)**. Severe stenosis in an obtuse marginal **(pink arrow)** was missed by the CT reader, but detected by **(B)** FFR_{CT} of 0.76 and confirmed on **(C)** ICA showing severe stenosis, with subsequent PCI. Circumflex stenosis **(yellow arrow)** was mild and not revascularized. The second patient **(D to F)** was referred to ICA for **(D)** severe mid left anterior descending stenoses on CTA **(pink arrows)**. **(E)** FFR_{CT} of 0.83 suggests no hemodynamically significant stenosis; **(F)** ICA demonstrated mild stenosis that was not revascularized. Abbreviations as in Figure 1.

We demonstrate that noninvasive FFR_{CT} values decrease with increasing luminal stenosis, but also that there is substantial disagreement between anatomic significance (severe stenosis) and hemodynamic significance (FFR_{CT} ≤0.80) for both CTA (31%) and ICA (29%), similar to the 25% discrepancy rate between invasive FFR and ICA found in the FAME trial (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) (4). In addition, patients with an FFR_{CT} of ≤0.80 were substantially more likely to suffer revascularization or MACE compared with those with an FFR_{CT} of >0.80 (HR: 4.31; $p < 0.001$). Although the prognostic value of FFR has been shown in invasive studies such as DEFER (Fractional Flow Reserve to Determine the Appropriateness of Angioplasty in Moderate Coronary Stenosis: A Randomized Trial) (16) and FAME (7), it has not been previously reported for noninvasive FFR_{CT} in an observational setting where FFR_{CT} did not alter clinical management. Moreover, the association of FFR_{CT} with revascularization and MACE was significantly stronger than for severe stenosis on CTA (HR 4.31 vs. 2.90; $p = 0.033$), a notable result because stenosis guided the clinical decision for coronary revascularization, whereas FFR_{CT} was not available to caregivers in the trial.

Multicenter trials of CTA in patients with acute (17,18) and stable chest pain (10) suggest that CTA leads to greater referral to ICA compared with usual care. In PROMISE, patients in the CTA arm had 51% more ICA than those in the functional arm (12.2% vs. 8.1%). Our results suggest that adding FFR_{CT} to anatomic CTA, with a positive FFR_{CT} of ≤0.80 as a criterion for referral to ICA, may address this by reducing referral to ICA from CTA by up to 28%. Extrapolation to all 550 patients in PROMISE who

FIGURE 3 Box and Whisker Plots of Per-Patient FFR_{CT} by Categories of CTA and ICA Stenosis



The **horizontal line** corresponds to the FFR_{CT} threshold for a positive test ($FFR_{CT} \leq 0.80$). FFR_{CT} decreased with increasing degrees of stenosis on CTA and ICA (both $p < 0.001$). Abbreviations as in Figure 1.

underwent ICA as part of the anatomic CTA strategy should be interpreted with caution, but could decrease the rate of referral to ICA in the anatomic arm from 12.2% to 9.5%, which is more comparable to the ICA rate of 8.1% observed in the functional testing arm (10). Furthermore, adding FFR_{CT} to CTA could increase the proportion of ICA leading to coronary revascularization from 49% to 61%. Such projections may be justified as the burden of CAD and coronary revascularization were similar between the 181 patients in whom we measured FFR_{CT} and the 369 patients who were also referred for ICA but did not have FFR_{CT} (Online Table 1).

Our study included PROMISE patients with stable chest pain referred to ICA after CTA. Thus, FFR_{CT} was not assessed in isolation, but in the context of CTA findings that prompted referral to ICA. We did not include patients whose CTA results did not prompt referral to ICA, and so our results do not address use of FFR_{CT} in this broader group. Our findings suggesting that the addition of FFR_{CT} could be incremental to anatomic CTA as a gatekeeper to ICA within a North American trial support and expand on a recent European cohort study (PLATFORM [Prospective LongitudinAl Trial of FFR_{CT} Outcome and Resource IMpacts]) of patients with planned ICA, which reported that combined CTA/FFR_{CT} led to a very low (12%) rate of ICA without ≥50% stenosis and a high rate of ICA leading to revascularization (72%), similar to the rates we found by adding FFR_{CT} to CTA in PROMISE (15% and 61%, respectively) (19). The similarity of these numbers is remarkable; all of our patients were referred to ICA from CTA, whereas this was not the case in PLATFORM.

In our study, 91% of coronary revascularizations (80 of 88) had a positive FFR_{CT}. This mirrors FAME, which found that 90% of patients considered for stenosis-guided revascularization had a positive invasive FFR (7). The sound agreement of positive FFR_{CT} with observed clinical decisions to pursue revascularization in PROMISE is notable, because FFR_{CT} was measured independent of clinical care and not available to caregivers. This finding is also important because, in PROMISE, nearly all revascularization decisions were made without the guidance of invasive FFR, which reflected practice in the community at that time (20). Although there was no difference in outcomes between CTA and functional arms of PROMISE, our data provide some reassurance that most coronary revascularizations were likely performed in hemodynamically significant lesions.

STUDY LIMITATIONS. Limitations of the data and FFR_{CT} technique should be considered. One-half of patients referred to ICA from CTA were excluded by prespecified entry criteria, mostly because they did

not follow Society of Cardiovascular Computed Tomography guidelines for standard CTA, including administration of nitroglycerin and high image pixel resolution (12). Guidelines recommend nitroglycerin and high-resolution images for standard coronary CTA because they aid the diagnosis of stenosis; they are also necessary for FFR_{CT} because they provide a better approximation of the vessel anatomy under maximal hyperemia (13,21). Presumably, more sites would have followed these now standard practices had they known that FFR_{CT} would be performed. Furthermore, CT technology has advanced rapidly since PROMISE, and the data likely do not represent the current state of the art. In PROMISE, most CTA was performed on standard 64-slice CT scanners, with only 17% using advanced CT scanners that have since been succeeded by a new generation of CT equipment.

FFR_{CT} has different image quality requirements than traditional assessment for stenosis. When confronted with motion artifact, physicians interpreting CTA for stenosis often integrate multiple cardiac phases to piece together a complete coronary artery. In contrast, the current implementation of FFR_{CT} requires that the entire coronary tree and myocardium be evaluable on a single cardiac phase. One-third (33%) of the CTAs sent to the FFR_{CT} core laboratory were inadequate for FFR_{CT} analysis; this is higher than reported in dedicated FFR_{CT} trials such as NXT (13% inadequate, 10 European and Asian sites) and PLATFORM (12% inadequate, 11 European sites) (9,19). This may be explained by the fact that NXT and PLATFORM were dedicated FFR_{CT} studies, with sites receiving specific FFR_{CT} training and feedback, including standard administration of nitroglycerin and appropriate image reconstruction. In contrast, PROMISE sites did not know that FFR_{CT} would be performed and did not receive specific FFR_{CT} training or feedback.

In this observational study, the results of FFR_{CT} were not available to caregivers and did not affect clinical decision making. We can only project how physicians would have used the FFR_{CT} results had they been available. Six patients had PCI with an FFR_{CT} of >0.80. Previous trials found that FFR_{CT} has good accuracy compared with invasive FFR and that revascularization can be safely deferred with an FFR_{CT} of >0.80, but due to the observational design we cannot know for certain what would have happened in these 6 patients. A final limitation is the small sample size and low number of outcomes in keeping with the low event rate in the PROMISE trial. Hospitalization for unstable angina was the most common adverse event and had the potential for bias, because it may have been triggered by the knowledge that CAD was present on CTA.

CONCLUSIONS

In this hypothesis-generating study of patients with stable chest pain referred to ICA after CTA, we found that adding FFR_{CT} may improve the efficiency of referral to ICA, addressing a major concern of an anatomic CTA strategy. FFR_{CT} has incremental value over anatomic CTA in predicting revascularization or major adverse cardiovascular events.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: FFR_{CT} can assess the functional importance of coronary lesions.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Guidelines recommend determining the functional significance of coronary lesions before revascularization.

TRANSLATIONAL OUTLOOK: These PROMISE FFR_{CT} substudy data suggest that FFR_{CT} is associated with observed revascularization and MACE. The addition of FFR_{CT} to CTA has the potential to improve efficiency of management of patients with stable chest pain who are referred to ICA after CTA.

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KEY WORDS computational fluid dynamics, coronary angiography, coronary artery disease, coronary computed tomography angiography, fractional flow reserve

APPENDIX For a supplemental table, please see the online version of this article.