Radiology

ORIGINAL RESEARCH • CARDIAC IMAGING

Prognostic Value and Risk Continuum of Noninvasive Fractional Flow Reserve Derived from Coronary CT Angiography

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Conflicts of interest are listed at the end of this article.

See also the editorial by Dennie and Rubens in this issue.

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Background: Coronary CT angiography with noninvasive fractional flow reserve (FFR) predicts lesion-specific ischemia when compared with invasive FFR. The longer term prognostic value of CT-derived FFR (FFR_{CT}) is unknown.

Purpose: To determine the prognostic value of FFR_{CT} when compared with coronary CT angiography and describe the relationship of the numeric value of FFR_{CT} with outcomes.

Materials and Methods: This prospective subanalysis of the NXT study (Clinicaltrials.gov: NCT01757678) evaluated participants suspected of having stable coronary artery disease who were referred for invasive angiography and who underwent FFR, coronary CT angiography, and FFR_{CT}. The incidence of the composite primary end point of death, myocardial infarction, and any revascularization and the composite secondary end point of major adverse cardiac events (MACE: cardiac death, myocardial infarction, unplanned revascularization) were compared for an FFR_{CT} of 0.8 or less versus stenosis of 50% or greater on coronary CT angiograms, with treating physicians blinded to the FFR_{CT} result.

Results: Long-term outcomes were obtained in 206 individuals (age, 64 years ± 9.5), including 64% men. At median follow-up of 4.7 years, there were no cardiac deaths or myocardial infarctions in participants with normal FFR_{CT}. The incidence of the primary end point was more frequent in participants with positive FFR_{CT} compared with clinically significant stenosis at coronary CT angiography (73.4% [80 of 109] vs 48.7% [91 of 187], respectively; $P < .001$), with the majority of outcomes being planned revascularization. Corresponding hazard ratios (HRs) were 9.2 (95% confidence interval [CI]: 5.1, 17; $P < .001$) for FFR_{CT} and 5.9 (95% CI: 1.5, 24; $P = .01$) for coronary CT angiography. FFR_{CT} was a superior predictor compared with coronary CT angiography for primary end point (C-index FFR_{CT}, 0.76 vs coronary CT angiography, 0.54; $P < .001$) and MACE (FFR_{CT}, 0.71 vs coronary CT angiography, 0.52; $P = .001$). Frequency of MACE was higher in participants with positive FFR_{CT} compared with coronary CT angiography (15.6% [17 of 109] vs 10.2% [19 of 187], respectively; $P = .02$), driven by unplanned revascularization. MACE HR was 5.5 (95% CI: 1.6, 19; $P = .006$) for FFR_{CT} and 2.0 (95% CI: 0.3, 14; $P = .46$) for coronary CT angiography. Each 0.05-unit FFR_{CT} reduction was independently associated with greater incidence of primary end point (HR, 1.7; 95% CI: 1.4, 1.9; $P < .001$) and MACE (HR, 1.4; 95% CI: 1.1, 1.8; $P < .001$).

Conclusion: In stable patients referred for invasive angiography, a CT-derived fractional flow reserve (FFR_{CT}) value of 0.8 or less was a predictor of long-term outcomes driven by planned and unplanned revascularization and was superior to clinically significant stenosis on coronary CT angiograms. Additionally, the numeric value of FFR_{CT} was an independent predictor of outcomes.

Online supplemental material is available for this article.

Invasive coronary angiography remains the clinical reference standard for diagnosing coronary artery disease; however, stenosis severity alone is a poor predictor of functional significance (1). Treatment strategies guided by invasive fractional flow reserve (FFR) have demonstrated superior outcomes compared with an anatomic strategy alone (2,3). Although FFR is often interpreted in a dichotomous manner (≤ 0.80), recent studies have demonstrated a risk continuum where lower FFR values are associated with a higher rate of clinical events and greater benefit from revascularization (4,5).

Coronary CT angiography is a well-established diagnostic modality that provides anatomic assessment of stenosis severity with an excellent negative predictive value but is limited by poor specificity for

Abbreviations

CI = confidence interval, FFR = fractional flow reserve, FFR_{CT} = CT-derived FFR, HR = hazard ratio, MACE = major adverse cardiac events, NXT = Analysis of Coronary Blood Flow Using Coronary CT Angiography: Next Steps

Summary

A CT-derived fractional flow reserve (FFR_{CT}) value of 0.8 or less is a predictor of long-term clinical outcomes and is superior to clinically significant stenosis on coronary CT angiograms. A normal FFR_{CT} is associated with favorable long-term prognosis and the numeric value of FFR_{CT} also demonstrates an independent and inversely related risk continuum.

Key Points

- The results from this NXT substudy demonstrate that in individuals with stable coronary artery disease, positive CT-derived fractional flow reserve ($FFR_{CT} \leq 0.8$) was a predictor of both the primary composite end point of death, nonfatal myocardial infarction, and any revascularization (hazard ratio [HR], 9.2; $P < .001$) and major adverse cardiac events (MACE, defined as cardiac death, nonfatal myocardial infarction, and unplanned revascularization) (HR, 5.5; $P = .006$). These findings were driven by planned and unplanned revascularization.
- A positive FFR_{CT} was a superior predictor of the primary end point and MACE when compared with the presence of clinically significant stenosis (≥ 50%) on CT coronary angiograms (primary end-point C-statistic: FFR_{CT}, 0.76 vs coronary CT angiography, 0.54, $P < .001$; MACE C-index: FFR_{CT}, 0.71 vs coronary CT angiography, 0.52; $P = .001$).
- The numeric value of FFR_{CT} was an independent predictor of outcomes, with each 0.05-unit decrement of FFR_{CT} associated with greater incidence of the primary end point (HR, 1.7; $P < .001$) and MACE (HR, 1.4; $P = .009$).

detecting lesion-specific ischemia (6,7). The principles of computational fluid dynamics can now be applied to standard coronary CT angiography to permit the calculation of noninvasive FFR (ie, CT-derived FFR [FFR_{CT}]). Several prospective multicenter trials (8–10), including the Analysis of Coronary Blood Flow Using Coronary CT Angiography: Next Steps (NXT) trial, have demonstrated that FFR_{CT} accurately predicts lesion-specific ischemia when compared with invasive FFR, with a per-participant sensitivity and specificity of 86% and 79%, respectively (10).

The combination of anatomic and functional assessment with coronary CT angiography and a normal FFR_{CT} (> 0.8) demonstrates the ability to safely defer unnecessary invasive coronary angiography (11–13). Furthermore, a positive FFR_{CT} (≤ 0.8) improves the diagnostic yield of invasive coronary angiography (13,14) and is a better predictor of clinical outcomes compared with severe stenosis on coronary CT angiograms at medium-term follow-up (14). However, the long-term prognostic value of FFR_{CT} in comparison to coronary CT angiography and the risk continuum of FFR_{CT} values is not known.

The purpose of this NXT substudy is to determine the prognostic value of FFR_{CT} in predicting death, nonfatal myocardial infarction, and revascularization in a study population with stable coronary artery disease and to describe the relationship of the numeric value of FFR_{CT} with clinical outcomes.

Materials and Methods

Study Population and Protocol

This prospective study is a subanalysis of NXT (Clinicaltrials.gov: NCT01757678), the design and results of which have been previously reported (10,15), and is the only substudy from the NXT trial to report clinical outcomes. The original NXT trial was sponsored by HeartFlow (Redwood City, Calif). Control of the data and analysis were performed by authors independent to HeartFlow (A.R.I., B.S.K.). One coauthor (J.L.) is a consultant to HeartFlow but had no control of data presented in this study. The ethics committee of each site approved the study protocol and all patients provided written informed consent.

Study Participants

For this substudy investigating clinical outcomes, we invited all original sites from the NXT trial to participate with requirement of additional ethics approval to acquire long-term clinical outcome data. The NXT study included individuals suspected of having stable coronary artery disease with at least one stenosis at coronary CT angiography with a luminal diameter between 30% and 90% in a vessel segment of 2 mm or greater (10). Coronary CT angiography was performed within 60 days prior to clinically indicated, nonurgent invasive coronary angiography between 2012 to 2013. Exclusion criteria included prior stent implantation or coronary bypass surgery; contraindications to beta blockers, nitrates, or adenosine; suspicion of acute coronary syndrome; clinically significant arrhythmia; and body mass index of 35 kg/m^2 or greater.

In this substudy, we included all participants for whom the coronary CT angiogram was of adequate quality for FFR_{CT} analysis as determined by the core laboratory in the original NXT study. Participants originally excluded from NXT study were further screened to assess eligibility for this substudy. Those with an incomplete coronary CT angiography data set (absence of site-read coronary CT angiograms) were then excluded. Participants from sites that declined to participate were excluded.

Coronary CT Angiogram Acquisition

Coronary CT angiography was performed as per NXT protocol (10,15) by using CT scanners with at least 64 detector rows (Table E1 [online]). Clinically significant stenosis on site-read coronary CT angiograms was defined as 50% or greater.

Computation of FFR_{CT}

Computation of FFR_{CT} was performed by an independent core laboratory (HeartFlow, Redwood City, Calif) blinded to patient characteristics, clinical outcomes, and coronary CT angiograms read (16). FFR_{CT} was computed throughout the coronary tree in all major epicardial vessels and side branches measuring 2 mm or greater, including the vessels that were not interrogated by invasive FFR in the original NXT study. Occluded arteries were assigned FFR_{CT} values of 0.50. The lowest FFR_{CT} value was recorded and an FFR_{CT} of 0.80 or less was defined as positive for coronary ischemia. All FFR_{CT} analyses

were performed blinded to coronary CT angiography findings and clinical outcomes. Treating physicians were blinded to the results of FFR_{CT}, and hence FFR_{CT} results did not influence clinical management.

Clinical End Points

The primary end point was a composite of death from any cause, nonfatal myocardial infarction, and any revascularization. Revascularization with either percutaneous coronary intervention or coronary artery bypass grafting was categorized as planned or unplanned. Revascularization decisions were made at the discretion of treating physicians. Planned revascularization was defined as that planned to occur after index invasive coronary angiography. Unplanned revascularization was any subsequent revascularization following the initial treatment decision at index invasive coronary angiography and occurring at a minimum of 6 weeks after index invasive coronary angiography. There were two secondary end points: *(a)* major adverse cardiac events (MACE, a composite of cardiac death, nonfatal myocardial infarction, and unplanned revascularization) and *(b)* any revascularization. Cardiac death and myocardial infarction were defined as per recently published guidelines (17,18). Furthermore, we assessed the relationship of the primary end point and MACE with each 0.05-unit strata decrement of FFR_{CT} adjusted for clinical and coronary CT angiography features. All clinical events were obtained from the medical records and/or telephone interview at a single review between October to December 2017. At each participating site, clinical events were adjudicated by physicians blinded to FFR_{CT} results.

Statistical Analysis

Descriptive statistics are presented as mean and standard deviation for continuous variables and frequencies and percentages for categorical variables. Comparisons of baseline characteristics between participants with a positive versus normal FFR_{CT} were performed by using the Student *t* test or χ^2 as appropriate. Comparison of the cumulative incidence of the primary and secondary end points was performed by using the log-rank test. Analysis (or censoring) of time to first event was performed with Cox proportional hazard regression models to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) to assess the relationship of a positive FFR_{CT} ($\leq$ 0.8) and clinically significant stenosis ($\geq$ 50%) on coronary CT angiograms compared with a normal result for the primary and secondary end points. Proportional hazards assumption was verified by us-

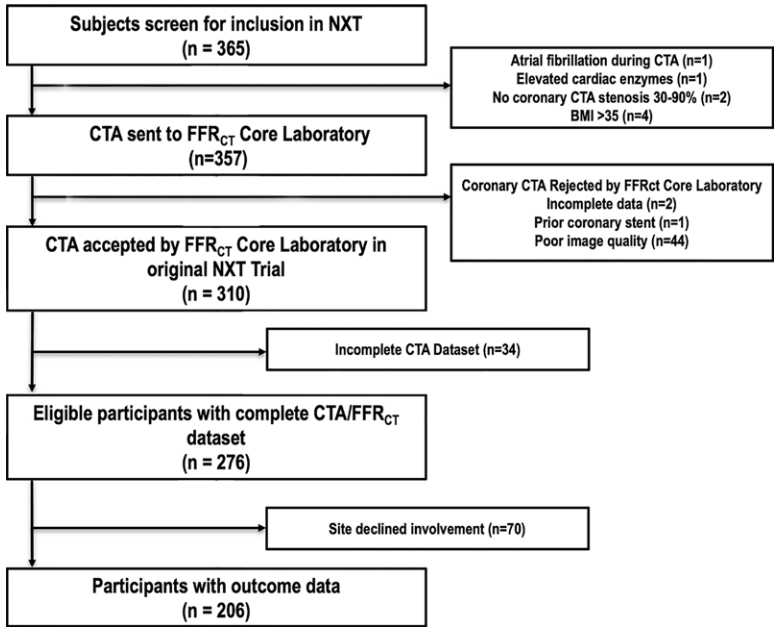

Figure 1: Inclusion flowchart. BMI = body mass index, CTA = coronary CT angiography, FFR_{CT} = CT-derived fractional flow reserve, NXT = Analysis of Coronary Blood Flow Using Coronary CT Angiography: Next Steps.

Table 1: Study Participant and Coronary CT Angiography Characteristics Stratified by CT-derived Fractional Flow Reserve

Variable (n = 206)	$FFR_{CT} \leq 0.80$ (n = 109)	$FFR_{CT} > 0.8$ (n = 97)	*P* Value
Age (y)*	63.0 ± 9.7	65.1 ± 9.2	.10
No. of men†	82 (75)	50 (52)	<.001
Race†			
White	66 (60.6)	75 (77.3)	.01
Asian	43 (39.4)	22 (22.7)	
Diabetes†	29 (26.6)	18 (18.6)	.17
Hypertension†	73 (67.0)	62 (63.9)	.65
Hypercholesterolemia†	89 (81.7)	78 (80.4)	.82
Smoking†	24 (22.0)	15 (15.5)	.23
Symptoms†‡			
Typical	51 (56.7)	29 (36.2)	.01
Atypical	33 (36.7)	39 (48.8)	.14
Nonanginal chest pain	1 (1.1)	8 (10)	.01
Dyspnea	5 (5.5)	4 (5)	.87
Updated Diamond-Forrester risk score*	59.7 ± 21.1	48.1 ± 21.7	<.001
Creatinine (mg/dL)*	0.87 ± 0.16	0.84 ± 0.19	.39
Left ventricular ejection fraction (%)*	61.6 ± 7.7	62.5 ± 5.3	.37
Body mass index (kg/m^2)*	25.6 ± 3.7	25.4 ± 3.5	.77

Note.—FFR_{CT} = CT-derived fractional flow reserve.

* Data are mean ± standard deviation.

† Data are number of participants. Data in parentheses are percentages.

‡ Data available for 170 participants.

Table 2: Primary and Secondary End Points Stratified by CT-derived Fractional Flow Reserve

End Point	Cumulative Incidence				
	$FFR_{CT} \leq 0.80$ (n = 109)*	$FFR_{CT} > 0.80$ (n = 97)*	P Value	Hazard Ratio†	P Value
Primary					
Composite of death, nonfatal MI, and revascularization	80 (73.4)	13 (13.4)	<.001	9.2 (5.1, 17)	<.001
Death from any cause	3 (2.8)	3 (3.1)	.89		
Cardiac death	0	0	>.99		
Nonfatal MI	3 (2.8)	0	.1		
Any revascularization	78 (71.6)	10 (10.3)	<.001		
Secondary					
Composite of composite death, nonfatal MI, unplanned revascularization (MACE)	17 (15.6)	3 (3.1)	.002	5.5 (1.6, 19)	.006
Cardiac death, nonfatal MI	3 (2.8)	0	0.1		
Any revascularization‡	78 (71.6)	10 (10.3)	<.001	11.2 (5.8, 22)	<.001
Planned§	76 (69.7)	8 (8.2)	<.001	13.1 (6.3, 27)	<.001
Unplanned‖	16 (14.7)	3 (3.1)	.004	5.2 (1.5, 18)	.009
Repeat revascularization#	14 (12.8)	1 (1.0)	.001		
De novo revascularization**	2 (1.8)	2 (2.1)	.91		

Note.—FFR_{CT} = CT-derived fractional flow reserve, MACE = major adverse cardiac event, MI = myocardial infarction.

* Data are number of participants. Data in parentheses are percentages.

† Hazard ratio represents time to first event. Data in parentheses are 95% confidence intervals.

‡ Any revascularization represents the number of participants who had any revascularization procedure during follow-up.

§ Planned revascularization is defined as that planned to occur after index invasive coronary angiogram.

‖ Unplanned revascularization is any subsequent revascularization following the initial treatment decision at index invasive coronary angiogram.

Repeat revascularization represents the number of participants who required further revascularization following initial planned revascularization strategy.

** De novo revascularization represents the number of participants who failed initial medical treatment strategy.

ing the Schoenfeld residuals test. Nelson-Aalen cumulative hazard curves were constructed for the primary end point. The ability of a positive FFR_{CT} to predict clinical outcomes compared to clinically significant stenosis on coronary CT angiograms was assessed by using Harrell C-index (19). A sensitivity analysis was performed using a coronary CT angiography stenosis severity of greater than 70%. The optimal FFR_{CT} value for predicting the primary end point and MACE was calculated by using the Youden Index, with confidence intervals determined by bootstrapping with 1000 repetitions. A univariable analysis was performed on clinically relevant variables with inclusion into a multivariable model if the P value was less than .2 (20) to obtain the relationship of the primary end point and MACE with each 0.05-unit strata reduction in FFR_{CT}. A two-tailed P value less than .05 was considered indicative of statistical significance. Statistical analysis was performed using STATA-14 (StataCorp, College Station, Tex).

Results

Study Participants

The participant flow diagram is illustrated in Figure 1. Among the 310 participants from the NXT study with coronary CT angiograms of acceptable quality by FFR_{CT} core laboratory, 34 were excluded from this substudy due to incomplete coronary CT angiogram site-read. Among the remaining 276 study participants with complete data sets of coronary CT angiogram and FFR_{CT}, 254 had been included in the original NXT study and 22 had been excluded because invasive FFR measurements were deemed not suitable by the core laboratory. These 22 participants were included in this substudy, as this study compared the prognostic value of FFR_{CT} and coronary CT angiography for predicting outcomes, with treatment decisions at the discretion of local physicians that were not mandated by invasive FFR results. Among the 276 participants, 70 participants were excluded from four of the 10 original NXT enrolling sites that declined participation in this substudy. The final analysis was performed including the remaining 206 participants, with a median follow-up duration of 4.7 (range, 4.4–5.3) years.

The mean age of the 206 study participants (64% men) was 64.0 years ± 9.5. The average updated Diamond and Forrester score (based on age, sex, angina typicality) for the presence of obstructive coronary artery disease was 54% ± 22. Per-participant characteristics are summarized in Table 1. Participant demographics and updated Diamond and Forrester risk scores were comparable with those of participants from nonparticipating centers and those from the original NXT study (Table E2 [online]). Approximately 91% (187 of 206) of participants had at least one clinically significant (≥ 50%) stenosis at coronary CT

angiography; the majority (158 of 187 [84.5%]) of these stenoses were between 50% and 90%. The mean per-participant FFR_{CT} value was 0.76 ± 0.13, with 52.9% (109 of 206) of participants having an FFR_{CT} of 0.80 or less.

Primary and Secondary End Points

The incidence of the composite primary end point of death from any cause, nonfatal myocardial infarction, and any revascularization occurred in 45.1% (93 of 206) of participants, driven predominantly by planned revascularization (40.8% [84 of 206]). The secondary end point of MACE occurred in 9.7% (20 of 206) of participants. Most events were unplanned revascularization (9.2% [19 of 206]), with three participants (2.8%) having a nonfatal myocardial infarction. In all cases of death (3.0% [six of 206]), the cause was noncardiac in origin.

FFR_{CT} and Clinical Outcomes

The incidence and Cox regression analysis of the primary and secondary end points stratified by FFR_{CT} are summarized in Table 2. In participants with an FFR_{CT} of 0.80 or less, the incidence of the primary end point was higher compared with participants with an FFR_{CT} greater than 0.80 (73.4% [80 of 109] vs 13.4% [13 of 97], respectively; HR, 9.2 [95% CI: 5.1, 17]; $P < .001$) (Fig 2a). This was driven predominantly by higher rates of any revascularization (71.6% [78 of 109] vs 10.3% [10 of 97]; HR, 11.2 [95% CI: 5.8, 21.6]; $P < .001$), in particular planned revascularization (69.7% [76 of 109] vs 8.2% [eight of 97]); $P < .001$). In participants with an FFR_{CT} of 0.80 or less, the incidence of MACE was also higher (15.6% [17 of 109] vs 3.1% [three of 97]; HR, 5.5 [95% CI: 1.6, 19]; $P = .002$) (Fig 2b), driven predominantly by higher rates of unplanned revascularization (14.7% [16 of 109] vs 3.1% [three of 97]; $P = .004$).

In participants with an FFR_{CT} greater than 0.8 (47.1% [97 of 206]), there were no cardiac deaths or myocardial infarctions. In this group, 10 participants underwent revascularization; two of the revascularizations were unplanned for treatment of stable angina. In the remaining eight planned revascularizations, six occurred in vessels with a corresponding invasive FFR value of greater than 0.8 (mean FFR, 0.88 ± 0.04).

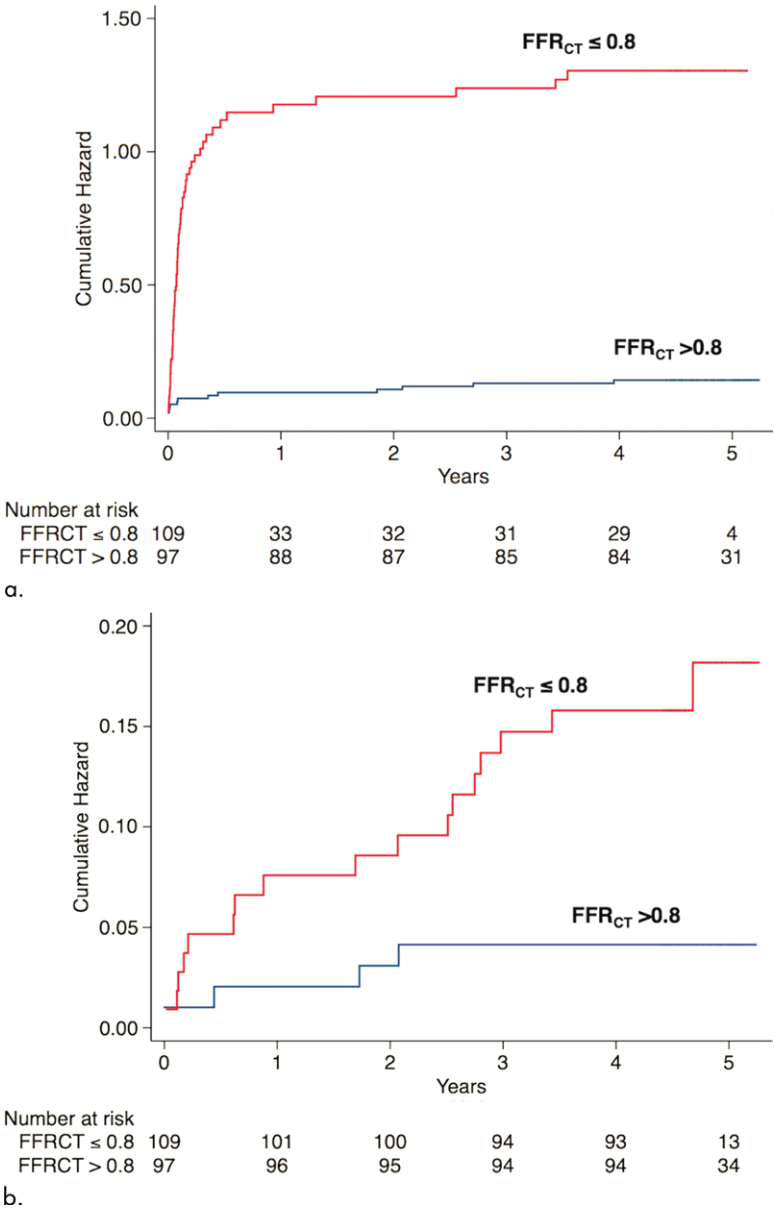

Figure 2: Cumulative hazard of the primary end point and major adverse cardiac events (MACE) for CT-derived fractional flow reserve (FFR_{CT}). Nelson-Aalen cumulative hazard curves for FFR_{CT} are demonstrated for the **(a)** primary end point (composite of death, nonfatal myocardial infarction, and any revascularization) and **(b)** MACE (composite of cardiac death, nonfatal myocardial infarction, and unplanned revascularization).

FFR_{CT} versus Coronary CT Angiography

The incidence of the primary end point was more frequent in participants with an FFR_{CT} of 0.80 or less (73.4% [80 of 109]) compared with clinically significant stenosis of 50% or greater on coronary CT angiograms (48.7% [91 of 187]; $P < .001$). The incidence of MACE was higher in participants with positive FFR_{CT} (15.6% [17 of 109]) compared with clinically significant stenosis on coronary CT angiograms (10.2% [19 of 187]; $P = .02$). The HR and Harrell C-index for FFR_{CT} and coronary CT angiography (using thresholds ≥ 50% and > 70%) for primary and secondary end points are summarized in Table 3. The HR for the primary end point for FFR_{CT} was 9.2 (95% CI: 5.1, 17; $P < .001$), compared with 5.9 for coronary CT angiography (95% CI: 1.5, 24; $P < .01$). A positive FFR_{CT} was a significant predictor of MACE, with an HR of 5.5 (95% CI: 1.6, 19; $P = .006$); in comparison, the MACE HR for clinically significant stenosis on coronary CT angiograms was not statistically significant (HR, 2.0 [95% CI: 0.3, 14]; $P = .46$). FFR_{CT} of 0.8 or less was a superior predictor compared with the presence of clinically significant stenosis on coronary

Table 3: Cox Regression Analysis and Predictive Measures for CT-derived Fractional Flow Reserve of 0.80 or Less and Coronary CT Angiography with Stenosis of 50% or Greater and Stenosis of Greater than 70%

	$FFR_{CT} \leq 0.80$		CT Angiography with ≥ 50% Stenosis		CT Angiography with > 70% Stenosis	
Parameter	Value	*P* Value	Value	*P* Value	Value	*P* Value
Hazard ratio*						
Primary end point						
Composite of death, nonfatal MI, and revascularization	9.2 (5.1, 17)	< .001	5.9 (1.5, 24)	.01	5.3 (3.3, 8)	< .001
Secondary end points						
Composite of death, nonfatal MI, unplanned revascularization (MACE)	5.5 (1.6, 19)	.006	2.0 (0.3, 14)	.46	2.4 (0.9, 6.0)	.07
Any revascularization	11.2 (5.8, 22)	< .001	5.5 (1.4, 22)	.02	5.3 (3.3, 9)	< .001
Planned revascularization	13.1 (6.3, 27)	< .001	10.5 (1.5, 75)	.02	5.9 (3.5, 10)	< .001
Unplanned revascularization	5.2 (1.5, 18)	.009	1.9 (0.3, 14)	.54	2.8 (1.1, 7)	.04
C-index†						
Primary end point						
Composite of death, nonfatal MI, and revascularization	0.76 (0.71, 0.81)		0.54 (0.52, 0.57)	< .001	0.69 (0.64, 0.74)	.005
Secondary end points						
Composite of cardiac death, nonfatal MI, unplanned revascularization (MACE)	0.71 (0.59, 0.78)		0.52 (0.47, 0.57)	.001	0.60 (0.49, 0.70)	.01
Any revascularization	0.76 (0.71, 0.80)		0.54 (0.52, 0.57)	< .001	0.69 (0.64, 0.74)	.007
Planned revascularization	0.76 (0.71, 0.81)		0.55 (0.52, 0.58)	< .001	0.70 (0.65, 0.75)	.007
Unplanned revascularization	0.72 (0.60, 0.84)		0.52 (0.46, 0.58)	< .001	0.62 (0.51, 0.73)	.02

Note.—FFR_{CT} = CT-derived fractional flow reserve, MACE = major adverse cardiac events, MI = myocardial infarction.

* Data are hazard ratios. Data in parentheses are 95% confidence intervals.

† Data are C-indices. Data in parentheses are 95% confidence intervals. *P* value represents C-index comparison with $FFR_{CT} \leq 0.80$.

CT angiograms for the primary end point (C-index FFR_{CT}, 0.76 [95% CI: 0.71, 0.81] vs coronary CT angiography, 0.54 [95% CI: 0.52, 0.57]; $P < .001$) and for MACE (C-index FFR_{CT}, 0.71 [95% CI: 0.59, 0.82] vs coronary CT angiography, 0.52 [95% CI: 0.47, 0.57]; $P = .001$). The latter was driven predominately by unplanned revascularization (C-index FFR_{CT}, 0.72 vs coronary CT angiography, 0.52; $P < .001$). When compared with clinically significant stenosis (defined as greater than 70%) on coronary CT angiograms, FFR_{CT} remained a superior predictor of the primary and secondary end points. Clinical outcomes stratified by stenosis severity on coronary CT angiograms and by FFR_{CT} are summarized in Figure E1 (online).

FFR_{CT} as Risk Continuum

The incidence and relative HR of the primary end point and MACE per 0.05-unit decrement of FFR_{CT} is illustrated in Figure 3. A univariable analysis was performed for clinical and coronary CT angiography predictors of the primary end point and MACE (Table 4). After adjusting for these potential confounders, each 0.05-unit lower FFR_{CT} was associated with a greater incidence of the primary end point (adjusted HR, 1.7 [95% CI: 1.4, 1.9]; $P < .001$) and MACE (adjusted HR, 1.4 [95% CI: 1.1, 1.8]; $P = .009$). The optimal FFR_{CT} value for predicting the primary end point was determined at 0.79 or less (sensitivity, 86.4%; specificity, 77.1%; 95% CI: 0.74, 0.85; $P < .001$) and for MACE at 0.72 or less (sensitivity, 70.0%; specificity, 67.2%; 95% CI: 0.61, 0.84; $P = .002$).

Discussion

Although coronary CT angiography with noninvasive fractional flow reserve (FFR_{CT}) has been shown to predict lesion-specific ischemia, the longer-term prognostic value of FFR_{CT} has not been previously evaluated. In this study, we evaluated patient outcomes following FFR_{CT} for approximately 5 years. An FFR_{CT} of 0.80 or less was a significant predictor of the primary composite end point of death, nonfatal myocardial infarction, and any revascularization (hazard ratio [HR], 9.2 [95% confidence interval {CI}: 5.1, 17]; $P < .001$). This was driven predominantly by short-term outcomes, namely revascularization occurring at the time of index invasive coronary angiography. In addition, FFR_{CT} of 0.8 or less was a predictor of major adverse cardiac events (MACE) driven by unplanned revascularization (HR, 5.5 [95% CI: 1.6, 19]; $P = .006$). An FFR_{CT} of 0.8 or less was a superior predictor of both the primary end point and MACE when compared with the presence of clinically significant stenosis of 50% or greater (primary end point: C-index FFR_{CT}, 0.76 vs coronary CT angiogram, 0.54 [$P < .001$]; and MACE C-index FFR_{CT}, 0.71 vs coronary CT angiogram, 0.52; $P = .001$) or 70% or greater on coronary CT angiograms (Table 3). Conversely, FFR_{CT} (> 0.8) was associated with a favorable long-term prognosis with no incidence of cardiac death or myocardial infarction. In adjusted analyses, each 0.05-unit decrement of FFR_{CT} was associated with greater incidence of the primary end point (HR, 1.7 [95%

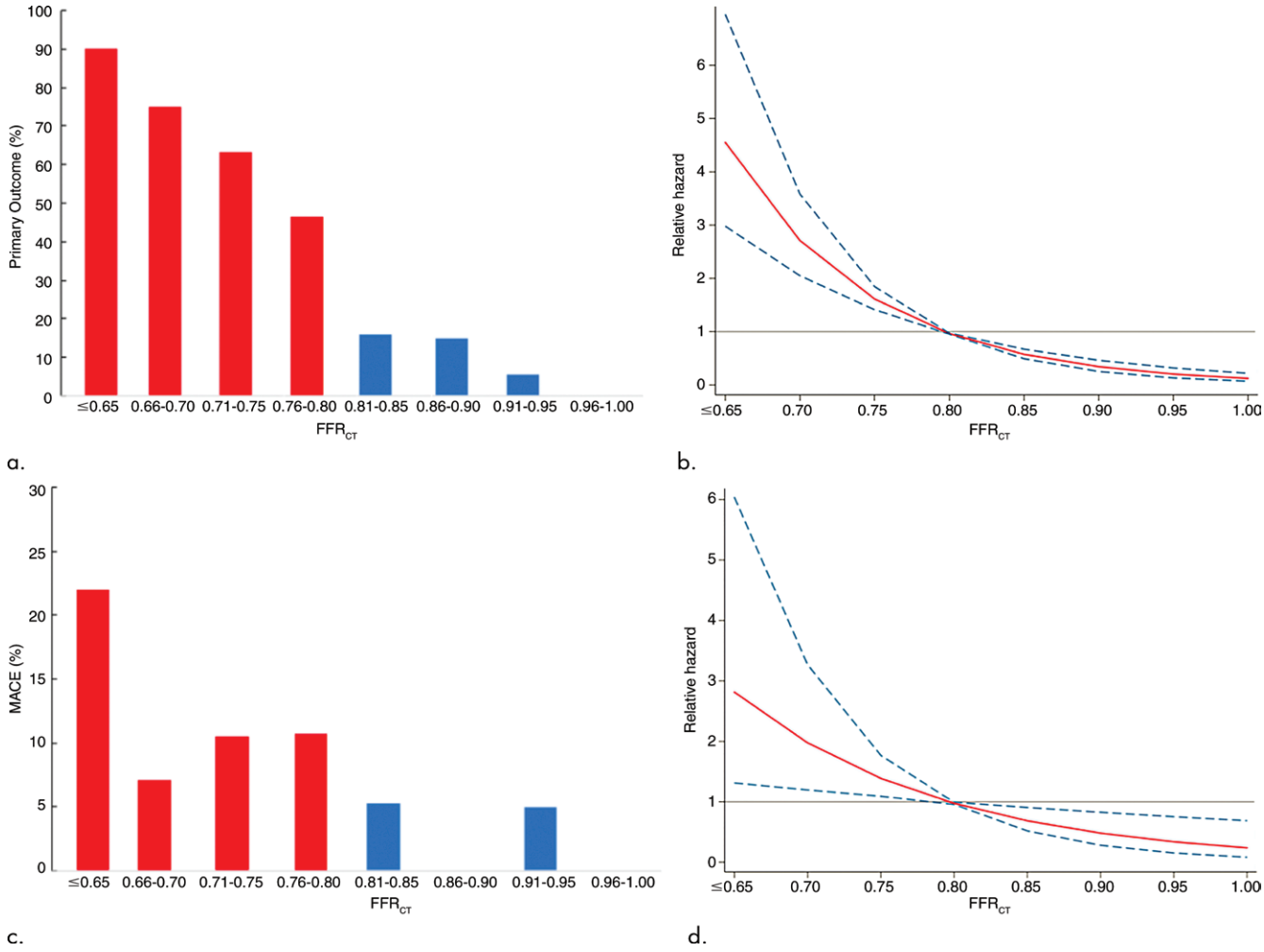

Figure 3: Relationship between primary end point and major adverse cardiac events (MACE) with numeric value of CT-derived fractional flow reserve (FFR$_{CT}$). This figure illustrates the incidence of **(a)** primary end point (composite of death, nonfatal myocardial infarction, and any revascularization) and **(c)** MACE (composite of cardiac death, nonfatal myocardial infarction, and unplanned revascularization). The relative hazard ratio with 95% confidence intervals by 0.05 strata of FFR$_{CT}$ at median follow-up of 4.7 years are shown for the **(b)** primary end point and **(d)** MACE.

CI: 1.4, 1.9]; $P < .001$) and MACE (HR, 1.4 [95% CI: 1.1, 1.8]; $P = .009$). Treating physicians had no a priori knowledge of FFR$_{CT}$ results; this suggests the prognostic importance of FFR$_{CT}$ was not biased from the results of CT-derived fractional flow reserve.

The recently published PROMISE FFR$_{CT}$ substudy performed retrospective FFR$_{CT}$ analysis in participants with suitable coronary CT angiography referred for invasive coronary angiography (14). In a cohort of 181 participants at a median follow-up of 2.4 years, FFR$_{CT}$ was superior to coronary CT angiography at predicting the composite end point of revascularization or MACE (death, nonfatal myocardial infarction, and hospitalization for unstable angina) (14). Similar to our results, the overall superiority of FFR$_{CT}$ was driven predominantly by revascularization. This NXT substudy design differs from PROMISE FFR$_{CT}$ in that FFR$_{CT}$ was determined prospectively, duration of follow-up was longer (median, 4.7 years), invasive FFR was mandated in all participants, and the cut-off for clinically significant stenosis at coronary CT angiography was 50% or greater compared with greater than 70%. Yet consistent with PROMISE FFR$_{CT}$ results, our results demonstrate superiority of FFR$_{CT}$ in predicting clinical outcomes compared with stenosis on coronary CT angiograms of both 50% or greater and greater than 70%. Importantly, both studies assessed the prognostic utility of FFR$_{CT}$ while treating physicians were blinded to FFR$_{CT}$ results. Hence FFR$_{CT}$ had no influence on clinical decision making.

In contrast to the PROMISE FFR$_{CT}$ study, our work demonstrates the superiority of a positive FFR$_{CT}$ at predicting MACE when compared with normal FFR$_{CT}$ (> 0.8) or clinically significant stenosis on coronary CT angiograms driven predominantly by unplanned revascularization. Furthermore, a recent single-center real-world study demonstrated a favorable prognosis associated with a normal FFR$_{CT}$ at 2 years follow-up (21). Our results are consistent and extend the safety of a normal FFR$_{CT}$ result to approximately 5 years. Our findings highlight the prognostic utility of FFR$_{CT}$ in identifying participants with coronary artery disease who may require no further diagnostic testing.

Invasive FFR clinical studies have typically interpreted FFR in a dichotomous manner, with a cut-off of 0.8 or less used to

Table 4: Univariable and Multivariable Cox Regression Analysis for Primary End Point and Major Adverse Cardiac Events

	Primary End Point				MACE			
	Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis	
Variable	Hazard Ratio*	*P* Value	Hazard Ratio*	*P* Value	Hazard Ratio*	*P* Value	Hazard Ratio*	*P* Value
FFR_{CT} (0.05-unit strata)	1.7 (1.5, 1.9)	<.001	1.7 (1.4, 1.9)	<.001	1.5 (1.2, 1.9)	.001	1.4 (1.1, 1.8)	.009
Age	1 (0.97, 1)	.59			1 (0.9, 1)	.29		
Sex	1.7 (1.1, 2.7)	.02	1 (0.6, 1.7)	.97	3.3 (1, 11)	.06	2.2 (0.6, 8)	.23
Race	0.7 (0.4, 1)	.06	1 (0.6, 1.6)	.97	0.7 (0.3, 1.6)	.37		
Hypertension	1.8 (1, 2.8)	.02	1.8 (1.1, 3)	.02	2.3 (0.8, 6.8)	.14	2.3 (0.8, 7.1)	.14
Hyperlipidemia	1.7 (0.9, 3)	.09	0.9 (0.5, 1.7)	.71	1.4 (0.4, 4.6)	.63		
Diabetes	1.2 (0.8, 2.0)	.40			1.5 (0.6, 3.8)	.43		
Prior MI	5.5 (2.0, 15)	.001	2.6 (0.9, 7.5)	.07	9.2 (2.1, 40)	.003	5.7 (1.3, 25)	.02
Smoking	1.0 (0.6, 1.7)	.89			0.7 (0.2, 2.5)	.62		
Typical angina	2.8 (1.8, 4.4)	<.001	2.0 (1.2, 3.2)	.005	1.8 (0.7, 4.7)	.22		
CT angiography with ≥ 50% stenosis	5.9 (1.5, 24)	.01	1.8 (0.4, 7.5)	.43	2.0 (0.3, 14)	.51		

Note.—FFR_{CT} = CT-derived fractional flow reserve, MACE = major adverse cardiac events (composite of cardiac death, nonfatal MI, unplanned revascularization), MI = myocardial infarction.

* Data in parentheses are 95% confidence intervals.

define clinically significant myocardial ischemia and guide revascularization decisions (2,3). In practice, FFR represents a risk continuum, with lower values representing a greater severity or "depth" of ischemia, and is associated with a higher rate of clinical events and greater benefit from revascularization (4). To our knowledge, our study for the first time demonstrates a significant and independent relationship between the numeric value of FFR_{CT} and risk of clinical outcomes, with each 0.05-unit decrement in FFR_{CT} independently associated with a greater incidence of the primary end point and MACE. These important findings illustrate the relationship between the depth of ischemia with the numeric value of FFR_{CT} and further add credence to FFR_{CT} simulating invasive physiology. The potential to incorporate lesion-specific FFR_{CT}-derived depth of ischemia with CT-derived myocardium at risk ("extent") has yet to be explored and has potential to improve prognostication of coronary stenosis and guide clinical decision making in a manner not readily available with other invasive or noninvasive tests (22).

There are several limitations of this study. Selection bias was present because study participants were awaiting clinically indicated elective coronary angiography. This means study participants had a higher pretest probability of coronary artery disease compared with stable patients otherwise referred for coronary CT angiography. Long-term outcomes were only available for 74.6% of participants with a complete coronary CT angiogram site-read and FFR_{CT} data set. In the original NXT trial, 13.2% of participants were excluded due to poor coronary CT angiogram quality (deemed not suitable for FFR_{CT} analysis); therefore, the applicability of our findings to the broader population referred for coronary CT angiography is not known. Despite a difference in MACE, all end points were driven predominantly by revascularization. Our study had limited power for evaluation of cardiac death and myocardial infarction due to small sample size and therefore the results of these composite end points should be viewed as exploratory. The Assessing Diagnostic Value of Noninvasive FFR_{CT} in Coronary Care, or ADVANCE, registry will help further define the prognostic utility of FFR_{CT} in a real-world setting (23). Finally, the evaluation of plaque morphology, burden, and shear stress using coronary CT angiography is also associated with clinical outcomes, including in participants with nonobstructive coronary artery disease (24–26). These may be superior to measures of ischemia at predicting cardiac death and myocardial infarction. Comparison of their prognostic utility with FFR_{CT} was outside the scope of our study.

In conclusion, for study participants with stable coronary artery disease referred for invasive coronary angiography and with treating physicians blinded to CT-derived fractional flow reserve (FFR_{CT}) results, an FFR_{CT} of 0.8 or less was a predictor of long-term clinical outcomes and was superior compared with the finding of clinically significant stenosis on coronary CT angiograms. This was driven by both planned and unplanned revascularization. Furthermore, normal FFR_{CT} was associated with favorable long-term prognosis and the numeric value of FFR_{CT} demonstrated an independent and inversely related risk continuum with clinical outcomes.

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