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Radiology

ORIGINAL RESEARCH • CARDIAC IMAGING

Prognostic Value of Coronary CT Angiography–derived Fractional Flow Reserve on 3-year Outcomes in Patients with Stable Angina

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

See also the editorial by Sinitsyn in this issue.

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Background: The prognostic value of coronary CT angiography (CTA)–derived fractional flow reserve (FFR) beyond 1-year outcomes and in patients with high levels of coronary artery calcium (CAC) is uncertain.

Purpose: To assess the prognostic value of coronary CTA–derived FFR test results on 3-year clinical outcomes in patients with coronary stenosis and among a subgroup of patients with high levels of CAC.

Materials and Methods: This study represents a 3-year follow-up of patients with new-onset stable angina pectoris who were consecutively enrolled in the Assessing Diagnostic Value of Noninvasive CT-FFR in Coronary Care, known as ADVANCE (ClinicalTrials.gov: NCT02499679) registry, between December 2015 and October 2017 at three Danish sites. A high CAC was defined as an Agatston score of at least 400. A lesion-specific coronary CTA–derived FFR value of 2 cm with distal-to-stenosis value at or below 0.80 represented an abnormal test result. The primary end point was a composite of all-cause death and nonfatal spontaneous myocardial infarction. Event rates were estimated using the one-sample binomial model, and relative risk was compared between participants stratified by results of coronary CTA–derived FFR.

Results: This study included 900 participants: 523 participants with normal results (mean age, 64 years ± 9.6 [SD]; 318 male participants) and 377 with abnormal results from coronary CTA–derived FFR (mean age, 65 years ± 9.6; 264 male participants). The primary end point occurred in 11 of 523 (2.1%) and 25 of 377 (6.6%) participants with normal and abnormal coronary CTA–derived FFR results, respectively (relative risk, 3.1; 95% CI: 1.6, 6.3; $P < .001$). In participants with high CAC, the primary end point occurred in four of 182 (2.2%) and 19 of 212 (9.0%) participants with normal and abnormal coronary CTA–derived FFR results, respectively (relative risk, 4.1; 95% CI: 1.4, 11.8; $P = .001$).

Conclusion: In individuals with stable angina, a normal coronary CTA–derived FFR test result identified participants with a low 3-year risk of all-cause death or nonfatal spontaneous myocardial infarction, both in the overall cohort and in participants with high CAC scores.

Clinical trial registration no. NCT02499679

Supplemental material is available for this article.

Current guidelines recommend coronary CT angiography (CTA) as the first-line test in symptomatic patients suspected of having coronary artery disease (1,2). However, because the image quality and diagnostic performance of CTA can be negatively impacted by coronary artery calcium (CAC), CTA is not recommended in patients with high levels of CAC (1). Moreover, degree of stenosis at CTA may not precisely correspond to coronary physiologic estimates by fractional flow reserve (FFR), which is the established reference standard for decision-making regarding coronary revascularization (3,4). Consequently, noninvasive functional assessment is recommended in patients with intermediate-range stenosis determined with CTA to optimize management strategies (1,2). Noninvasive CTA-derived FFR shows high diagnostic performance, correlates well with invasively measured FFR (4,5), and provides diagnostic information beyond what can be obtained at CTA alone across a wide range of CAC levels

Abbreviations

ADVANCE = Assessing Diagnostic Value of Noninvasive CT-FFR in Coronary Care, CAC = coronary artery calcium, CTA = CT angiography, FFR = fractional flow reserve

Summary

Coronary CT angiography-derived fractional flow reserve values greater than 0.80 were associated with a reduced risk of adverse 3-year outcomes in participants with stable angina and in a subset of participants with high coronary artery calcium scores.

Key Results

- In this prospective 3-year follow-up study of 900 participants with stable angina, a coronary CT angiography (CTA)–derived fractional flow reserve (FFR) value of 0.80 or less was associated with a 3.2-fold increased risk of all-cause death and spontaneous myocardial infarction ($P < .001$) and an 8.8-fold increased risk of cardiovascular death and spontaneous myocardial infarction ($P = .001$) compared with a coronary CTA–derived FFR value greater than 0.80.
- The reduced risk of adverse outcomes for participants with coronary CTA–derived FFR values greater than 0.80 persisted after adjustment for coronary artery calcium score and degree of stenosis.

(6,7). Furthermore, previous studies have shown that coronary CTA–derived FFR is associated with 1-year clinical outcomes composed of all-cause death, nonfatal myocardial infarction, and revascularization in patients with stable coronary artery disease (8–13). However, it is uncertain whether the prognostic value of coronary CTA–derived FFR can be extended to longer term follow-up and whether it applies to patients with high levels of CAC. Therefore, the purpose of this study was to assess 3-year clinical outcomes after coronary CTA–derived FFR testing in a large cohort of prospectively enrolled symptomatic patients with coronary stenosis determined at CTA and to assess the prognostic value of coronary CTA–derived FFR in patients with high levels of CAC.

Materials and Methods

Study Design and Study Sample

The study sample consisted of patients who were consecutively enrolled in the Assessing Diagnostic Value of Noninvasive CT-FFR in Coronary Care (ADVANCE; ClinicalTrials.gov: NCT02499679) registry (8,14) between December 2015 and October 2017 at the three Danish ADVANCE registry sites (Fig 1). The design of the ADVANCE registry was described previously (14), and a complete list of all publications is available in Table S1. In brief, patients with new-onset stable angina were eligible for inclusion if they had at least one coronary stenosis that was 30% or greater and did not have persistent atrial fibrillation or prior coronary revascularization. Patients were excluded if the coronary CTA–derived FFR analysis was inconclusive. Baseline patient characteristics for this study were provided from the original ADVANCE registry database. In the original ADVANCE registry (8), follow-up of all patients was 1 year, whereas our study shows extended outcome data for up to 3 years. Moreover, unlike the original ADVANCE study, all patients in the Danish ADVANCE cohort included in our study had available CAC scores. This study was approved by the Danish Data Protection Agency (2008–58–0035; 1563 and 1–16–02–633–20). All patients provided written informed consent.

Coronary CTA Procedure and Image Evaluation

A second- or third-generation dual-source CT system (Somatom Definition Flash or Force; Siemens Healthcare) was used to perform CTA according to best-practice guidelines (15). Oral β-blockers (metoprolol, 50–200 mg) or ivabradine (5–15 mg) were administered, if necessary, targeting a heart rate of 60 beats per minute or less. Noncontrast-enhanced cardiac CT using a prospective 120-kV echocardiography-triggered high-pitch examination was routinely performed in all participants before CTA to assess CAC score according to the method described by Agatston et al (16). CAC score data were retrospectively retrieved from the Western Denmark Heart Registry (17). The extent of CAC in participants was graded as follows: none, 0; moderate, 1–399; high, 400–999; and extensive, 1000 or greater (18–20). Participants were administered sublingual nitroglycerine (0.40–0.80 mg) before undergoing CTA. Basic CTA acquisition parameters are provided in Table S2. On-site evaluation of CTA data was performed by 11 cardiologists (of whom six are coauthors: B.L.N., K.A.Ø., J.M.J., E.L.G., H.M., and N.P.R.S., each with 6–12 years of experience as CTA imaging physicians). Specifically, vessels of at least 2-mm diameter were assessed and the degree of stenosis (0%–29%, 30%–49%, 50%–69%, 70%–89%, and ≥90%) was graded visually. Obstructive coronary artery disease was defined as coronary stenosis of at least 50%. Stenosis location was defined as proximal or distal (21).

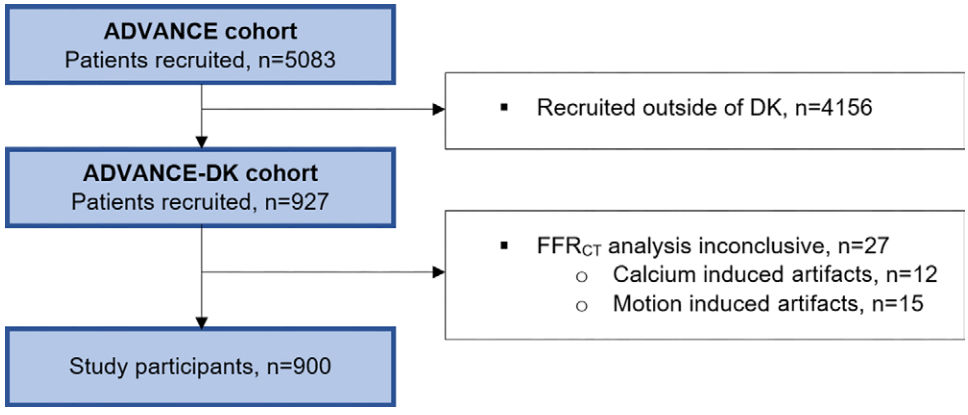

Figure 1: Flow diagram of participant selection. ADVANCE = Assessing Diagnostic Value of Noninvasive CT-FFR in Coronary Care, DK = Denmark, FFR_{CT} = coronary CT angiography–derived fractional flow reserve.

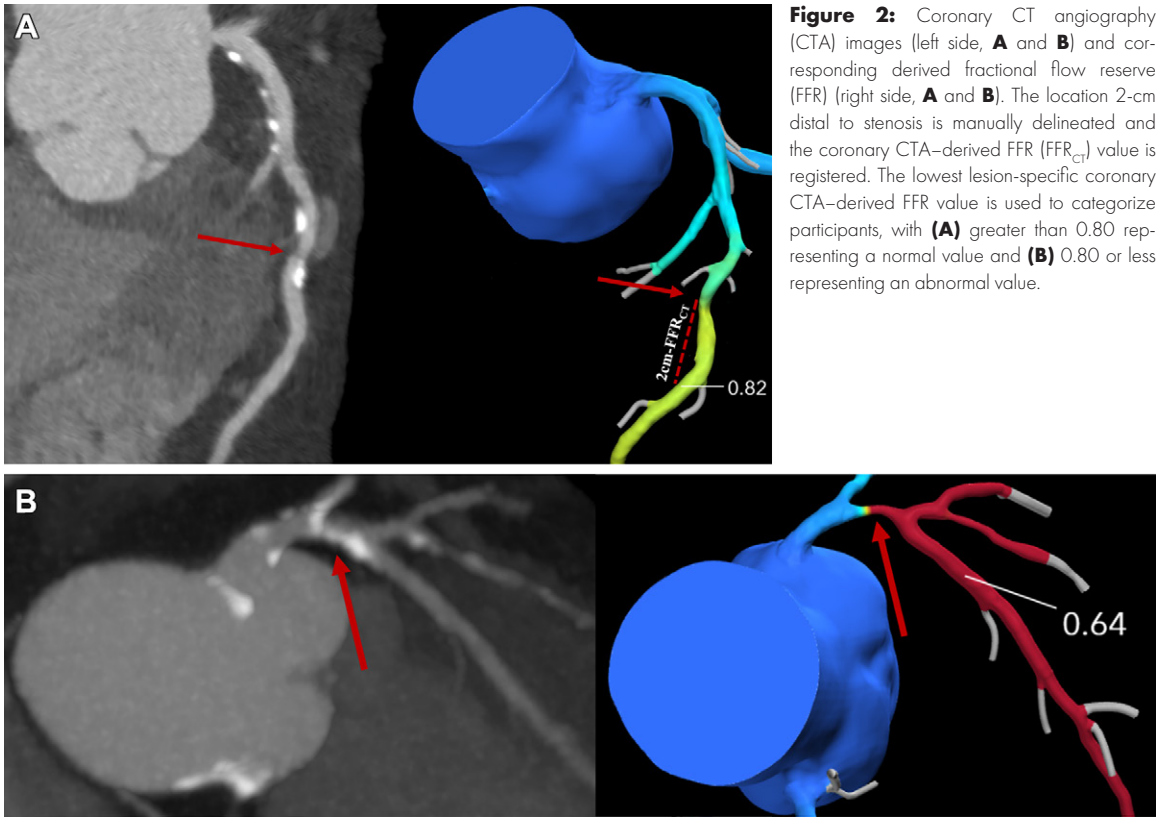

Figure 2: Coronary CT angiography (CTA) images (left side, **A** and **B**) and corresponding derived fractional flow reserve (FFR) (right side, **A** and **B**). The location 2-cm distal to stenosis is manually delineated and the coronary CTA–derived FFR (FFR_{CT}) value is registered. The lowest lesion-specific coronary CTA–derived FFR value is used to categorize participants, with **(A)** greater than 0.80 representing a normal value and **(B)** 0.80 or less representing an abnormal value.

Interpretation of Coronary CTA–derived FFR

Participant CTA data were transmitted to an independent core laboratory (HeartFlow) and coronary CTA–derived FFR analysis was performed by core laboratory personnel blinded to participant characteristics, treatment, and outcomes. The ADVANCE protocol did not dictate a specific coronary CTA–derived FFR interpretation algorithm. Therefore, in our study all stenoses were identified at CTA, and coronary CTA–derived FFR values were measured within manually delineated regions 2-cm distal to stenosis (Fig 2) (22). An abnormal coronary CTA–derived FFR test was defined as a coronary CTA–derived FFR value of 0.80 or less (22). This dichotomous lesion-specific coronary CTA–derived FFR interpretation strategy was chosen because of its enhanced diagnostic and prognostic performance compared with distal vessel coronary CTA–derived FFR interpretation and because it reflects clinical practice (23,24). If more than one stenoses were identified in the same vessel, the coronary CTA–derived FFR value corresponding to the most severe stenosis was registered. If stenoses were equally severe, the coronary CTA–derived FFR value for the most proximally located stenosis was registered. HeartFlow was not involved in planning, collecting, or analysis of the 3-year Danish ADVANCE registry follow-up data.

Clinical Outcomes and Follow-up

The primary end point in this study was a composite of all-cause death and nonfatal spontaneous myocardial infarction, and the secondary end point was composed of cardiovascular death and nonfatal spontaneous myocardial infarction. End points and information regarding invasive procedures and revascularization occurring during the entire follow-up were based on information from the Western Denmark Heart Registry (17) and hospital electronic patient records. An independent committee adjudicated clinical events according to the Academic Research Consortium-2 consensus document (25). All participants were followed for exactly 3 years from the index CTA examination or until death. The last follow-up was conducted on October 19, 2020. No participants were lost to follow-up.

Statistical Analysis

For demographic data, continuous variables were described using means ± SDs and compared using the two-sample *t* test. Categorical variables were described using counts and percentages and compared using χ^2 test or Fisher exact test as appropriate. Event rates were estimated using the one-sample binomial model, and event rates were compared between groups of participants with normal and abnormal coronary CTA–derived FFR using the relative risk and the hypothesis of no difference in event rates using the χ^2 or Fisher exact test as appropriate. CIs for the relative risk were termed nonassessable if less than four events occurred in either of the two comparison groups. Wilcoxon rank sum testing was performed to test for equality of medians for continuous data. Event rates as a function of time were estimated using the Kaplan-Meier method when the event included all-cause death and were estimated using the Aalen-Johansen method

when death was a competing risk for the event of interest and compared using both the log-rank test and Cox proportional hazards model. To reduce potential bias caused by confounding variables, propensity matching for the CAC score was used to match high-CAC participants with coronary CTA–derived FFR greater than 0.80 and 0.80 or less, after which occurrence of clinical end points, invasive procedures, and revascularization according to the coronary CTA–derived FFR result was assessed. Adjustment for degree of stenosis by CTA and CAC score was performed using a log-binomial regression model. Due to the limited number of primary events, it was not possible to obtain robust results from a binary logistic regression model with three or more explanatory variables (26). Therefore, we were unable to perform multivariable binary regression to model the event rate as a function of continuous variables including CAC score, degree of stenosis, or coronary CTA–derived FFR values. Diagnostic performance of baseline risk variables (diabetes, hypertension, dyslipidemia, and smoking), coronary stenosis at CTA, CAC score, and coronary CTA–derived FFR were assessed using receiver operating characteristic curves, and differences between areas under the receiver operating characteristic curve were evaluated using the DeLong method. Correlation assessments between categorical categories of CAC scores and end points, overall and in relation to coronary CTA–derived FFR test results, were performed using Spearman rank correlation. The primary analysis of the study was the comparison of primary end point rates in participants with normal and abnormal coronary CTA–derived FFR. $P < .05$ was considered to indicate statistical significance. False discovery rate using the Benjamin-Hochberg procedure was performed for all secondary analyses. For secondary analyses, the statistical analyses with $P < .03$ indicated statistical significance (discovery) at a false discovery rate of 5%. All statistical analyses were performed using software (Stata version 17.0, StataCorp; analyses performed by K.T.M., with 6 years of experience conducting statistical analysis, and E.P., with more than 40 years of experience conducting statistical analysis).

Table 1: Characteristics of Participants in the Danish ADVANCE Registry

Parameter	Total (n = 900)	Coronary CTA–derived FFR > 0.80 (n = 523)	Coronary CTA–derived FFR ≤ 0.80 (n = 377)	P Value
Demographics and risk factors				
Age (y)	64.4 ± 9.6	64.0 ± 9.6	65.0 ± 9.6	.10
Sex				
Male participants	582 (65)	318 (61)	264 (70)	.005
Female participants	318 (35)	205 (39)	113 (30)	.005
BMI (kg/m^2)	26.8 ± 4.1	27.0 ± 4.2	26.5 ± 3.9	.04
Diabetes	109 (12)	64 (12)	45 (12)	.92
Hypertension	469 (52)	278 (53)	191 (51)	.50
Dyslipidemia	428 (48)	239 (46)	189 (50)	.20
Ever smokers*	616 (68)	347 (66)	269 (71)	.13
Baseline symptoms†				.08‡
Typical angina§	279 (31)	144 (28)	135 (36)	
CCS grade I	42 (15)	25 (17)	17 (13)	
CCS grade II	219 (78)	113 (78)	106 (79)	.18‖
CCS grade III	18 (6)	6 (4)	12 (9)	
Atypical angina	349 (39)	210 (40)	139 (37)	
Noncardiac chest pain	127 (14)	83 (16)	44 (12)	
Dyspnea	138 (15)	82 (16)	56 (15)	
CAC score				< .001#
0	61 (7)	44 (8)	17 (5)	
1–399	445 (49)	297 (57)	148 (39)	
400–999	241 (27)	124 (24)	117 (31)	
≥1000	153 (17)	58 (11)	95 (25)	

Note.—Unless otherwise indicated, data are numbers of participants; data in parentheses are percentages. Mean data are ± SDs. The lowest lesion-specific coronary CT angiography (CTA)–derived fractional flow reserve (FFR) value was used to categorize participants, with greater than 0.80 representing a normal value and 0.80 or less representing an abnormal value. P values are a comparison between patients with coronary CTA–derived FFR less than or equal to 0.80 versus coronary CTA–derived FFR greater than 0.80. P values were calculated using the Fisher exact test and two sample t tests. ADVANCE = Assessing Diagnostic Value of Noninvasive CT-FFR in Coronary Care, BMI = body mass index, CCS = Canadian Cardiovascular Society grading of angina pectoris.

* Smoking, ever; current smokers and former smokers.

† Seven patients with unknown or no symptoms at baseline

‡ P value refers to difference between categories (typical, atypical, noncardiac, dyspnea) of baseline symptoms.

§ No participants were graded as CCS IV

‖ P value refers to difference between CCS classifications.

P value refers to difference between categories (0, 1–399, 400–999, and ≥1000) of CAC scores.

Results

Characteristics of Study Participants

The original ADVANCE study recruited 5083 patients, of whom 4156 were excluded from this study because they were recruited outside of Denmark (Fig 1). Of the remaining 927 participants who underwent CTA, 27 were excluded because of inconclusive coronary CTA–derived FFR analysis (12 for calcium-induced artifacts and 15 for motion-induced artifacts). Thus, 900 participants were

Table 2: Anatomic Characteristics in Participants Stratified by Coronary CT Angiography–derived Fractional Flow Reserve Result and Stenosis Extent

Parameter	Overall (n = 880)*	Coronary CTA–derived FFR > 0.80 (n = 512)	Coronary CTA–derived FFR ≤ 0.80 (n = 368)	P Value
Stenosis < 50%†	150	133	17	
LAD/LM‡	146 (97)	130 (98)	16 (94)	.39
Proximal‡	135 (90)	118 (89)	17 (100)	.22
CAC score	242 (92–543) [0–3235]	232 (96–533) [0–2471]	372 (92–721) [26–3235]	.26
Coronary CTA–derived FFR value	0.89 (0.85–0.93) [0.50–0.98]	0.90 (0.86–0.93) [0.81–0.98]	0.73 (0.72–0.76) [0.50–0.80]	
Stenosis ≥ 50%†	730	379	351	
LAD/LM‡	569 (78)	281 (74)	288 (82)	.01
Proximal‡	693 (95)	357 (94)	336 (95)	.40
CAC score	318 (71–742) [0–7070]	201 (42–507) [0–5164]	518 (112–973) [0–7070]	<.001
Coronary CTA–derived FFR value	0.82 (0.70–0.88) [0.50–0.98]	0.88 (0.85–0.91) [0.81–0.98]	0.70 (0.53–0.76) [0.50–0.80]	
Total				
CAC score	312 (80–732) [0–7070]	212 (53–533) [0–5164]	521 (115–1003) [0–7070]	<.001
Coronary CTA–derived FFR value	0.83 (0.72–0.89) [0.50–0.98]	0.88 (0.85–0.92) [0.81–0.98]	0.70 (0.55–0.76) [0.50–0.80]	

Note.—Unless otherwise indicated, data in parentheses are IQRs; data in brackets are ranges. Patients were categorized according to the most severe stenosis at CT angiography (CTA). The lowest lesion-specific coronary CTA–derived fractional flow reserve (FFR) value was used to categorize participants, with greater than 0.80 representing a normal value and 0.80 or less representing an abnormal value. P values are comparisons between patients with coronary CTA–derived FFR values of 0.80 or less versus coronary CTA–derived FFR values greater than 0.80. P values were calculated using the Fisher exact test and Wilcoxon rank sum testing. CAC = coronary artery calcification, LAD = left anterior descending coronary artery, LM = left main coronary artery.

* Data not shown for patients with degree of stenosis not evaluable at CTA (n = 20).

† Data are numbers of patients.

‡ Data are numbers of patients; data in parentheses are percentages.

included in the current study. The frequency of male participants was higher in the abnormal coronary CTA–derived FFR group (264 of 377; 70.0%) compared with the normal coronary CTA–derived FFR group (318 of 523; 60.8%; P = .005, but no other differences in demographics were observed between groups (Table 1). No CAC was observed in 61 of 900 (6.8%) participants, whereas moderate and high CAC scores were observed in 445 of 900 (49.4%) and 394 of 900 (43.8%) participants, respectively (Table 1). Extensive CAC was observed in 153 of 394 (38.8%) participants with high CAC scores. Coronary stenosis of at least 50% was present in 730 of 900 (81.1%) participants (Table 2), of whom 252 (34.5%) had stenosis of at least 70%. Comparison between baseline characteristics of participants in this study versus patients in the full ADVANCE cohort are in Table S3. Information on medication at the end of follow-up is in Table S4.

Relationship between Anatomic and Physiologic Characteristics

In participants with degree of stenosis of at least 50%, 569 of 730 (77.9%) stenoses were present in the left anterior descending coronary artery and/or left main coronary artery. Participants with abnormal coronary CTA–derived FFR results more frequently had stenoses of at least 50% in the left anterior descending coronary artery and/or left main coronary artery compared with those with normal coronary CTA–derived FFR results (288 of 351 [82.0%] vs 281 of 379 [74.1%]; P = .01). Additionally, higher CAC scores were observed in those with an abnormal versus normal coronary CTA–derived FFR test result (mean score, 518 vs 201, respectively; P < .001) (Table 2). Physiologic characteristics stratified by CAC score classifications are shown in Table S5. In participants with degree of stenosis of at least 50%, a negative correlation was demonstrated between CAC severity (CAC score, 0; 1–399; 400–999; and ≥1000) and coronary CTA–derived FFR values (Spearman ρ = −0.25; P < .001) (Table S5).

Primary and Secondary Outcomes in All Participants

All-cause death occurred in 25 of 900 (2.8%) participants and myocardial infarction occurred in 12 of 900 (1.3%) participants, resulting in a total of 37 of 900 (4.1%) primary end point events. A total of 23 of 900 (2.5%) secondary end point events occurred: cardiovascular death in 11 of 900 (1.2%) participants and myocardial infarction in 12 of 900 (1.3%) participants. None of the participants with nonfatal myocardial infarction died during follow-up. In participants with a primary or secondary end point, coronary CTA–derived FFR analysis was successful in 36 of 37 (97%) and 22 of 23 (96%) participants, respectively. The primary end point occurred in 11 of 523 (2.1%) participants with normal coronary CTA–derived FFR values and in 25 of 377 (6.6%) participants with abnormal coronary CTA–derived FFR values (relative risk, 3.2 [95% CI: 1.6, 6.3; P < .001]; hazard ratio, 3.2 [95% CI: 1.6, 6.6; P = .001]) (Table 3, Fig 3). The

Table 3: Clinical End Points and Invasive Procedures in Participants Stratified by Coronary CT Angiography–derived Fractional Flow Reserve Result

Parameter	Coronary CTA–derived FFR > 0.80 (*n* = 523)	Coronary CTA–derived FFR ≤ 0.80 (*n* = 377)	*P* Value
Total			
Primary end point	11 (2.1) [1.1, 3.7]	25 (6.6) [4.3, 9.6]	.001
Secondary end point	3 (0.6) [0.1, 1.7]	19 (5.0) [3.1, 7.8]	<.001
All-cause death	10 (1.9) [0.9, 3.5]	14 (3.7) [2.0, 6.2]	.14
Cardiovascular death	2 (0.4) [0.0, 1.4]	8 (2.1) [0.9, 4.1]	.02
Spontaneous myocardial infarction	1 (0.2) [0.0, 1.1]	11 (2.9) [1.5, 5.2]	<.001
Invasive coronary angiography	183 (35.0) [31, 39]	339 (89.9) [86, 93]	<.001
Revascularization	21 (4.0) [3, 6]	243 (64.5) [59, 69]	<.001
CAC score < 400*	341	165	
Primary end point	7 (2.0) [0.8, 4.2]	6 (3.6) [1.3, 7.8]	.37
Secondary end point	2 (0.6) [0.1, 2.1]	5 (3.0) [1.0, 6.9]	.04
All-cause death	6 (1.8) [0.6, 3.8]	3 (1.8) [0.4, 5.2]	>.99
Cardiovascular death	1 (0.3) [0.0, 1.6]	2 (1.2) [0.1, 4.3]	.25
Spontaneous myocardial infarction	1 (0.3) [0.0, 1.6]	3 (1.8) [0.4, 5.2]	.10
Invasive coronary angiography	91 (26.7) [22, 32]	143 (86.7) [80, 91]	<.001
Revascularization	13 (3.8) [2.0, 6.4]	107 (64.8) [57, 72]	<.001
CAC score ≥ 400*	182	212	
Primary end point	4 (2.2) [0.6, 5.5]	19 (9.0) [5.5, 13.6]	.004
Secondary end point	1 (0.5) [0.0, 3.0]	14 (6.6) [3.7, 10.8]	.001
All-cause death	4 (2.2) [0.6, 5.5]	11 (5.2) [2.6, 9.1]	.19
Cardiovascular death	1 (0.5) [0.0, 3.0]	6 (2.8) [1.0, 6.1]	.13
Spontaneous myocardial infarction	0 (0) [NA]	8 (3.8) [1.6, 7.3]	.01
Invasive coronary angiography	92 (50.5) [43, 58]	196 (92.3) [88, 96]	<.001
Revascularization	8 (4.4) [2, 8]	136 (64.2) [57, 71]	<.001

Note.—Data are numbers of participants; data in parentheses are percentages and data in brackets are 95% CIs. The lowest lesion-specific coronary CT angiography (CTA)-derived fractional flow reserve (FFR) value was used to categorize participants: greater than 0.80 represents a normal value and 0.80 or less represents an abnormal value. The primary end point was a composite of all-cause death and spontaneous myocardial infarction; the secondary end point was a composite of cardiovascular death and spontaneous myocardial infarction. *P* values were calculated using the Fisher exact test. CAC = coronary artery calcification, NA = not assessable.

* Data are numbers of participants.

secondary end point occurred in three of 523 (0.6%) participants with normal coronary CTA–derived FFR values and 19 of 377 (5.0%) participants with abnormal coronary CTA–derived FFR values (relative risk, 8.8 [95% CI: nonassessable; *P* = .001]; hazard ratio, 9.0 [95% CI: nonassessable; *P* < .001]) (Table 3, Fig 3). The observed increased risk of adverse outcomes for participants with coronary CTA–derived FFR of 0.80 or less versus greater than 0.80 persisted after adjustment for degree of stenosis (<50% or ≥50%) and CAC score (<400 or ≥400) (primary end point adjusted relative risk, 2.5 [95% CI: 1.2, 5.2; *P* = .02]; secondary end point adjusted relative risk, 8.0 [95% CI: 2.1, 30.2; *P* = .002]).

Primary and Secondary Outcomes in Participants with CAC Scores of 400 or Greater

Primary and secondary outcome event rates were more frequent in participants with higher CAC scores (*P* = .002 and *P* = .004, respectively; Figs S1, S2). In participants with CAC scores that were 400 or greater, those with an abnormal coronary CTA–derived FFR test result showed an increased event rate for the primary end point (19 of 212; 9.0%) compared with those with a normal coronary CTA–derived FFR result (four of 182; 2.2%) (relative risk, 4.1 [95% CI: 1.4, 11.8; *P* = .001]; hazard ratio, 4.2 [95% CI: 1.4, 12.4; *P* = .009]). Higher event rates for the secondary end point were also observed in participants with CAC scores of 400 or greater and abnormal coronary CTA–derived FFR (6.6%; 14 of 212) compared with those with CAC scores of 400 or greater but normal coronary CTA–derived FFR (0.5%; one of 182) (relative risk, 12.0 [95% CI: nonassessable; *P* = .01]; hazard ratio, 12.4 [95% CI: nonassessable; *P* = .02]) (Table 3, Fig 3). Among participants with normal coronary CTA–derived FFR with CAC scores less than 400 and CAC scores of 400 or greater, respectively, the 3-year risk of the primary end point (seven of 341 [2.0%] vs four of 182 [2.2%]; *P* = .91), secondary end point (two of 341 [0.6%] vs one of 182 [0.5%]; *P* = .96), or revascularization (13 of 341 [3.8%] vs eight of 182 [4.4%]; *P* = .75) was similar (Table 3).

Assessing the Prognostic Value of Coronary CTA–derived FFR Values for Discriminating Clinical End Points

Receiver operating characteristic curve analysis showed that the addition of coronary CTA–derived FFR to baseline risk variables

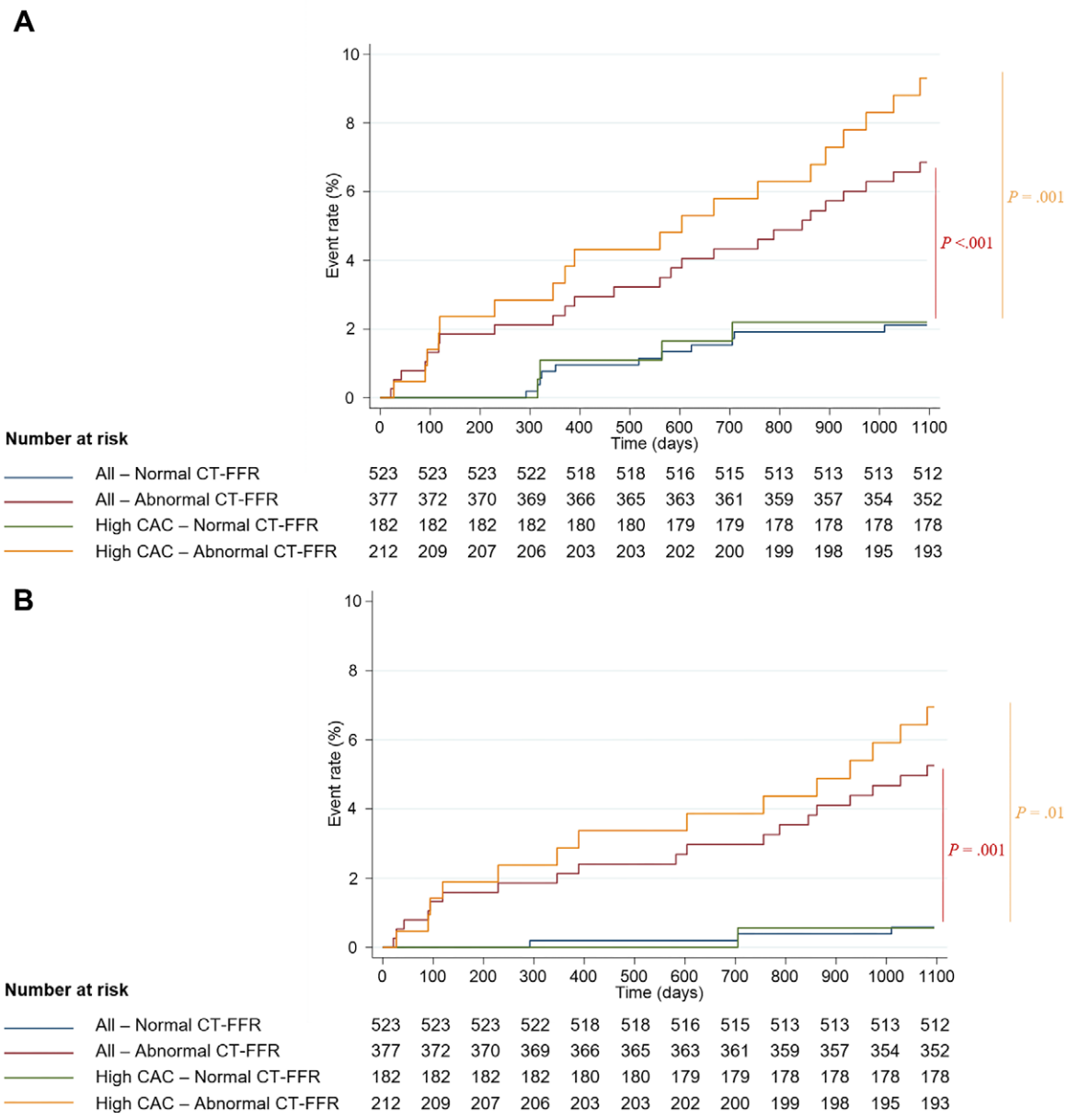

Figure 3: Kaplan-Meier Curves show the primary and secondary study end points in all participants (blue and red lines) and in those with a coronary artery calcium (CAC) score of 400 or greater (green and orange lines), stratified by coronary CT angiography (CTA)–derived fractional flow reserve (FFR; CT-FFR) result. Compared with participants with normal coronary CTA–derived FFR results (value, >0.80), participants with abnormal coronary CTA–derived FFR results (value, ≤0.80) had a higher occurrence of events. This included **(A)** the primary end point, a composite of all-cause death and spontaneous myocardial infarction (log-rank test $P < .001$ and $P = .001$, respectively), and **(B)** the secondary end point, a composite of cardiovascular death and spontaneous myocardial infarction (log-rank test $P = .001$ and $P = .01$, respectively).

(diabetes, hypertension, dyslipidemia, and smoking), CAC score, and degree of stenosis improved the overall discrimination of the primary and secondary end points, resulting in an area under the receiver operating characteristic curve of 0.74 versus 0.62 ($P < .001$) and an area under the receiver operating characteristic curve of 0.81 versus 0.66 ($P = .02$), respectively (Fig 4). Propensity matching in participants with high CAC demonstrated a higher incidence of both composite end points for participants with abnormal versus normal coronary CTA–derived FFR results (15 of 182 [8.2%] vs four of 182 [2.2%] [$P = .01$] and 11 of 182 [6.0%] vs one of 182 [0.5%] [$P = .003$], respectively) (Table S6). In the matched sample, the group with abnormal coronary CTA–derived FFR compared with normal coronary CTA–derived FFR results had a higher frequency of male participants (138 of 182 [75.8%] vs 120 of 182 [65.9%]; $P = .03$), a lower mean body mass index (26.4 kg/m^2 ± 3.8 [SD] vs 27.5 kg/m^2 ± 4.5; $P = .01$), and a lower frequency of hypertension (102 of 182 [56.0%] vs 122 of 182 [67.0%]; $P = .03$), respectively. No other differences in risk factors were observed between groups (Table S6). In the subgroup of participants with extensive CAC, an abnormal versus a normal coronary CTA–derived FFR result was associated with an almost twofold risk of the primary end point and more than

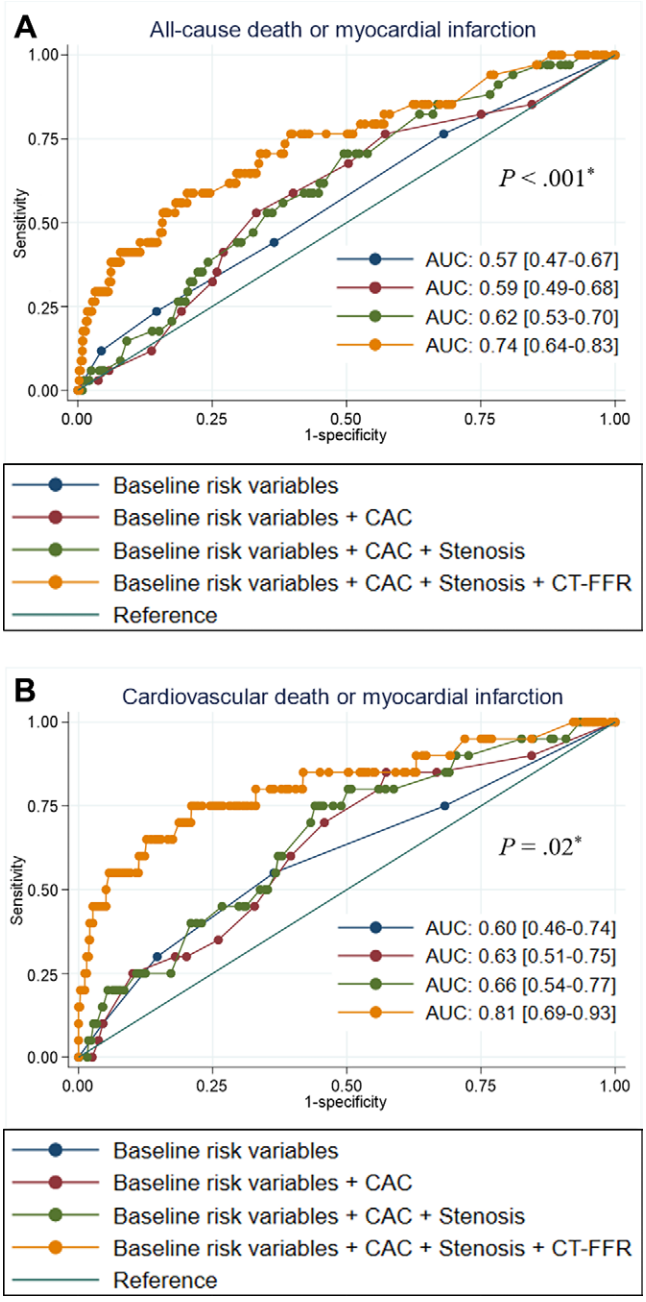

Figure 4: Graphs show performance evaluation of models created using combinations of baseline participant characteristics for discriminating clinical outcomes. Receiver operating characteristic curves show that the model that included baseline risk variables (diabetes, hypertension, dyslipidemia, and ever-smoker), coronary artery calcium (CAC) score categories, coronary stenosis extent category as assessed at coronary CT angiography (CTA), and dichotomous CTA-derived fractional flow reserve (FFR; CT-FFR) results (normal, >0.80; abnormal, ≤0.80) performed best for discriminating **(A)** primary end point events (area under the receiver operating characteristic curve [AUC], 0.74; DeLong $P < .001$) and **(B)** secondary end point events (AUC, 0.81; method by DeLong $P < .02$). * *P* values represent the difference between the AUC for baseline risk variables, CAC, and stenosis versus baseline risk variables, CAC, stenosis, and CT-derived FFR.

fourfold risk of the secondary end point, albeit these were not statistically significant (Table S7). Details pertaining to participants undergoing coronary CTA–derived FFR testing who had subsequent myocardial infarction are presented in Table S8.

Discussion

The prognostic value of coronary CT angiography (CTA)–derived fractional flow reserve (FFR) beyond 1-year outcomes and in patients with high levels of coronary artery calcium (CAC) is uncertain. Our study evaluated clinical outcomes across a 3-year period in participants with new-onset stable angina pectoris and coronary stenosis at CTA who underwent coronary CTA–derived FFR testing. In participants with abnormal compared with normal coronary CTA–derived FFR results, the risk of all-cause death or spontaneous myocardial infarction was 3.2-fold increased (95% CI: 1.6, 6.3; $P < .001$) and the risk of cardiovascular death or spontaneous myocardial infarction was 8.8-fold increased (95% CI: nonassessable; $P = .001$). In participants with high CAC scores, a normal coronary CTA–derived FFR result was associated with a low rate of all-cause death or spontaneous myocardial infarction (2.2%; four of 182) and cardiovascular death or spontaneous myocardial infarction (0.5%; one of 182), whereas an abnormal coronary CTA–derived FFR result was associated with a 4.1-fold (95% CI: 1.4, 11.8; $P = .001$) and 12.0-fold (95% CI: nonassessable; $P = .01$) increased risk, respectively. The addition of coronary CTA–derived FFR to prognostic models with baseline risk variables (diabetes, hypertension, dyslipidemia, and smoking), CAC score, and degree of stenosis led to improved discrimination of participant clinical outcomes (area under the receiver operating characteristic curve for all-cause death or myocardial infarction, 0.74 vs 0.62 [$P < .001$]; area under the receiver operating characteristic curve for cardiovascular death or myocardial infarction, 0.81 vs 0.66 [$P = .02$]).

Previous single-center real-world registry prospective trials have reported the prognostic value of coronary CTA–derived FFR testing in patients with stable angina and coronary artery disease (8–13). However, these studies applied different definitions of clinical outcomes than our study and most had varying follow-up periods of approximately 1 year (8,9,13). Long-term follow-up (median, 4.7 years) was accomplished in one study (11) based on 206 patients, which found that a dichotomous coronary CTA–derived FFR interpretation model was a predictor of long-term composite end points composed of all-cause death and/or cardiac death, nonfatal myocardial infarction, and any revascularization. Of note, revascularization was the main event observed in all previous studies (composite end points also including all-cause death and myocardial infarction) (8–10,12), which may have resulted in confounding because revascularization is the less bias-resistant of the reported end points (12). Therefore, revascularization was not considered to be part of the composite outcomes in our study. A recent meta-analysis (12) including 5460 patients analyzed outcome measures (all-cause death or myocardial infarction) during 12 months of follow-up and demonstrated lower rates of adverse events in patients with a normal coronary CTA–derived FFR result compared with an abnormal coronary CTA–derived FFR result (0.6% vs 1.4%; relative risk, 2.31; $P = .005$). Those results agree with the results from our study.

In patients with high CAC scores (≥400), the performance of coronary CTA–derived FFR in diagnosing hemodynamically significant stenosis, with FFR as the reference, has been shown to be better than that of CTA alone (6,23). CAC is an important predictor of adverse cardiovascular events, independently

of stenosis severity by CTA and adverse plaque characteristics (27,28). However, the majority of studies (8–11,13,29) assessing the prognostic value of coronary CTA–derived FFR did not report CAC scores, which may have confounded the observed differences in clinical outcomes. One single-center observational study (7) composed of 241 patients reported CAC scores. The study found that among patients with high CAC scores (≥ 400), an abnormal versus a normal coronary CTA–derived FFR result was associated with a nonsignificant twofold increase in the risk of all-cause death, myocardial infarction, hospitalization for unstable angina, or unplanned revascularization during a median follow-up period of 2.2 years. Our study provides evidence for the prognostic potential of coronary CTA–derived FFR in patients with high CAC scores. Specifically, in participants with CAC scores of at least 400, those with normal coronary CTA–derived FFR results had a lower frequency of adverse cardiac events at 3-years follow up (cardiovascular deaths, 0.5% [one of 182]; spontaneous myocardial infarctions, 0% [0 of 182]) compared with those with abnormal coronary CTA–derived FFR results (cardiovascular deaths, 2.8% [six of 212]; spontaneous myocardial infarctions, 3.8% [eight of 212]).

Our study had several limitations. First, this was a substudy of the nonrandomized ADVANCE cohort, in which clinical management decisions were at the discretion of the local treating physicians and were subject to potential selection bias. Second, our findings may have lacked generalizability to other healthcare settings using alternative CT scanning systems or patient categories. Third, data regarding medication treatment duration was unknown. Fourth, coronary CTA–derived FFR was unable to be analyzed in all patients because of inadequate CTA image quality (2.9% coronary CTA–derived FFR reject rate). Fifth, end point information from the Western Denmark Heart Registry and hospital records may not have contained information regarding nonfatal myocardial infarctions occurring outside of Denmark. Finally, the primary and secondary end points were composites, which may have introduced bias (30).

In conclusion, participants with new-onset stable angina pectoris who had normal coronary CT angiography (CTA)–derived fractional flow reserve (FFR) values showed a reduced risk of adverse outcomes at 3-year follow-up compared with those with abnormal coronary CTA–derived FFR test results. This was observed in the overall cohort and in participants with high coronary artery calcium scores (≥400). Future studies are needed to assess the clinical utility of coronary CTA–derived FFR relative to the total atherosclerotic burden.

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Data sharing: All data generated or analyzed during the study are included in the published paper.

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