Radiology: Cardiothoracic Imaging

ORIGINAL RESEARCH

Impact of Coronary CT Angiography–derived Fractional Flow Reserve on Downstream Management and Clinical Outcomes in Individuals with and without Diabetes

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See also the commentary by Ghoshhajra in this issue.

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Purpose: To compare the clinical use of coronary CT angiography (CCTA)–derived fractional flow reserve (FFR) in individuals with and without diabetes mellitus (DM).

Materials and Methods: This secondary analysis included participants (enrolled July 2015 to October 2017) from the prospective, multicenter, international The Assessing Diagnostic Value of Noninvasive CT-FFR in Coronary Care (ADVANCE) registry (ClinicalTrials.gov identifier, NCT 02499679) who were evaluated for suspected coronary artery disease (CAD), with one or more coronary stenosis ≥30% on CCTA images, using CT-FFR. CCTA and CT-FFR findings, treatment strategies at 90 days, and clinical outcomes at 1-year follow-up were compared in participants with and without DM.

Results: The study included 4290 participants (mean age, 66 years ± 10 [SD]; 66% male participants; 22% participants with DM). Participants with DM had more obstructive CAD (one or more coronary stenosis ≥50%; 78.8% vs 70.6%, $P < .001$), multivessel CAD (three-vessel obstructive CAD; 18.9% vs 11.2%, $P < .001$), and proportionally more vessels with CT-FFR ≤ 0.8 (74.3% vs 64.6%, $P < .001$). Treatment reclassification by CT-FFR occurred in two-thirds of participants which was consistent regardless of the presence of DM. There was a similar graded increase in coronary revascularization with declining CT-FFR in both groups. At 1 year, presence of DM was associated with higher rates of major adverse cardiovascular events (hazard ratio, 2.2; 95% CI: 1.2, 4.1; $P = .01$). However, no between group differences were observed when stratified by stenosis severity (<50% or ≥50%) or CT-FFR positivity.

Conclusion: Both anatomic CCTA findings and CT-FFR demonstrated a more complex pattern of CAD in participants with versus without DM. Rates of treatment reclassification were similar regardless of the presence of DM, and DM was not an adverse prognostic indicator when adjusted for diameter stenosis and CT-FFR.

Clinical trial registration no. NCT 02499679

Supplemental material is available for this article.

The prevalence, extent, severity, and progression of coronary artery disease (CAD) is worse in individuals with diabetes mellitus (DM) (1–3) and is a major contributor to higher risk of heart disease (4). Despite the recognized elevated atherosclerotic cardiovascular risk associated with CAD, management of the disease in people with DM remains challenging. The control of aggressive risk factors forms the mainstay of

Abbreviations

ADVANCE = The Assessing Diagnostic Value of Noninvasive CT-FFR in Coronary Care, CABG = coronary artery bypass grafting, CAD = coronary artery disease, CCTA = coronary CT angiography, CT-FFR = CT fractional flow reserve, DM = diabetes mellitus, MACE = major adverse cardiovascular events, MI = myocardial infarction, OMT = optimal medical therapy, PCI = percutaneous coronary intervention

Summary

Coronary CT angiography–derived fractional flow reserve identified a more complex pattern of coronary artery disease in individuals with versus without diabetes mellitus, but maintained similarly safe treatment reclassification rates between both groups.

Key Points

- In a large, multicenter international registry of individuals with stable chest pain evaluated with coronary CT angiography and CT fractional flow reserve, a more complex pattern of coronary artery disease was identified in participants with diabetes mellitus (DM). Compared with participants without DM, higher rates of obstructive coronary artery disease (78.8% vs 70.6%, $P < .001$), multivessel coronary artery disease (18.9% vs 11.2%, $P < .001$), and CT fractional flow reserve positivity (74.3% vs 64.8%, $P < .001$) were identified in those with DM.
- Rates of treatment reclassification were similar regardless of the presence of DM, and DM was not an adverse prognostic indicator when adjusted for diameter stenosis and CT fractional flow reserve findings.

Keywords

Fractional Flow Reserve, CT Angiography, Diabetes Mellitus, Coronary Artery Disease

treatment and has been shown to lower rates of atherosclerotic cardiovascular events (5,6) but is difficult to achieve in real-world clinical practice. Rates of atherosclerotic cardiovascular events remain unacceptably high in people with DM, highlighting a need for patient-specific diagnosis and treatment strategies targeted at individuals' risk factors and CAD profiles.

When compared with optimal medical therapy (OMT) alone, invasive fractional flow reserve (FFR)–guided revascularization of CAD is superior to anatomic-guided revascularization, leading to lower rates of repeat revascularization and myocardial infarction (MI) (7). One study showed that this technique safely and effectively guided treatment decisions around suitability for revascularization in patients with DM, reclassifying treatment strategy in almost half (41%) of patients (8). Noninvasive assessment of FFR is now possible with coronary CT angiography (CCTA). This correlates well with invasive measures and improves detection of flow-limiting coronary lesions (9). Moreover, patients with a negative CT-FFR have lower rates of revascularization, MI, and cardiovascular death than those with a positive CT-FFR (10). As with invasive FFR, however, the comparable clinical use of CT-FFR in guiding treatment decisions in individuals with versus without DM remains unknown.

This study aimed to assess whether CT-FFR as an adjunct to CCTA would change the management of CAD to a similar extent in individuals with and without DM.

Materials and Methods

The Assessing Diagnostic Value of Noninvasive CT-FFR in Coronary Care (ADVANCE) registry was sponsored by HeartFlow via individual clinical study agreements with each enrolling institution and with the Duke Clinical Research Institute for Core Laboratory activities and Clinical Event Committee for adjudication of adverse events. All data in the study were held by the authors, and data analysis, reporting, and submission were performed independent of the sponsor. This study complied with the Declaration of Helsinki, with each participating institution acquiring local institutional review board approval and all participants providing written informed consent.

Study Participants

This study used data from the ADVANCE registry (ClinicalTrials.gov identifier, NCT 02499679), an international multicenter prospective cohort study designed to evaluate the real-world utility and clinical outcomes of CT-FFR–guided treatment in patients diagnosed with CAD across 38 sites in North America, Europe, and Japan.

The study design and rationale have been previously described in detail (11). In brief, the ADVANCE registry recruited stable, symptomatic patients who underwent CCTA for evaluation of CAD and were subsequently found to have coronary stenosis ≥30% at imaging review. Further inclusion criteria for enrollment included the following: *(a)* over 18 years old, *(b)* able to provide informed consent, and *(c)* met eligibility criteria for CT-FFR analysis based on CAD severity. Individuals were excluded if any of the following were met: *(a)* no CAD on CCTA images; *(b)* uninterpretable CCTA image; *(c)* active, serious, life-threatening disease with a life expectancy of <1 year adjudicated by a clinician; or *(d)* unable to meet follow-up requirements. Individuals whose CCTA images were rejected from CT-FFR analysis, typically related to image quality, were also excluded.

Participant demographics, cardiovascular risk factors, and angina status were collected for each participant at time of enrollment. Additionally, baseline antihyperglycemic treatments were collected from those with DM, categorized as follows: diet-control, oral hypoglycemic agent(s) only, or insulin-treated.

CCTA and CT-FFR

Acquisition of CCTA images was performed according to current Society of Cardiovascular Computed Tomography guidelines (12). CCTA images were acquired with ≥64–detector row scanners following administration of sublingual nitroglycerin while targeting a heart rate < 60 beats per minute, with β-blocker usage at the discretion of the supervising physician. The presence of coronary stenosis was then assessed in all vessels ≥ 2 mm, with stenosis severity dichotomized as anatomically obstructive or nonobstructive, defined as ≥50% degree of stenosis or <50% degree of stenosis, respectively. Among those with obstructive CAD, the affected epicardial vessels were recorded to further characterize the extent and location of disease. In participants with a history of previous percutaneous coronary intervention (PCI), CT-FFR analysis, when required, was performed only in vessels with no coronary stents.

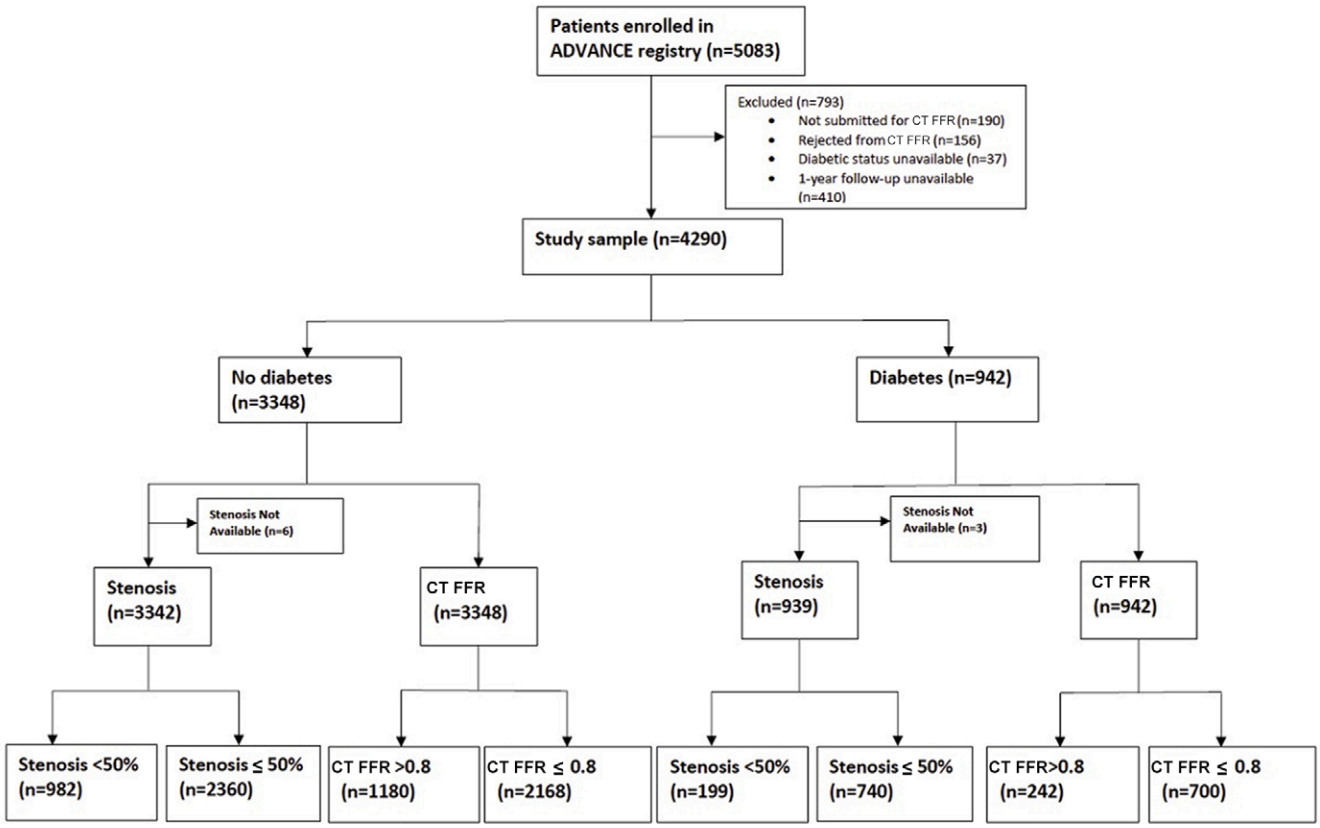


Figure 1: Flowchart shows summary of included participants. ADVANCE = Assessing Diagnostic Value of Noninvasive CT-FFR in Coronary Care, CT-FFR = CT fractional flow reserve.

The decision to submit participants for CT-FFR analysis was directed by site investigators based on CCTA findings, with a recommendation to consider CT-FFR in cases with 30%–90% diameter stenosis. CT-FFR analysis was performed by HeartFlow as previously described, with results made available within 48 hours to guide treatment decisions (13). Participants were evaluated for their lowest poststenotic CT-FFR value on a per-vessel basis. Minimum CT-FFR values were then recorded for each participant based on the presence of CT-FFR positivity for stenosis-specific ischemia, defined as ≤0.80, and the number of epicardial vessels affected. The Duke Clinical Research Institute acted as a core laboratory, analyzing all CCTA and CT-FFR study data in a blinded manner.

Treatment Strategies and Clinical Outcomes

Site investigators reported an initial management plan and treatment strategy based on the CCTA findings alone. Once CT-FFR findings were available, investigators were instructed to redetermine their treatment strategies based on the new combined information incorporating both the CCTA and CT-FFR results. Actual treatment received by each participant was reported at 90-day follow-up and recorded in the registry as OMT with or without PCI or coronary artery bypass grafting (CABG). Clinical outcomes were then adjudicated by a blinded clinical events committee at the Duke Clinical Research Institute through 1-year follow-up. Clinical events of interest included major adverse cardiovascular events (MACE) (death, MI, and unplanned hospitalization for acute coronary syndrome leading to urgent revascularization cardiovascular death, all-cause mortality, nonfatal MI, and unplanned hospitalization for acute coronary syndrome leading to urgent revascularization).

Statistical Analysis

Participants within the registry were grouped by DM status, as present or absent. Participant characteristics, CCTA and CT-FFR data, treatment strategies, and clinical outcomes are presented with counts and percentages for categorical variables and means and SDs for continuous variables. Between-group comparisons were performed using generalized linear models, with adjustment for age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared), and cardiovascular risk factors. CCTA, CT-FFR, treatment, and outcome data were compared between groups stratified by stenosis severity and CT-FFR findings, also with adjustment for age, sex, body mass index, and cardiovascular risk factors. The main effects and interactions between DM status, stenosis severity, and CT-FFR positivity on treatment strategy with adjustment for the same covariates (age, sex, body mass index, and cardiovascular risk factors) were also tested. Reclassification rates of the coronary management plans before and after incorporation of the combined CCTA and CT-FFR findings were calculated. Survival analysis was undertaken for each clinical outcome comparing participants with and without DM using a Cox proportional hazards model adjusted for the same factors. Survival curves were also produced using a Kaplan-Meier model to visualize the relationship between diabetic status and

Table 1: Baseline Characteristics and Coronary CT Angiographic and CT Fractional Flow Reserve Findings of Included Participants

Characteristic	All Participants (n = 4290)	No Diabetes (n = 3348)	Diabetes (n = 942)	P Value
Age (y) (mean ± SD)	66.1 ± 10.2	65.8 ± 10.3	67.2 ± 9.7	<.001
Male participants	2848 (66.4)	2207 (65.9)	641 (68.1)	.22
Body mass index*	26.3 (4.7)	26.1 (4.6)	26.9 (5.1)	<.001
Diabetes treatment				
Diet controlled	NA	NA	306 (32.5)	NA
Oral hypoglycemic agent(s)	NA	NA	666 (70.7)	NA
Insulin	NA	NA	184 (19.5)	NA
Comorbidities				
Hypertension	2580 (60.3)	1864 (55.8)	716 (76.3)	<.001
Hyperlipidemia	2536 (59.6)	1861 (56.2)	675 (72.0)	<.001
Prior PCI	146 (3.4)	95 (2.8)	51 (5.4)	<.001
Smoking history				
Never	1792 (41.8)	1411 (42.1)	381 (40.5)	.31
Former	1490 (34.7)	1148 (34.3)	342 (36.3)	NA
Current	714 (16.6)	550 (16.4)	164 (17.4)	NA
Angina status				
Typical	934 (21.8)	732 (21.9)	202 (21.4)	<.001
Atypical	1548 (36.1)	1236 (36.9)	312 (33.1)	NA
Noncardiac pain	276 (6.4)	229 (6.8)	47 (5.0)	NA
Dyspnea	434 (10.1)	344 (10.3)	90 (9.6)	NA
Unknown or none	1098 (25.6)	807 (24.1)	291 (30.9)	NA
CCTA-derived coronary stenosis				
Nonobstructive (all vessels < 50%)	1181 (27.6)	982 (29.4)	199 (21.2)	<.001
Obstructive (any vessel ≥ 50%)	3100 (72.4)	2360 (70.6)	740 (78.8)	<.001
Single vessel	1909 (61.6)	1504 (63.7)	405 (54.7)	<.001
Two vessel	787 (25.4)	592 (25.1)	195 (26.4)	.49
Three vessel	404 (13.0)	264 (11.2)	140 (18.9)	<.001
≥50% stenosis				
LAD	2480 (57.8)	1881 (56.2)	599 (63.6)	<.001
LCX	1049 (24.5)	739 (22.1)	310 (32.9)	<.001
RCA	1166 (27.2)	860 (25.7)	306 (32.5)	<.001
LMS	121 (2.8)	93 (2.8)	28 (3.0)	.75
CT-FFR				
CT-FFR > 0.8 (all)	1422 (33.2)	1180 (35.2)	242 (25.7)	<.001
CT-FFR ≤ 0.8 (any vessel)	2868 (66.9)	2168 (64.8)	700 (74.3)	<.001
CT-FFR ≤ 0.8				
Single vessel	1614 (56.3)	1285 (59.3)	329 (47.0)	<.001
Two vessel	867 (30.2)	631 (29.1)	236 (33.7)	.021
Three vessel	387 (13.5)	252 (11.6)	135 (19.3)	<.001

Note.—Between-group coronary CT angiography (CCTA) and CT fractional flow reserve (CT-FFR) comparisons are adjusted for age, sex, body mass index, smoking status, hypertension, and hyperlipidemia. Unless otherwise noted, data are expressed as numbers of participants with percentages in parentheses. LAD = left anterior descending artery, LCX = left circumflex artery, LMS = left main stem artery, NA = not applicable, PCI = percutaneous coronary intervention, RCA = right coronary artery.
* Calculated as weight in kilograms divided by height in meters squared.

clinical outcome. An additional survival analysis was undertaken within the DM group to explore associations between clinical outcomes and DM treatment. The primary study end point was CAD treatment reclassification rate before and after incorporation of combined CCTA and CT-FFR findings. Key secondary end points were management strategy and clinical

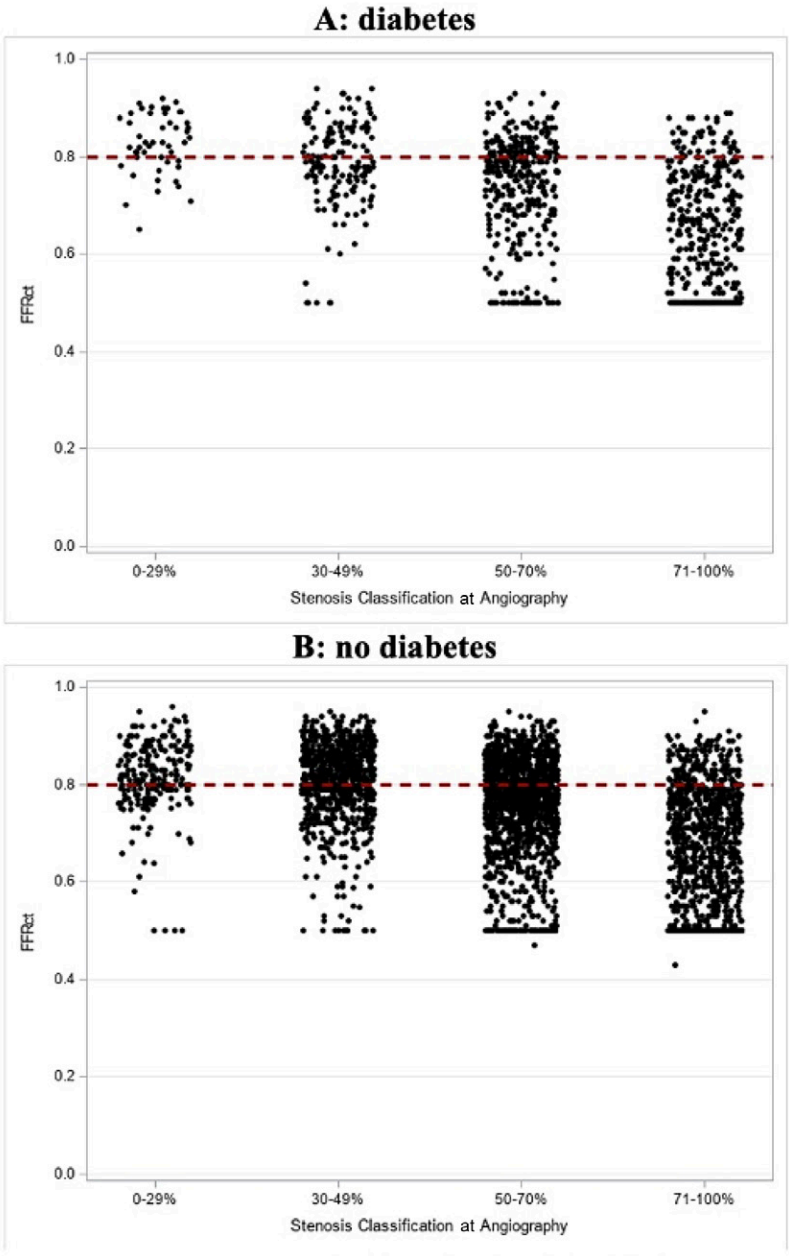


Figure 2: Scatterplots illustrate the relationship between stenosis classification and CT fractional flow reserve (FFR) in participants **(A)** with and **(B)** without diabetes.

outcomes stratified by stenosis severity and CT-FFR findings. All statistical analysis was performed by an independent study statistician using SAS software 9.2 (SAS Institute). *P* values < .05 were considered statistically significant.

Results

Participant Characteristics

An overview of included participants is displayed in Figure 1. In total, 5083 participants were enrolled in the ADVANCE registry. Of these, 4893 (96.2%) participants were submitted by investigators for CT-FFR analysis. A total of 156 (3.2%) CCTA studies were rejected from CT-FFR analysis due to insufficient image quality (comprising 103 [3.0%] participants without DM and 53 [5.3%] participants with DM), and an additional 37 participants were excluded from analysis due to unavailable DM status. Among the remaining 4700 participants, 4290 (91.3%) had 1-year outcome data available and were included in these analyses.

Baseline demographic and clinical characteristics are outlined in Table 1. Of the 4290 participants (mean age, 66 years ± 10 [SD]; 2848 male participants, 1442 female participants) included in the study, 942 (22.0%) were participants with DM. Individuals with DM were older and had a higher mean body mass index; a higher prevalence of hypertension, hyperlipidemia, and cigarette smoking; and a higher prevalence of prior PCI. One-third of participants with DM were diet controlled, with the remainder requiring treatment with one or more oral hypoglycemic agents with or without insulin. Angina status differed between groups. Participants in the DM group reported slightly lower rates of atypical angina, noncardiac pain, and/or dyspnea compared with those without DM, and a higher proportion had unknown symptom status.

Coronary Stenosis and CT-FFR

CCTA and CT-FFR findings are presented in Table 1. Overall, 3900 out of 4290 (72.4%) participants were found to have obstructive CAD (≥50% stenosis in any vessel). After adjustment for demographics and cardiovascular risk factors, the prevalence of obstructive CAD was higher in participants with DM than those without DM (78.8% vs 70.6%, $P < .001$). Among those with obstructive CAD, participants with DM had significantly higher proportions of three-vessel involvement when compared with participants without DM (18.9% vs 11.2%, $P < .001$).

At CT-FFR analysis, 2868 (66.9%) participants out of the entire cohort of 4290 participants were CT-FFR positive (≤0.80), with increasing proportions of CT-FFR positivity with stenosis severity (Fig 2). Participants with DM were more likely to have positive CT-FFR values than those without DM (74.3% vs 64.8%, $P < .001$) and had higher rates of CT-FFR positivity in multiple vessels (two-vessel CT-FFR positivity, 33.7% vs 29.1%, $P = .021$; three-vessel CT-FFR positivity, 19.3% vs 11.6%, $P < .001$). Within the DM group, no significant association was observed between DM treatment and prevalence of obstructive CAD or CT-FFR positivity (Table 2).

Treatment Strategies

Comparisons of treatment strategies among participants with and without DM are outlined in Table 3. Integration of CT-

Table 2: Association between Diabetes Treatment and Coronary CT Angiographic and CT Fractional Flow Reserve Results

Parameter	Diet Controlled (n = 170)	Oral Hypoglycemic Agent(s) (n = 588)	Insulin (n = 184)	P Value
CCTA coronary stenosis				
Nonobstructive (all vessels < 50%)	37 (21.9)	119 (20.3)	43 (23.4)	.65
Obstructive (any vessel ≥ 50%)	132 (78.1)	467 (79.7)	141 (76.6)	.65
Single vessel	76 (57.6)	251 (53.8)	78 (55.3)	.73
Two vessel	33 (25.0)	126 (27.0)	36 (25.5)	.87
Three vessel	23 (17.4)	90 (19.3)	27 (19.2)	.89
≥50% stenosis				
LAD	98 (57.7)	383 (65.1)	118 (64.1)	.20
LCX	51 (30.0)	202 (34.4)	57 (31.0)	.47
RCA	62 (36.5)	188 (32.0)	56 (30.4)	.44
LMS	3 (1.8)	22 (3.7)	3 (1.6)	.20
CT-FFR				
CT-FFR > 0.8 (all)	44 (25.9)	153 (26.0)	45 (24.5)	.91
CT-FFR ≤ 0.8 (any vessel)	126 (74.1)	435 (74.0)	139 (75.5)	.91
CT-FFR ≤ 0.8				
Single vessel	62 (49.2)	209 (48.1)	58 (41.7)	.37
Two vessel	48 (38.1)	138 (31.7)	50 (36.0)	.34
Three vessel	16 (12.7)	88 (20.2)	31 (22.3)	.10

Note.—Between-group comparisons are adjusted for age, sex, body mass index, hypertension, and hyperlipidemia. Unless otherwise noted, data are expressed as numbers of participants with percentages in parentheses. CCTA = coronary CT angiography, CT-FFR = CT fractional flow reserve, LAD = left anterior descending artery, LCX = left circumflex artery, LMS = left main stem artery, RCA = right coronary artery.

FFR findings was similar regardless of the presence of DM, with treatment strategy according to positive or negative CT-FFR being similar in both groups. Overall, a revascularization strategy (OMT plus PCI or CABG) was pursued in 30.7% of participants with DM and 24.1% of participants without DM. Both obstructive CAD and positive CT-FFR were associated with increased rates of revascularization, and there was a similar graded increase in revascularization with either PCI or CABG observed with declining CT-FFR among both groups (Fig 3).

Figure 4 shows reclassification patterns of clinical management following CCTA, following CT-FFR, and actual management at 90 days in participants with and without DM. Both groups showed similar treatment reclassification rates and a high rate of adherence to CT-FFR findings. Main effects and interactions of DM status with stenosis severity and CT-FFR findings on treatment strategy are presented in Table S1.

Clinical Outcomes

Clinical outcome data among participants with and without DM at 1-year follow-up are presented in Table 4. Across all study participants, the overall event rate was low, with the MACE end point met in 55 participants. Overall, participants with DM experienced higher rates of MACE after adjusting for demographics and other cardiovascular risk factors (hazard ratio, 2.198; 95% CI: 1.182, 4.809, P = .013; Fig S1). However, after stratifying participants by stenosis severity and CT-FFR positivity, we found no evidence of differences in the rates of any clinical outcome between the two groups (Table 5 and Figs S2 and S3). No evidence of differences in clinical outcomes among participants with DM was observed, regardless of the hyperglycemia management strategy (Table S2).

Discussion

In this secondary analysis of the ADVANCE registry, we assessed the impact of CCTA and CT-FFR results on clinical management of participants with CAD with or without DM. We found that CCTA and CT-FFR identified more severe anatomic and functional CAD in participants with DM. In participants with and without DM, CCTA and CT-FFR had similar clinical utility, reclassifying two out of three participants and predicting revascularization and MACE for up to 1 year following examination.

As in previous studies, CCTA identified a higher prevalence, extent, and severity of CAD in participants with DM when compared with those without DM (1,2). In our cohort, CCTA demonstrated approximately 8% greater prevalence of obstructive CAD in those with DM. However, classification of CAD severity was clearly refined by the addition of CT-FFR. As expected, we observed a graded increase in CT-FFR positivity with stenosis severity in both groups, although not in all cases. This is consistent with invasive FFR studies and the recognition that stenosis severity alone is not enough to identify hemodynamically

Table 3: Comparison of Medical Therapy and Total Revascularization according to Diabetes Status, Stratified by Stenosis Severity and CT Fractional Flow Reserve Findings

Parameter	No Diabetes	Diabetes	*P* Value
Maximum stenosis ≥ 50% and CT-FFR > 0.80 (*n* = 765; no DM = 620; DM = 145)			
OMT only	563 (90.8)	138 (95.2)	.09
OMT + PCI	50 (8.1)	7 (4.8)	.18
OMT + CABG	7 (1.1)	0 (0)	.20
Maximum stenosis ≥ 50% and CT-FFR ≤ 0.80 (*n* = 2355; No DM = 1740; DM = 595			
OMT only	1036 (59.5)	321 (54.0)	.02
OMT + PCI	614 (35.3)	231 (38.8)	.12
OMT + CABG	90 (5.2)	43 (7.2)	.06
Maximum stenosis < 50% and CT-FFR > 0.80 (*n* = 659; No DM = 560; DM = 96)			
OMT only	555 (99.1)	96 (100.0)	.35
OMT + PCI	4 (0.7)	0 (0)	.41
OMT + CABG	1 (0.2)	0 (0)	.68
Maximum stenosis < 50% and CT-FFR ≤ 0.80 (*n* = 525; No DM = 422; DM = 103)			
OMT only	386 (91.5)	96 (93.2)	.56
OMT + PCI	34 (8.1)	7 (6.8)	.67
OMT + CABG	2 (0.5)	0 (0)	.48

Note.—Between-group comparisons are adjusted for age, sex, body mass index, smoking status, hypertension, and hyperlipidemia. Data are expressed as numbers of participants with percentages in parentheses. CABG = coronary artery bypass grafting, CT-FFR = CT fractional flow reserve, DM = diabetes mellitus, OMT = optimal medical therapy, PCI = percutaneous coronary intervention.

significant CAD, with mismatch observed in up to one-third of lesions (14,15). Of all participants in this study with CCTA-adjudicated nonobstructive CAD, 44% demonstrated CT-FFR positivity, once again highlighting the inadequacy of anatomic assessment in isolation when determining the functional significance of CAD. Only a small proportion of these participants (8%), however, subsequently underwent revascularization. We speculate that several reasons may account for the relatively low use of revascularization among these participants, including recognition that OMT remains the bedrock of CAD management in most patients, less suitability of lesions for PCI or CABG, a higher likelihood of improvement in symptoms with antianginal medications, clinician bias toward revascularization in more anatomically severe disease, and patient preference. It is important to emphasize that this was not a diagnostic accuracy study of CT-FFR, and no comparison with invasive physiologic assessment was performed. Nevertheless, our observed relationship between stenosis severity and CT-FFR positivity, with mismatch in a proportion of cases, mirrors findings observed in invasive studies (15). The proportion of participants with DM and physiologically significant coronary stenoses (as determined by CT-FFR ≤ 0.8) was lower than adjudicated by anatomic assessment alone: 74% of participants with DM had CT-FFR ≤ 0.8 compared with 79% of participants with obstructive stenoses (≥50%) by visual assessment. Similarly, in participants without DM, obstructive disease by anatomic CCTA assessment alone was diagnosed in 71% of participants compared with 65% by CT-FFR. Although absolute rates of MACE were higher in participants with DM (driven by higher risk of noncardiovascular death), when both anatomy and lesion-specific physiologic features were taken into consideration to guide management, no evidence of a difference in MACE was observed between participants with and without DM. This suggests that CT-FFR enables risk stratification and appropriate selection of participants suitable for OMT or revascularization, regardless of the presence of DM, which in turn leads to comparable low clinical event rates for patients without DM at 1 year.

Interestingly, the higher overall rates of MACE in our DM cohort were primarily related to noncardiovascular causes of death, which are known to be important contributors to mortality in individuals with DM (16). With intensive control of multiple modifiable risk factors in DM, the Steno-2 trial found a 53% lower risk

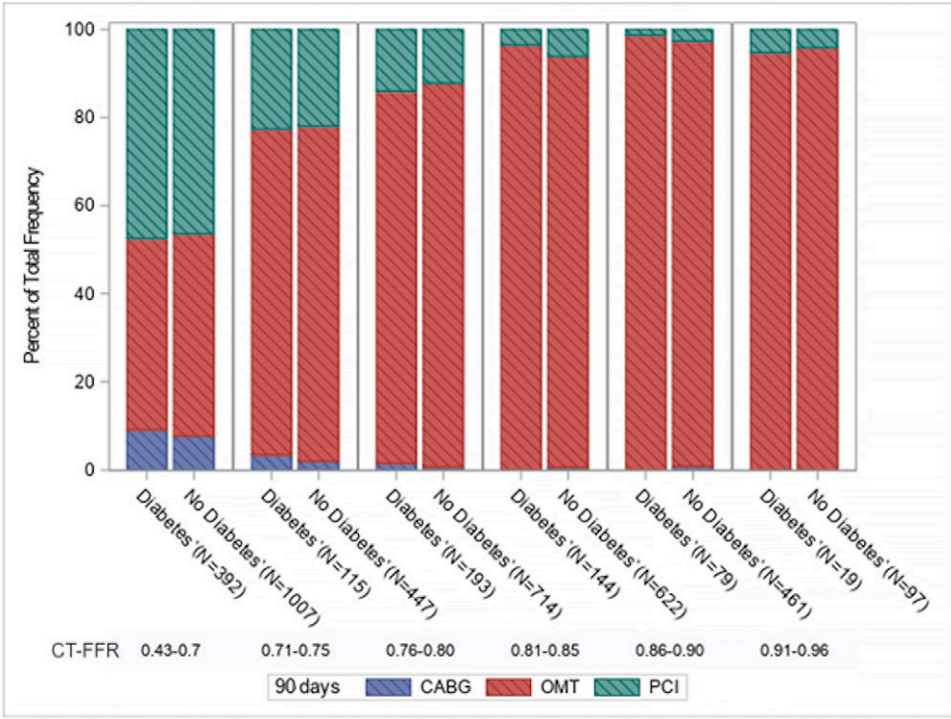
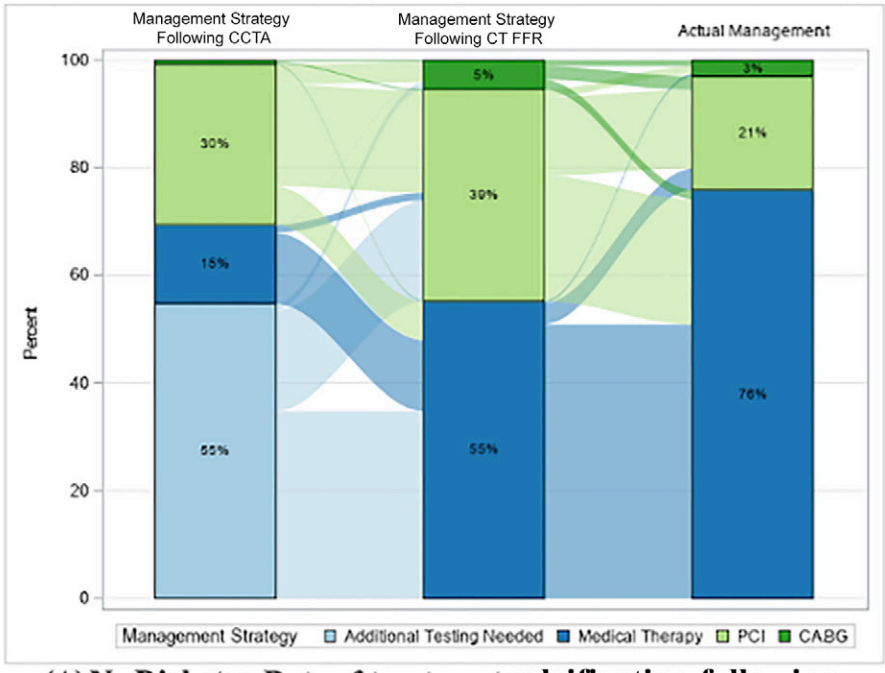


Figure 3: Graph shows the management strategy (optimal medical therapy [OMT], percutaneous coronary intervention [PCI], or coronary artery bypass grafting [CABG]) in participants with and without diabetes, stratified according to CT fractional flow reserve (FFR) values: <0.71, 0.71–0.75, 0.76–0.80, 0.81–0.85, 0.86–0.90, and >0.90.

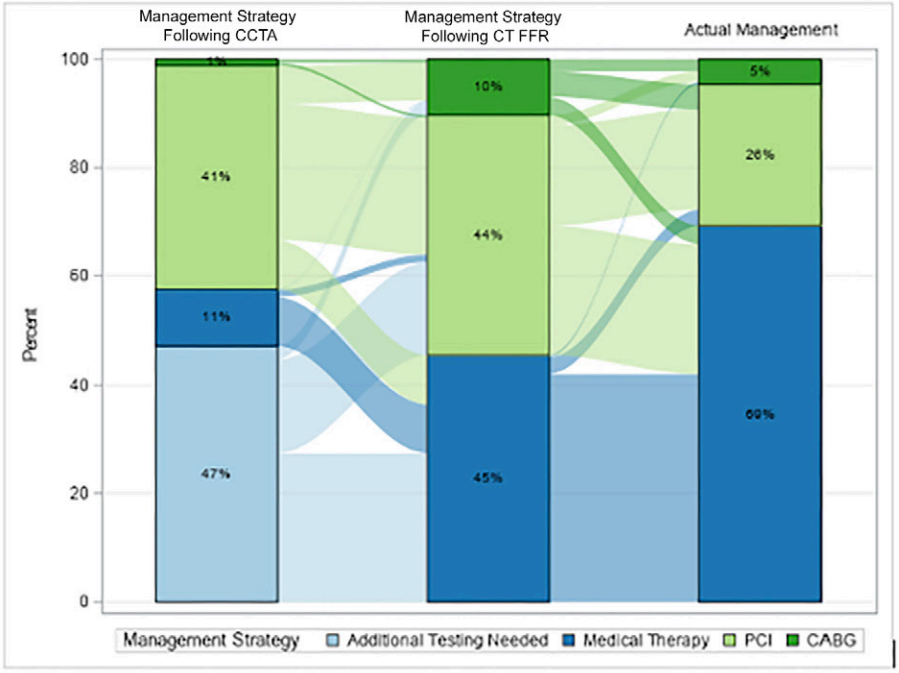
of the composite primary end point of cardiovascular death, nonfatal MI, nonfatal stroke, revascularization, and amputation after 7.8 years of follow-up (5). Similarly, in a recent large (n = 271 174) observational study of patients with type 2 DM, maintenance of five risk factors (dysglycemia, hypertension, smoking, albuminuria, and dyslipidemia) within target ranges was associated with a stepwise risk reduction in death, MI, and stroke over 5.7 years of follow-up. When all five risk factors were maintained within their specified target ranges, people with type 2 DM had little or no excess atherosclerotic cardiovascular risk compared with the general population (6). These studies suggest that multifactorial risk factor management is an effective strategy to lower risk of atherosclerotic cardiovascular disease in DM. Therefore, prompt identification and treatment of CAD by CCTA and CT-FFR in our cohort may have minimized the excess risk of cardiovascular disease in participants with DM such that the major contributors to mortality were noncardiovascular causes.

Our findings are consistent with studies examining the clinical use of invasive FFR in guiding treatment decisions and outcomes in people with and without DM. For example, in a large, observational study (n = 1983; age, 65 years ± 10; 77% male patients; 35% patients with DM) evaluating the routine integration of invasive FFR measurements in patients undergoing invasive coronary angiography, similar rates of management reclassification (eg, deferral of revascularization) were noted in individuals with and without DM (41.2% vs 37.5%, P = .37) (8). However, reclassification from OMT to revascularization was more frequent in those with DM (41.5% vs 31.5%, P = .001) and deferral of revascularization in individuals with DM was associated with lower rates of MACE at 12 months. These findings, taken together with our own study, highlight the added importance of routine integration of FFR and CT-FFR in guiding management (and especially selection or deferral for revascularization) among individuals with DM, with the added advantage that CT-FFR is a noninvasive test.

The more severe anatomic and functional pattern of epicardial CAD consistently observed in DM (including in our cohort) may explain why there was no evidence of a difference in mortality or cardiovascular outcomes between participants with DM and stable CAD (n = 2368) randomized to treatment with revascularization (either by CABG or PCI) versus OMT alone in a previous study (17). However, those whose revascularization was surgical rather than percutaneous did incur significantly lower rates of MI than those treated with OMT alone (17). This was supported by the later randomized controlled Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial, which also demonstrated lower rates of cardiovascular events and all-cause mortality in participants with DM and stable ischemic heart disease (n = 1900) treated with surgery versus PCI over a median follow-up period of 3.8 years (18). This effect was sustained even after longer-term follow-up (median 7.5 years) in the recent FREEDOM Follow-On study (19). This may be because the more obstructive, multivessel CAD disease pattern observed in DM is more amenable to treatment with a multivessel intervention strategy (eg, of those patients in the Bypass Angioplasty Revascularization Investigation 2 Diabetes [BARI 2D] study who underwent PCI rather than surgery, only 20% had multivessel revascularization) (17). The presence of DM is therefore highly likely to influence physician treatment decisions



(A) No Diabetes. Rate of treatment calcification following CT-FFR: 67.5%



(B) Diabetes. Rate of treatment reclassification following CT-FFR: 65.0%

Figure 4: Graph shows clinical management strategy following coronary CT angiography (CCTA), strategy and reclassification following CT fractional flow reserve (FFR), and actual management at 90 days in participants **(A)** without and **(B)** with diabetes. CABG = coronary artery bypass grafting, PCI = percutaneous coronary intervention.

surrounding revascularization, which is reflected in our study findings, where there was a trend (5.2% vs 7.2%, $P = .0620$) toward higher rates of CABG in participants with DM and maximum CCTA stenosis ≥ 50% and CT-FFR ≤ 0.80.

Strengths of our study are the large sample size from multiple international sites, an unselected cohort with a good representation of individuals with DM (approximately one in four participants), high rate of interpretability of CCTA studies for CT-FFR, and ability to evaluate the impact of CT-FFR results on clinical decision-making and 1-year outcomes. Limitations are the relatively crude phenotyping of DM status, with no discrimination between type 1 or type 2 DM, glycemic status, or presence of microvascular complications; short follow-up duration; low event rates; and lack of advanced quantitative plaque analyses.

Table 4: Clinical Outcomes in Participants with Diabetes

	Unadjusted			Adjusted		
Parameter	HR	95% CI	*P* Value	HR	95% CI	*P* Value
MACE composite (*n* = 55)	1.733	0.987, 3.045	.056	2.198	1.182, 4.089	.013
CV death (*n* = 15)	1.782	0.609, 5.213	.29	2.533	0.778, 8.252	.12
Non-CV death (*n* = 20)	4.359	1.806, 10.519	.001	4.846	1.903, 12.343	<.001
Nonfatal MI (*n* = 12)	0.324	0.042, 2.507	.28	0.551	0.066, 4.615	.58
Unplanned hospitalization for ACS leading to urgent revascularization (*n* = 8)	0.508	0.063, 4.133	.53	0	0	NA

Note.—Unadjusted and adjusted (age, sex, body mass index, smoking status, hypertension, hyperlipidemia) Cox proportional hazard ratios (HR) for participants with diabetes, using those without diabetes as the reference value. ACS = acute coronary syndrome, CV = cardiovascular, MACE = major adverse cardiovascular events, MI = myocardial infarction, NA = not applicable.

However, we did examine relationships between DM treatments, CCTA and CT-FFR findings, management strategy, and clinical outcomes, which provides some detail of the impact of DM type and glycemic control. As 80% of the DM cohort were treated either with lifestyle modification or oral hypoglycemic agents, it can be inferred that the vast majority of participants had type 2 DM. Although longer-term follow-up data may be available for a proportion of the ADVANCE study cohort, there is a risk of selection bias in limiting the analyses to this group. Last, there was no direct comparison between an up-front CT-FFR versus an initial invasive angiography-based approach. Therefore, superiority over invasive angiography is not inferred by our study.

In conclusion, integration of CT-FFR into the noninvasive initial evaluation of individuals with CAD identified a more anatomically and functionally severe pattern of CAD in those with DM and showed similar clinical utility in participants with and without DM. Routine integration of CT-FFR into noninvasive assessment of symptomatic CAD in patients with DM may refine selection of patients appropriate for medical management or coronary revascularization.

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References

1. Uddin SN, Malik F, Bari MA, et al. Angiographic severity and extent of coronary artery disease in patients with type 2 diabetes mellitus. Mymensingh Med J 2005;14(1):32–37.
2. Rana JS, Dunning A, Achenbach S, et al. Differences in prevalence, extent, severity, and prognosis of coronary artery disease among patients with and without diabetes undergoing coronary computed tomography angiography: results from 10,110 individuals from the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes): an InteRnational Multicenter Registry. Diabetes Care 2012;35(8):1787–1794.
3. Kim U, Leipsic JA, Sellers SL, et al. Natural History of Diabetic Coronary Atherosclerosis by Quantitative Measurement of Serial Coronary Computed Tomographic Angiography: Results of the PARADIGM Study. JACC Cardiovasc Imaging 2018;11(10):1461–1471.
4. American Diabetes Association. 9. Cardiovascular Disease and Risk Management: *Standards of Medical Care in Diabetes-2018*. Diabetes Care 2018;41(Suppl 1):S86–S104.
5. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348(5):383–393.
6. Rawshani A, Rawshani A, Franzén S, et al. Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med 2018;379(7):633–644.
7. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360(3):213–224.
8. Van Belle E, Cosenza A, Baptista SB, et al. Usefulness of Routine Fractional Flow Reserve for Clinical Management of Coronary Artery Disease in Patients With Diabetes. JAMA Cardiol 2020;5(3):272–281.
9. Driessen RS, Danad I, Stuijfzand WJ, et al. Comparison of Coronary Computed Tomography Angiography, Fractional Flow Reserve, and Perfusion Imaging for Ischemia Diagnosis. J Am Coll Cardiol 2019;73(2):161–173.
10. Patel MR, Nørgaard BL, Fairbairn TA, et al. 1-Year Impact on Medical Practice and Clinical Outcomes of FFR_{CT}: The ADVANCE Registry. JACC Cardiovasc Imaging 2020;13(1 Pt 1):97–105.

Table 5: Major Adverse Cardiovascular Events and Cardiovascular Death or Myocardial Infarction in Participants with and without Diabetes, Stratified by Stenosis Severity and CT Fractional Flow Reserve Findings

Parameter	No Diabetes	Diabetes	*P* Value
Maximum stenosis ≥ 50% and CT-FFR > 0.80 (*n* = 765; No DM = 620; DM = 145)			
MACE	7 (1.1%) [0.3%, 2.0%]	2 (1.4%) [0%, 3.3%]	.68
MI	3 (0.5%) [0%, 1.0%]	0 (0%)	>.99
All-cause mortality	3 (0.5%) [0%, 1.0%]	2 (1.4%) [0%, 3.3%]	.24
Unplanned hospitalization for ACS leading to urgent revascularization	1 (0.2%) [0%, 0.5%]	0 (0%)	>.99
CV death or MI	3 (0.5%) [0%, 1.0%]	0 (0%)	>.99
Maximum stenosis ≥ 50% and CT-FFR ≤ 0.80 (*n* = 2355; No DM = 1740; DM = 595)			
MACE	24 (1.4%) [0.8%, 1.9%]	13 (2.2%) [1.0%, 3.4%]	.17
MI	7 (0.4%) [0.1%, 0.7%]	1 (0.2%) [0%, 0.5%]	.69
All-cause mortality	12 (0.7%) [0.3%, 1.1%]	11 (1.9%) [0.8%, 2.9%]	.01
Unplanned hospitalization for ACS leading to urgent revascularization	5 (0.3%) [0.04%, 0.5%]	1 (0.2%) [0%, 0.5%]	>.99
CV death or MI	16 (0.9%) [0.5%, 1.4%]	5 (0.8%) [0.1%, 1.6%]	.86
Maximum stenosis < 50% and CT-FFR > 0.80 (*n* = 525; No DM = 422; DM = 103)			
MACE	2 (0.4%) [0%, 0.9%]	1 (1.0%) [0%, 3.1%]	.38
MI	0 (0%)	0 (0%)	NA
All-cause mortality	1 (0.2%) [0%, 0.5%]	1 (1.0%) [0%, 3.1%]	.27
Unplanned hospitalization for ACS leading to urgent revascularization	1 (0.2%) [0%, 0.5%]	0 (0%)	>.99
CV death or MI	0 (0%)	0 (0%)	NA
Maximum stenosis < 50% and CT-FFR ≤ 0.80 (*n* = 593; No DM = 471; DM = 113)			
MACE	3 (0.7%) [0%, 1.5%]	2 (1.9%) [0%, 4.6%]	.25
MI	1 (0.2%) [0%, 0.7%]	0 (0%)	>.99
All-cause mortality	2 (0.5%) [0%, 1.1%]	2 (1.9%) [0%, 4.6%]	.17
Unplanned hospitalization for ACS leading to urgent revascularization	0 (0%)	0 (0%)	NA
CV death or MI	2 (0.5%) [0%, 1.1%]	1 (1.0%) [0%, 2.9%]	.48

Note.—Between-group comparisons are adjusted for age, sex, body mass index, smoking status, hypertension, and hyperlipidemia. Unless otherwise noted, data are expressed as counts with percentages in parentheses and 95% CIs in brackets. ACS = acute coronary syndromes, CT-FFR = CT fractional flow reserve, CV = cardiovascular, DM = diabetes mellitus, MACE = major adverse cardiovascular events, MI = myocardial infarction, NA = not applicable.

11. Chinnaiyan KM, Akasaka T, Amano T, et al. Rationale, design and goals of the HeartFlow assessing diagnostic value of non-invasive FFR_{CT} in Coronary Care (ADVANCE) registry. J Cardiovasc Comput Tomogr 2017;11(1):62–67.
12. Leipsic J, Abbara S, Achenbach S, et al. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. J Cardiovasc Comput Tomogr 2014;8(5):342–358.
13. Taylor CA, Fonte TA, Min JK. Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve: scientific basis. J Am Coll Cardiol 2013;61(22):2233–2241.
14. Toth G, Hamilos M, Pyxaras S, et al. Evolving concepts of angiogram: fractional flow reserve discordances in 4000 coronary stenoses. Eur Heart J 2014;35(40):2831–2838.
15. Curzen N, Rana O, Nicholas Z, et al. Does routine pressure wire assessment influence management strategy at coronary angiography for diagnosis of chest pain?: the RIPCORD study. Circ Cardiovasc Interv 2014;7(2):248–255.
16. Baena-Díez JM, Peñafiel J, Subirana I, et al. Risk of Cause-Specific Death in Individuals With Diabetes: A Competing Risks Analysis. Diabetes Care 2016;39(11):1987–1995.
17. BARI 2D Study Group; Frye RL, August P, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med 2009;360(24):2503–2515.
18. Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 2012;367(25):2375–2384.
19. Farkouh ME, Domanski M, Dangas GD, et al. Long-Term Survival Following Multivessel Revascularization in Patients With Diabetes: The FREEDOM Follow-On Study. J Am Coll Cardiol 2019;73(6):629–638.