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ORIGINAL ARTICLE

Influence of Obesity on Coronary Artery Disease and Clinical Outcomes in the ADVANCE Registry

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BACKGROUND: The relationship between body size and cardiovascular events is complex. This study utilized the ADVANCE (Assessing Diagnostic Value of Noninvasive FFR_{CT} in Coronary Care) Registry to investigate the association between body mass index (BMI), coronary artery disease (CAD), and clinical outcomes.

METHODS: The ADVANCE registry enrolled patients undergoing evaluation for clinically suspected CAD who had >30% stenosis on cardiac computed tomography angiography. Patients were stratified by BMI: normal <25 kg/m^2, overweight 25–29.9 kg/m^2, and obese ≥30 kg/m^2. Baseline characteristics, cardiac computed tomography angiography and computed tomography fractional flow reserve (FFR_{CT}), were compared across BMI groups. Adjusted Cox proportional hazards models assessed the association between BMI and outcomes.

RESULTS: Among 5014 patients, 2166 (43.2%) had a normal BMI, 1883 (37.6%) were overweight, and 965 (19.2%) were obese. Patients with obesity were younger and more likely to have comorbidities, including diabetes and hypertension (all P<0.001), but were less likely to have obstructive coronary stenosis (65.2% obese, 72.2% overweight, and 73.2% normal BMI; P<0.001). However, the rate of hemodynamic significance, as indicated by a positive FFR_{CT}, was similar across BMI categories (63.4% obese, 66.1% overweight, and 67.8% normal BMI; P=0.07). Additionally, patients with obesity had a lower coronary volume-to-myocardial mass ratio compared with patients who were overweight or had normal BMI (obese BMI, 23.7; overweight BMI, 24.8; and normal BMI, 26.3; P<0.001). After adjustment, the risk of major adverse cardiovascular events was similar regardless of BMI (all P>0.05).

CONCLUSIONS: Patients with obesity in the ADVANCE registry were less likely to have anatomically obstructive CAD by cardiac computed tomography angiography but had a similar degree of physiologically significant CAD by FFR_{CT} and similar rates of adverse events. An exclusively anatomic assessment of CAD in patients with obesity may underestimate the burden of physiologically significant disease that is potentially due to a significantly lower volume-to-myocardial mass ratio.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: body mass index ■ coronary artery disease ■ coronary stenosis ■ obesity ■ overweight

The increasing prevalence of obesity among adolescents and adults has become a global health epidemic. It is estimated that up to 49% of the world's population is overweight or obese.[1] Obesity is a complex, multifactorial disease that can adversely affect cardiac structure and function.[1,2] Interestingly, although obesity is

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CLINICAL PERSPECTIVE

The association between body mass index (BMI), coronary artery disease, and clinical outcomes was examined among patients enrolled in the ADVANCE (Assessing Diagnostic Value of Noninvasive FFR_{CT} in Coronary Care) registry. Patients with suspected coronary artery disease and at least 30% stenosis on cardiac computed tomography angiography were stratified by BMI into normal, overweight, and obese groups. The diagnostic yield of cardiac computed tomography angiography was high across all groups, regardless of BMI, and there was a similarly low rejection rate for computed tomography fractional flow reserve (FFR_{CT}) among patients with normal, overweight, and obese BMI values. Patients with obesity were less likely to have obstructive coronary stenosis compared with patients with normal or overweight BMI ($P<0.001$). However, the rate of hemodynamic significance, as indicated by a positive FFR_{CT}, was similar ($P=0.07$) across BMI groups. The coronary volume-to-myocardial mass ratio was lower among patients with obesity (23.7) compared with overweight (24.8) or normal BMI (26.3) patients ($P<0.001$), suggesting a greater mismatch between coronary luminal volumes and myocardial mass in patients with obesity. The risk of major adverse cardiovascular events was similar regardless of BMI (all $P>0.05$). An exclusively anatomic assessment of coronary artery disease in patients with obesity may underestimate the burden of physiologically significant disease that is potentially due, at least in part, to a significantly lower volume-to-myocardial mass ratio.

Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
BMI	body mass index
CAD	coronary artery disease
CCTA	cardiac computed tomography angiography
CDC	Centers for Disease Control and Prevention
FFR_{CT}	CT fractional flow reserve
LV	left ventricle
MACE	major adverse cardiovascular events
MI	myocardial infarction
V/M	coronary volume-to-myocardial mass ratio

an independent risk factor for cardiovascular disease and frequently leads to the development of multiple atherosclerotic cardiovascular disease risk factors—including hypertension, hyperlipidemia, and diabetes—it has also been reported to exert a protective effect among overweight and patients with obesity with established cardiovascular disease. This phenomenon, coined the "obesity paradox," has now been reported in multiple cardiovascular disease processes including atrial fibrillation,[3,4] heart failure,[5–7] pulmonary hypertension,[8,9] and coronary artery disease (CAD).[10–14] The paradoxical association between larger body size and lower mortality has been demonstrated in patients with acute coronary syndrome (ACS)[15] and stable CAD undergoing coronary revascularization.[16,17] A large meta-analysis examining the effect of body mass index (BMI) in over 1.3 million patients with CAD found that an overweight or obese body habitus was associated with a lower risk of short-term mortality, yet the apparent benefits of a higher BMI appeared to dissipate after 5 years.[18] Despite increasing recognition of the obesity paradox across multiple cardiovascular disease processes, the biologic mechanisms underlying this phenomenon are not well understood.

In symptomatic patients undergoing evaluation for CAD, cardiac computed tomography angiography (CCTA) represents a key noninvasive cardiac imaging modality with high sensitivity for the presence and severity of coronary atherosclerotic disease. However, the severity of anatomic stenosis does not always correlate with flow-limiting or ischemia-inducing obstruction.[19] The addition of fractional flow reserve by computed tomography (FFR_{CT}) provides a noninvasive physiological assessment of the hemodynamic significance of coronary lesions detected by CCTA. The clinical impact of FFR_{CT} in conjunction with CCTA for the evaluation of patients with suspected CAD was assessed in the ADVANCE (Assessing Diagnostic Value of Noninvasive FFR_{CT} in Coronary Care) study, a large, international, multicenter, prospective registry.[20] Using the ADVANCE registry, we investigated if the anatomic and functional significance of CAD differed according to BMI and whether patients with obesity and overweight with CAD have better outcomes than those with a normal BMI.

METHODS

Study Cohort and Design

The ADVANCE registry prospectively enrolled 5083 patients from 38 sites in Europe, North America, and Japan from July 15, 2015 to October 20, 2017. Full details of the enrollment, definitions, and outcomes have been previously reported.[20,21] Briefly, patients who were undergoing clinical evaluation for suspected CAD with stable symptoms and had documented CAD by CCTA with at least 30% stenosis were eligible for enrollment. The ADVANCE registry demonstrated lower rates of revascularization, cardiovascular death, and myocardial infarction (MI) among patients with a negative FFR_{CT} (defined as >0.80).[21] FFR_{CT} was recommended for stenoses >30%, but left to the

discretion of the physician interpreting the CCTA as to whether this additional analysis should be performed. When FFR_{CT} was obtained, results were provided to the treating clinicians, and site investigators reported a treatment strategy based on this result. All subsequent management decisions were left to the discretion of the local referring physician. Patients enrolled in the registry had follow-up at 90 and 180 days and 12 months. All sites underwent Institutional Review Board approval, and all patients provided written informed consent. The data that support the findings of this study are available from the corresponding author upon reasonable request.

For this analysis, patients in the ADVANCE registry were included if they had data available for BMI determination. BMI was calculated using the standard equation of weight (kg)/height (m^2), and body surface area was calculated using the DuBois formula.[22] Patients were divided into 3 categories based on BMI: normal <25 kg/m^2, overweight 25–29.9 kg/m^2, and obese ≥30 kg/m^2 based on criteria from the World Health Organization and National Institutes of Health.[23] A secondary analysis evaluated additional groups based on the Centers for Disease Control and Prevention (CDC) obesity classes[24]: class 1 obesity with a BMI of 30 to <35 kg/m^2, CDC class 2 with a BMI of 35 to <40 kg/m^2 and CDC class 3 with a BMI of 40 kg/m^2 or higher.

The updated Diamond-Forrester risk algorithm was used to determine the pretest probability of obstructive CAD.[25] All CCTAs were initially interpreted locally for clinical management and then independently reviewed in an imaging core laboratory (Duke Clinical Research Institute, Durham, NC) by expert readers blinded to clinical information. Obstructive CAD by CCTA was anatomically defined as any vessel with ≥50% stenosis. All FFR_{CT} analyses were performed in a single center (HeartFlow, Redwood City, CA) blinded to clinical events. CCTA results were divided into nonobstructive (all lesions with anatomic stenosis <50%) and obstructive (at least one lesion ≥50% stenosis) CAD. Patients with obstructive disease were further divided into 1-, 2-, or 3-vessel obstructive CAD, and the distribution of obstructive disease was assessed (left anterior descending, left circumflex, right coronary, and left main). Similarly, patients were evaluated based on the presence of hemodynamically significant FFR_{CT}, defined as ≤0.8, and the number of vessels with a significant FFR_{CT} value.

All patients enrolled after the implementation of CCTA analysis software version 2.0 had left ventricular (LV) mass assessments completed. Those enrolled before this time (version 1.0) were excluded from this LV analysis. Ventricular mass and coronary luminal volume measured on the CCTA were indexed to body surface area. The coronary luminal volume was divided by the LV myocardial mass to calculate a volume-to-myocardial mass (V/M) ratio.[26] LV myocardial mass and LV mass index were evaluated based on BMI categories. Similarly, coronary lumen volume and luminal volume index were assessed by BMI, and the V/M ratio was calculated for each BMI group.

The primary outcome of interest was a composite of major adverse cardiovascular events (MACE) that included all-cause death, MI, or unplanned hospitalization for ACS leading to revascularization. Secondary outcomes included the individual end points of all-cause death, cardiovascular death, noncardiovascular death, nonfatal MI, and unplanned hospitalization for ACS leading to revascularization. A patient was considered to have an unplanned hospitalization for ACS leading to revascularization if they had (1) ischemic symptoms of unstable angina or ACS requiring at least a 24-hour hospitalization; (2) evidence of new or worsening ischemia by ECG, stress test, or troponin elevation; and (3) underwent urgent or emergent revascularization during the same hospitalization. Events were independently adjudicated by a Clinical Events Committee using standard definitions and were blinded to both clinical and imaging data.

Statistical Analyses

Baseline clinical characteristics, estimated CAD risk, anatomic stenosis on CCTA, burden of hemodynamically significant stenosis by FFR_{CT}, LV mass, and coronary luminal volume measurements were compared across the BMI categories (normal, overweight, and obese). Baseline patient characteristics were described using the mean (SD) for continuous variables and percentages for categorical variables. Downstream noninvasive and invasive evaluations for CAD after the enrollment in the CCTA were compared between BMI groups. For all comparisons, values across BMI categories were compared using ANOVA for continuous variables and the Pearson χ^2 test for categorical variables. Additionally, a sensitivity analysis was performed including only patients with complete data on CCTA stenosis, FFR_{CT}, LV mass, and coronary volume measurements.

Clinical outcomes were analyzed for each BMI category. A time-to-event analysis was completed using Kaplan-Meier estimates to determine survival curves; patients were censored after first event. A log-rank test was used to compare BMI categories. Using normal BMI as the reference group, an unadjusted and adjusted Cox proportional hazards model was used to compare clinical outcomes between the groups. Variables for adjustment included age, sex (female), diabetes, hypertension, hyperlipidemia, tobacco, BMI as a continuous variable, prior percutaneous coronary intervention, and continent of enrollment (Europe, Asia, or North America). To assess whether there was a differential impact on clinical outcomes, we assessed the interaction between BMI and V/M ratio. Two secondary analyses similarly evaluated clinical outcomes, first for patients with obesity only based on the CDC obesity class and second, examining patients with normal BMI versus combined patients with overweight or obese BMI. A *P* value of <0.05 was considered statistically significant for all analyses. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics

Among the 5083 patients enrolled in the ADVANCE registry, 5014 had data to calculate BMI. When categorized by BMI, 2166 (43.2%) patients had a normal BMI, 1883 (37.6%) were overweight, and 965 (19.2%) were obese. Among those classified as obese, 713 (73.9%) were CDC class 1 with a BMI of 30 to <35 kg/m^2, 179 (18.5%) were CDC class 2 with a BMI of 35 to <40 kg/m^2 and 73 (7.6%) were CDC class 3 with a BMI of 40 kg/m^2 or ≥ (Table S1). Patients with obesity were younger (normal BMI, 68 years, overweight BMI, 65

years, obese BMI, 63 years; *P*<0.001), more frequently male and were more likely to have multiple cardiovascular risk factors, including diabetes (normal BMI, 20.9%; overweight BMI, 21.0%; obese BMI, 28.9%; *P*<0.001), hypertension (normal BMI, 55.8%; overweight BMI, 61.0%; obese BMI, 68.0%; *P*<0.001), and hyperlipidemia (normal BMI, 54.8%; overweight BMI, 59.7%; obese BMI, 64.2%; *P*<0.001), but lower predicted risk by updated Diamond-Forrester score (normal BMI, 66.43; overweight BMI, 67.43; obese BMI, 63.17; *P*<0.001; Table 1). Patients with obesity were less likely to present with typical angina (normal BMI, 22.1%; overweight BMI, 21.2%; obese BMI, 18.2%) and more commonly had atypical chest pain (normal BMI, 36.2%; overweight BMI, 36.9%; obese BMI, 40.5%) or dyspnea (normal BMI, 7.2%; overweight BMI, 10.5%; obese BMI, 15.6%) as an angina equivalent for the presenting symptom.

CCTA and FFR_{CT} Results

There was no significant difference across BMI groups for CCTA interpretability: normal BMI, 99.8%; overweight BMI, 99.6%; obese BMI, 99.8%; *P*=0.48 (Table 2). The radiation dose, as expected, increased with increasing BMI (dose length product: normal BMI, 302; overweight BMI, 293; obese BMI, 381; *P*=0.01). Patients with obesity were significantly more likely to have exclusively nonobstructive CAD (34.8%) compared with 27.8% of overweight and 26.8% of individuals with a normal BMI (*P*<0.001). Obstructive disease was more prevalent among those with a normal BMI (normal BMI, 73.2%; overweight BMI, 72.2%; obese BMI, 65.2%; *P*<0.001). Among those with obstructive CAD, the left anterior descending artery had the most common distribution of stenosis ≥50% across all BMI categories (Table 2). However, obstructive left anterior descending disease was present in 60.0% of patients with normal BMI and 56.5% of patients with overweight BMI compared with 50.7% of patients with obesity (*P*<0.001). Segmental analyses revealed that proximal and mid-vessel coronary disease predominated across all BMI groups. There were no significant differences between BMI categories in the frequency of diffuse versus focal disease (diffuse disease: normal BMI, 8.9%; overweight BMI, 8.9%; obese BMI, 10.1%; *P*=0.66) or serial versus isolated lesions (serial lesions: normal BMI, 10.6%; overweight BMI, 9.2%; obese BMI, 10.6%; *P*=0.42; Tables S2 and S3).

Among the CCTAs sent for FFR_{CT} (normal BMI, n=2054; overweight BMI, n=1170; obese BMI, n=848) the FFR_{CT} rejection rate was low in all BMI groups (normal BMI, 3.0%; overweight BMI, 2.7%; obese BMI, 3.8%; *P*=0.25; Table 2). However, FFR_{CT}

Table 1. Baseline Patient Characteristics

	Normal BMI <25 kg/m² (n=2166)	Overweight BMI 25–29.9 kg/m² (n=1883)	Obese BMI ≥30 kg/m² (n=965)	*P* value
Age, y	68±10	65±10	63±10	<0.001
Sex, % female	843 (38.9)	523 (27.8)	343 (35.5)	<0.001
Body surface area,* m²	1.68±0.20	1.90±0.20	2.08±0.22	<0.001
Diabetes, type 2	452 (20.9)	395 (21.0)	279 (28.9)	<0.001
Diabetic treatment				
Diet	171 (37.8)	122 (30.9)	74 (26.5)	0.004
Oral meds	310 (68.6)	295 (74.7)	186 (66.7)	0.05
Insulin	82 (18.1)	74 (18.7)	73 (26.2)	0.02
Hypertension	1209 (55.8)	1148 (61.0)	656 (68.0)	<0.001
Hyperlipidemia	1186 (54.8)	1124 (59.7)	620 (64.2)	<0.001
Tobacco use–current or former	1064 (49.1)	980 (52.0)	502 (52.0)	0.12
Prior PCI (any vessel)	84 (3.9)	76 (4.0)	29 (3.0)	0.37
UDF† risk score	66.43±22.7	67.43±21.9	63.17±22.9	<0.001
Angina status				<0.001
Typical/cardiac pain	478 (22.1)	399 (21.2)	176 (18.2)	
Atypical/possibly cardiac pain	785 (36.2)	695 (36.9)	391 (40.5)	
Noncardiac pain	116 (5.4)	121 (6.4)	59 (6.1)	
Dyspnea	155 (7.2)	198 (10.5)	151 (15.6)	
Unknown/none	632 (29.2)	470 (25.0)	188 (19.5)	

Data are expressed as n (%) or mean±SD, as appropriate. BMI indicates body mass index; PCI, percutaneous coronary intervention; and UDF, updated Diamond-Forrester.

*Body surface area calculated by Du Bois formula.

†Updated Diamond-Forrester PreTest Probability available for n=1339 normal BMI patients, n=1164 overweight BMI patients, and n=598 obese BMI patients.

Table 2. CCTA and FFR_{CT} Results

	Normal BMI <25 kg/m² (n=2166)	Overweight BMI 25–29.9 kg/m² (n=1883)	Obese BMI ≥30 kg/m² (n=965)	*P* value
Diagnostic quality				
CCTA uninterpretable	4 (0.2)	7 (0.4)	2 (0.2)	0.48
FFR_{CT} rejection rate	65 (3.0)	51 (2.7)	37 (3.8)	0.25
CCTA coronary stenosis				
Nonobstructive (all vessels <50%)	579 (26.8)	522 (27.8)	335 (34.8)	<0.001
Obstructive (any vessel ≥50%)	1583 (73.2)	1354 (72.2)	628 (65.2)	<0.001
Single vessel	958 (60.5)	809 (59.8)	399 (63.5)	0.27
Two vessel	407 (25.7)	353 (26.1)	149 (23.7)	0.52
Three vessel	218 (13.8)	192 (14.2)	80 (12.7)	0.69
% with ≥50% stenosis				
Left anterior descending	1298 (60.0)	1062 (56.6)	488 (50.7)	<0.001
Left circumflex	527 (24.4)	496 (26.4)	203 (21.1)	0.007
Right coronary artery	601 (27.8)	533 (28.4)	246 (25.6)	0.26
Left main	72 (3.3)	50 (2.7)	15 (1.6)	0.02
FFR_{CT}¶	n=2054	n=1770	n=848	
FFR_{CT} ≤0.8 (any vessel)	1393 (67.8)	1170 (66.1)	538 (63.4)	0.07
FFR_{CT} ≤0.8				0.38
Single vessel	779 (55.9)	644 (55.0)	327 (60.8)	
Two vessel	417 (29.9)	365 (31.2)	150 (27.9)	
Three vessel	197 (14.1)	161 (13.8)	61 (11.3)	
Left ventricle¶	n=1349	n=1121	n=581	
LV myocardial mass, g	111.1±27.4	127.0±30.0	136.7±36.9	<0.001
LV mass index,* g/m²	65.9±13.9	66.5±13.4	65.3±14.6	0.20
Coronary lumen volume, mL	2856.1±892.1	3094.5±991.1	3166.4±1049.5	<0.001
Luminal volume index,† mL/m²	1701.1±503.0	1625.8±496.0	1517.3±463.8	<0.001
V/M ratio‡	26.3±7.5	24.8±7.3	23.7±6.8	<0.001
CCTA radiation exposure, median (Q1, Q3)				
CT dose index,§ mGy	19.7 (12.0, 37.35)	22.4 (13.8, 40.3)	27.3 (16.6, 44.3)	0.13
Dose length product,‖ mGy×cm	302 (156.0, 578.0)	293 (164.5, 613.5)	381 (219.0, 629.0)	0.01

Data are expressed as n (%) or mean±SD, as appropriate, unless otherwise noted. BMI indicates body mass index; BSA, body surface area; CCTA, cardiac computed tomography angiography; CTDI, computed tomography dose index; DLP, dose-length product; FFR_{CT}, computed tomography fractional flow reserve; LV, left ventricle; and V/M ratio, volume-to-myocardial mass ratio.

*LV mass index: LV mass/BSA.

†Luminal volume index: coronary lumen volume/BSA.

‡V/M ratio: coronary luminal volume/LV myocardial mass.

§CTDI available for n=1916 normal BMI patients, n=1574 overweight BMI patients, and n=728 obese BMI patients.

‖DLP available for n=2073 normal BMI patients, n=1772 overweight BMI patients, and n=863 obese BMI patients.

¶FFR_{CT}: Normal BMI n=2054, Overweight BMI n=1770, Obese BMI n=848; Left Ventricle: Normal BMI n=1349, Overweight BMI n=1121, Obese BMI n=581.

was less likely to be requested among patients with obesity (91.7%) compared with patients with overweight (96.7%) and normal BMI (97.8%). In those patients with FFR_{CT} performed, there was no difference in the frequency of hemodynamically significant disease (FFR_{CT}≤0.8): 63.4% obese; 66.1% overweight; and 67.8% normal BMI (*P*=0.07), despite the greater incidence of anatomically obstructive disease among those with normal BMI (Table 2).

Quantification of LV mass (normal BMI, n=1349; overweight BMI, n=1121; obese BMI, n=581) revealed that patients with obesity had higher myocardial mass (normal BMI, 111.1; overweight BMI, 127.0; obese BMI, 136.7; *P*<0.001), but this was not significantly different from patients with normal BMI or overweight after indexing myocardial mass by body surface area (normal BMI, 65.9; overweight BMI, 66.5; obese BMI, 65.3; *P*=0.20; Table 2). Patients with obesity also

had a higher coronary lumen volume (normal BMI, 2856.1; overweight BMI, 3094.5; obese BMI, 3166.4; *P*<0.001). However, after indexing for body surface area, coronary lumen volume was significantly lower among patients with obesity compared with patients who were overweight or had a normal BMI (normal BMI, 1701.1; overweight BMI, 1625.8; obese BMI, 1517.3; *P*<0.001; Table 2). Accordingly, the coronary lumen volume/myocardial mass (V/M) ratio was significantly lower for patients with a BMI ≥30 kg/m^2 (23.7 obese BMI versus 24.8 overweight BMI versus 26.3 normal BMI; *P*<0.001; Figure 1). This can also be seen in the negative correlation between V/M ratio and BMI (correlation −0.14; *P*<0.001; Figure 2).

In the sensitivity analysis performed that included only patients with complete data on CCTA stenosis, FFR_{CT}, and V/M ratio (normal BMI, n=1349; overweight BMI, n=1121; obese BMI, n=581), there was less anatomically obstructive CAD by CCTA among patients with obesity (73.2% normal BMI versus 72.4% overweight BMI versus 68.3% obese BMI; *P*=0.08); however, with fewer patients, this no longer met statistical significance. The FFR_{CT} was not different between the BMI groups (*P*=0.58), and V/M ratio remained significantly less for patients with obesity compared with those with overweight or normal range BMI (26.3 normal BMI versus 24.8 overweight BMI versus 23.7 obese BMI, *P*<0.001; Table S4).

Downstream Testing, Processes of Care, and Clinical Outcomes

After enrollment, 472 (48.9%) patients with obesity, 1034 (54.9%) patients with overweight, and 1291 (59.6%) patients with normal BMI underwent additional testing for CAD (*P*<0.001, Table 3). Less downstream, noninvasive testing was performed in patients with obesity than in patients who were overweight or had a normal BMI (normal BMI 31.2%, overweight BMI 25.6%, obese BMI 19.2%, *P*<0.001). Those with obesity were also less likely to undergo invasive coronary angiography (40.8% obese versus 45.5% overweight versus 47.8% normal BMI; *P*=0.001). Patients with obesity that did undergo coronary angiography were less likely to have

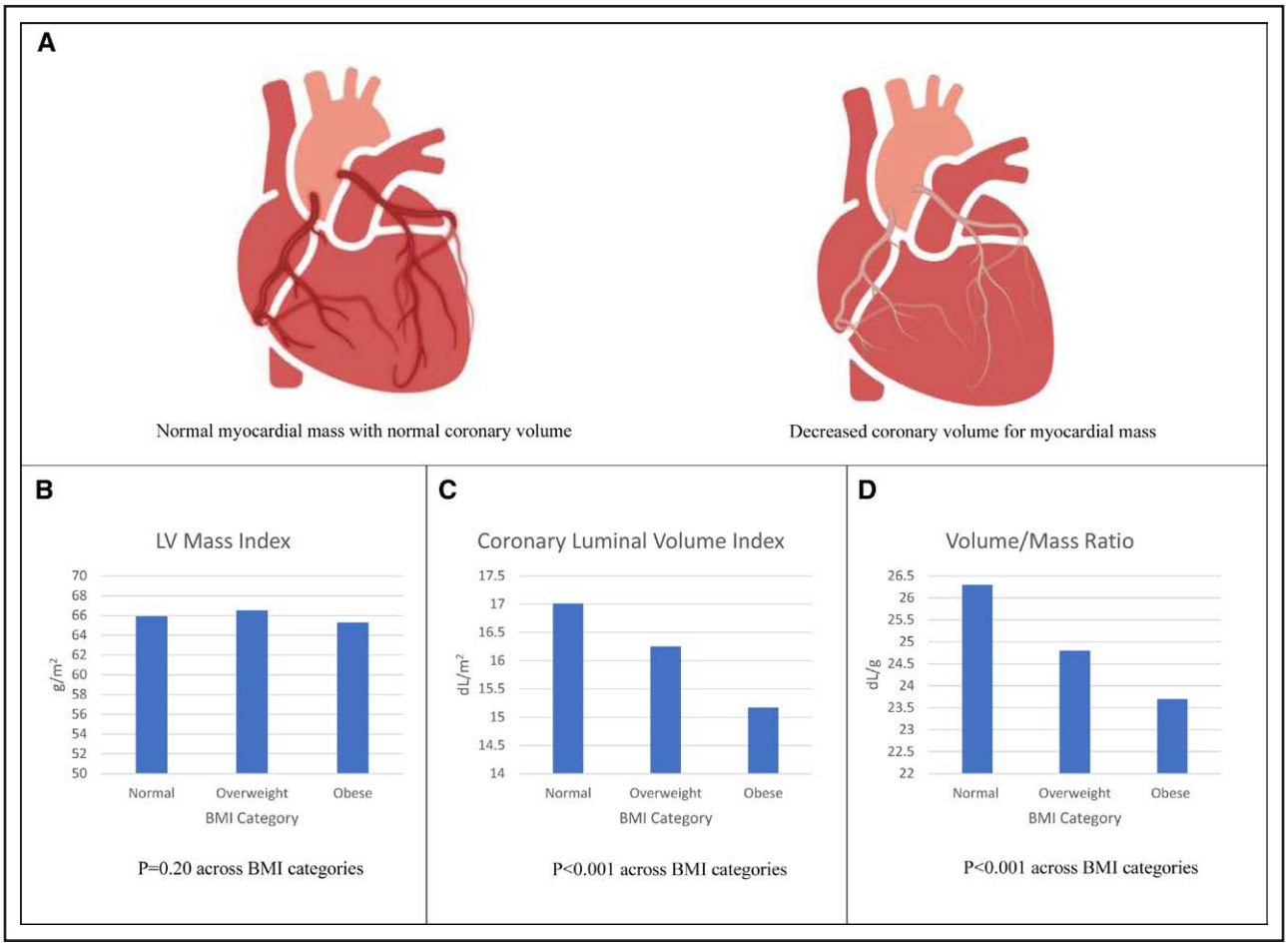

Figure 1. Coronary luminal volume and left ventricular (LV) mass by body mass index (BMI).
A, Illustration of normal myocardial mass with normal coronary volume vs insufficient coronary volume for myocardial mass. **B**, LV myocardial mass index by BMI category. **C**, Coronary luminal volume index by BMI category. **D**, Coronary luminal volume/LV myocardial mass ratio by BMI category.

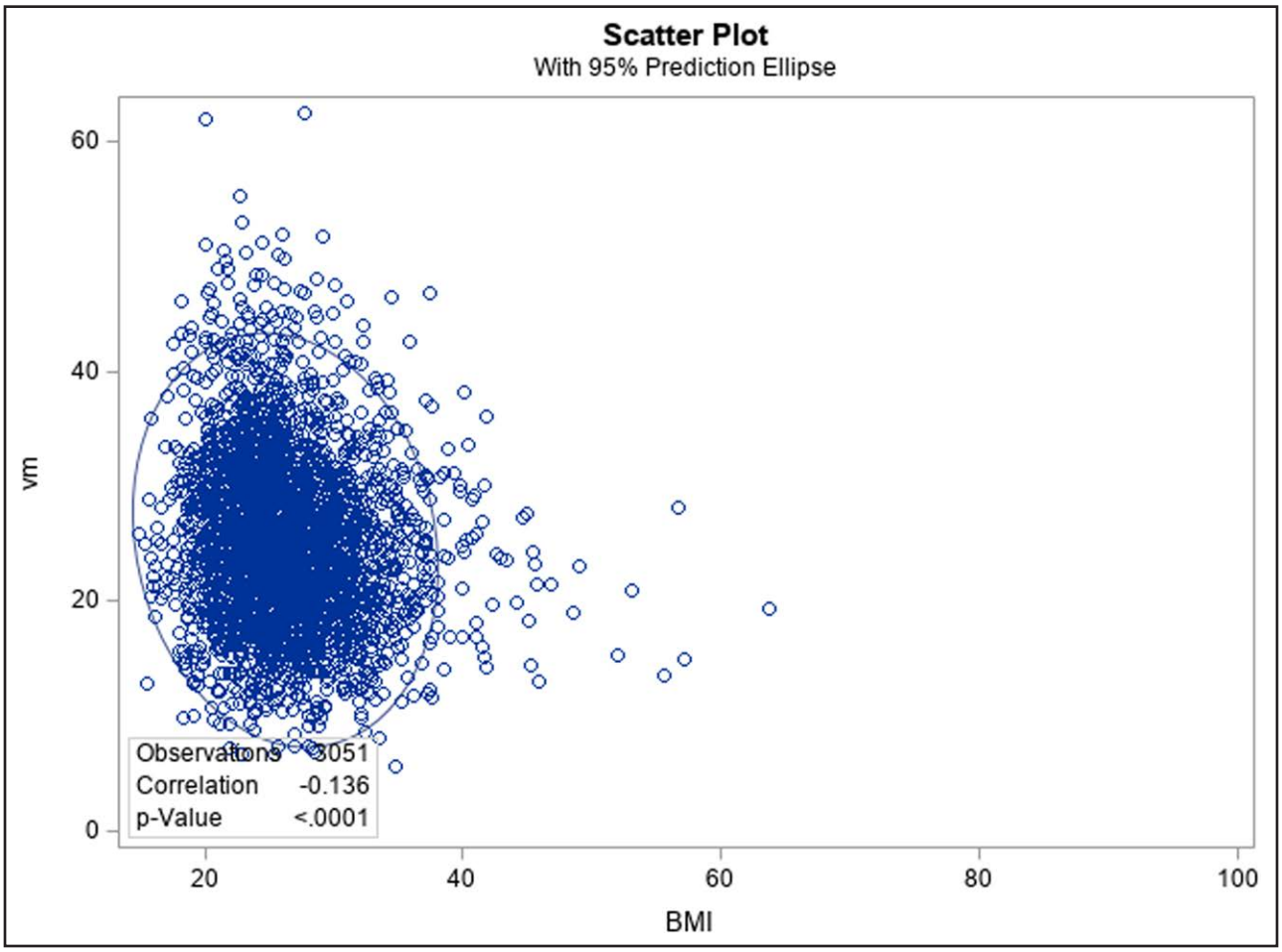

Figure 2. Correlation between volume-to-myocardial mass (V/M) ratio and body mass index (BMI).

a stenosis of >70% identified during invasive evaluation (normal BMI 55.9%, overweight BMI 56.2%, and obese BMI 48.5%; *P*<0.001). Correspondingly, patients with obesity were also less likely to undergo percutaneous coronary intervention (normal BMI 24.2%, overweight BMI 23.5%, and obese BMI 18.7%; *P*=0.002) and there was a similar trend toward less coronary artery bypass grafting (normal BMI 3.5%, overweight BMI 4.5%, and obese BMI 2.8%; *P*=0.05).

During a median follow-up of 1.0 year, there were a total of 62 MACE events, with 28 events (45.2%) among patients with normal BMI, 17 (27.4%) in patients with overweight BMI, and 17 (27.4%) in patients with obesity. There was no significant difference in the primary composite outcome of MACE (including MI, all-cause death, or unplanned hospitalization for ACS leading to revascularization; *P*=0.14; Figure 3) or any of the fatal or nonfatal secondary outcomes (Figures 4 and 5) across BMI categories. Using normal BMI as a reference, there was no significant difference in MACE among overweight (hazard ratio [HR], 0.70 [95% CI, 0.38–1.27]; *P*=0.24) or obese (HR, 1.37 [95% CI, 0.75–2.51]; *P*=0.30) patients. Results were similar after adjustment (overweight HR, 0.90 [95% CI, 0.34–2.37]; *P*=0.82 and obese HR, 2.08 [95% CI, 0.42–10.22]; *P*=0.37; Table 4). When individual clinical outcomes were evaluated, both unadjusted and adjusted analyses revealed no significant difference in the risk of an event based on BMI (Table 4). Exploration of the interaction between BMI and V/M ratio on the composite MACE outcome revealed that decreasing V/M ratio did not significantly increase the odds for MACE across BMI groups: normal BMI: OR, 1.00 (95% CI, 0.93–1.07; *P*=0.93); overweight BMI: OR, 0.96 (95% CI, 0.87–1.05; *P*=0.35); obese BMI: OR, 0.91 (95% CI, 0.82–1.02; *P*=0.10).

Among patients with obesity only, there were a total of 17 MACE events with 13 events (76.5%) among patients with CDC class 1 obesity, 2 events (11.8%) among patients with CDC class 2 obesity, and 2 events (11.8%) among patients with CDC class 3 obesity. Using normal BMI as a reference, there was no significant difference in MACE among the obesity categories (obese class 1 adjusted hazard ratio, 3.0 [95% CI, 0.46–19.56]; *P*=0.25; obese class 2 adjusted hazard ratio, 4.47 [95% CI, 0.24–82.6]; *P*=0.31, and obese class 3 adjusted hazard ratio, 9.08 [95% CI, 0.12–674.32]; *P*=0.32; Table S5).

Table 3. Processes of Care After Enrollment and Index CCTA

	Normal BMI <25 kg/m² (n=2166)*	Overweight BMI 25–29.9 kg/m² (n=1883)*	Obese BMI ≥30 kg/m² (n=965)*	*P* value
Downstream testing (any)	1291 (59.6)	1034 (54.9)	472 (48.9)	<0.001
Coronary evaluation				
Invasive coronary angiography	1036 (47.8)	856 (45.5)	394 (40.8)	0.001
Noninvasive coronary evaluation	676 (31.2)	482 (25.6)	185 (19.2)	<0.001
ETT (exercise only)	290 (13.4)	192 (10.2)	59 (6.1)	<0.001
Stress Echo	30 (1.4)	41 (2.2)	19 (2.0)	0.15
Nuclear MPI	421 (19.4)	266 (14.1)	103 (10.7)	<0.001
Cardiac MRI	21 (1.0)	26 (1.4)	16 (1.7)	0.23
Noninvasive coronary evaluation results				
Negative	697/983 (70.9)	434/675 (64.3)	143/235 (60.9)	<0.001
Positive	177/983 (18.0)	141/675 (20.9)	42/235 (17.9)	
Indeterminate	79/983 (8.0)	65/675 (9.6)	24/235 (10.2)	
Unknown	30/983 (3.1)	35/675 (5.2)	26/235 (11.1)	
Invasive coronary angiography results				
Stenosis <50%	256/1203 (21.3)	192/968 (19.8)	85/441 (19.3)	0.03
Stenosis ≥50% to ≤70%	201/1203 (16.7)	140/968 (14.5)	72/441 (16.3)	0.06
Stenosis >70%	672/1203 (55.9)	544/968 (56.2)	214/441 (48.5)	<0.001
Revascularization				
Percutaneous coronary intervention	524 (24.2)	442 (23.5)	180 (18.7)	0.002
Coronary artery bypass graft	76 (3.5)	85 (4.5)	27 (2.8)	0.05

Data are expressed as n (%). BMI indicates body mass index; cardiac MRI, cardiac magnetic resonance imaging; CCTA, cardiac computed tomography angiography; ETT, exercise tolerance test; and nuclear MPI, nuclear myocardial perfusion imaging.

*Percentages are calculated using the total population in that BMI category as denominator unless otherwise indicated.

Among the individual end points, there was a trend towards increased risk of all-cause and noncardiovascular death with increasing severity of obesity (Table S5).

Finally, when the obese and overweight BMI patient groups were combined and outcomes analyzed, there were a total of 34 MACE events among overweight or obese BMI patients. Using normal BMI as a reference, there was no difference in MACE among patients with an overweight/obese BMI (adjusted hazard ratio, 0.82 [95% CI, 0.34–2.0]; *P*=0.67). When each of the individual end points was examined, there were similarly no statistically significant differences in outcomes for all-cause death, cardiovascular death, noncardiovascular death, nonfatal MI, or unplanned revascularization; all *P*≥0.05; Table S6).

DISCUSSION

This study found that, in this real-world population of patients in the ADVANCE registry with at least 30% stenosis on CCTA, patients with obesity were younger but had a greater burden of cardiovascular comorbidities, and they were less likely to have anatomically obstructive (≥50%) CAD by CCTA but had similar cardiovascular outcomes when compared with overweight and normal BMI patients. Additionally, this study uniquely illustrated that while individuals with obesity less commonly had obstructive stenosis, they had a similar burden of hemodynamically significant disease by FFR_{CT}, which may be, at least in part, the result of an imbalance between lower coronary luminal volumes and increased myocardial mass in patients with obesity as reflected in the significantly lower V/M ratio. Thus, hemodynamic significance may reflect the underlying pathophysiology more accurately in patients with obesity and better stratify those at risk for adverse events compared with an exclusively anatomic assessment of CAD.

Similar to our analysis, patients with obesity in the Prospective Multicenter Imaging Study for Evaluation of Chest Pain trial were younger and had a higher burden of comorbidities.[27] While obesity class 2 or 3 patients in the Prospective Multicenter Imaging Study for Evaluation of Chest Pain had a similar pretest probability of CAD based on the updated Diamond-Forrester model,[25] physician estimation of a high likelihood of obstructive CAD increased with increasing BMI. However, patients with a BMI of at least 35 were less likely to have obstructive CAD on CCTA. In this study, we also found an inverse relationship between BMI and predicted risk based on updated Diamond-Forrester risk score and, similar to the Prospective Multicenter Imaging Study for Evaluation

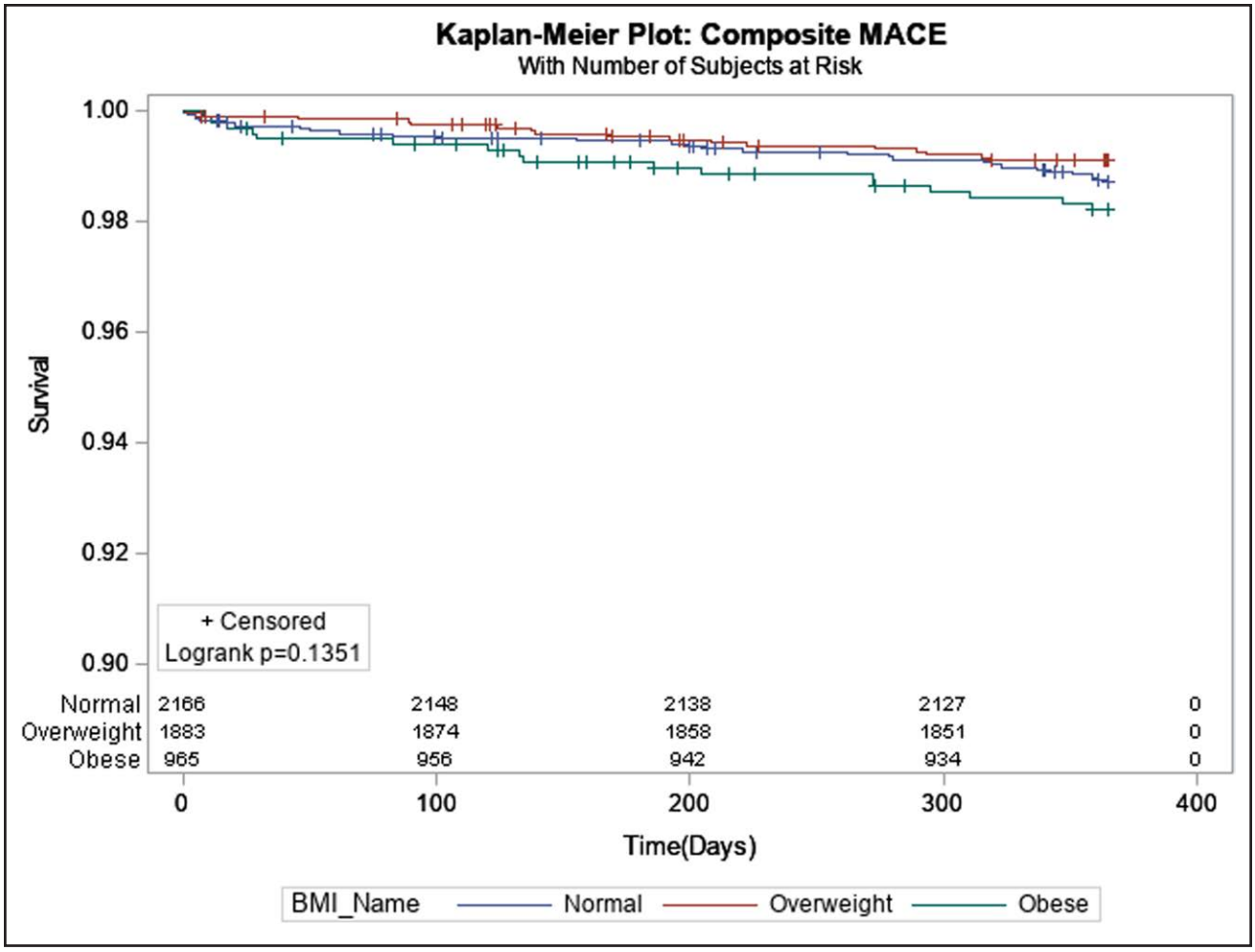

Figure 3. Composite major adverse cardiovascular events (MACE).
Kaplan-Meier plot for the composite outcome of MACE: myocardial infarction, all-cause death or unplanned hospitalization for acute coronary syndrome leading to revascularization. BMI indicates body mass index.

of Chest Pain, patients with obesity in ADVANCE were less likely to have obstructive disease by CCTA. A novel aspect of our study was the evaluation of physiological significance with FFR_{CT}. We found that a similar proportion of patients in all BMI categories had hemodynamically significant stenosis as defined by $FFR_{CT} \leq 0.80$. This discordance between anatomic and physiological significance has been previously described with invasive FFR_{CT} in the Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 trial and noninvasively with FFR_{CT},[28] but the influence of BMI on anatomic-functional discordance has not been previously evaluated.

A potential contributor to the anatomic-functional discordance observed in patients with obesity may be partially explained by a metabolic supply and demand mismatch secondary to a relatively small and inadequate coronary luminal volume for the myocardium supplied. This is supported by the significantly lower V/M ratio seen among patients with obesity in this study compared with those with overweight or normal BMIs. Given the lower coronary volume compared with LV mass observed in patients with obesity, an exclusively anatomic assessment of CAD stenosis may underestimate the burden of physiologically significant disease among individuals with obesity. Additionally, this anatomic-functional discordance could also be due to a greater burden of microvascular coronary disease among patients with obesity, who have a greater number of risk factors for not only epicardial CAD but microvascular disease as well. Although microvascular disease was not assessed in patients in the ADVANCE registry, a lower volume-to-mass ratio has been previously demonstrated in patients with microvascular disease compared with matched controls.[29] As the ease of obtaining a V/M ratio has been improved with increasing use of cardiac CT, the alterations of the V/M ratio across multiple cardiovascular disease processes, including LV hypertrophy, microvascular dysfunction, and CAD, have been increasingly described and represent an area of increasing interest to further clarify the underlying pathophysiology of cardiovascular disease.[30] Additionally, there are other possible etiologies for the observed anatomic-functional discordance that were not investigated in this

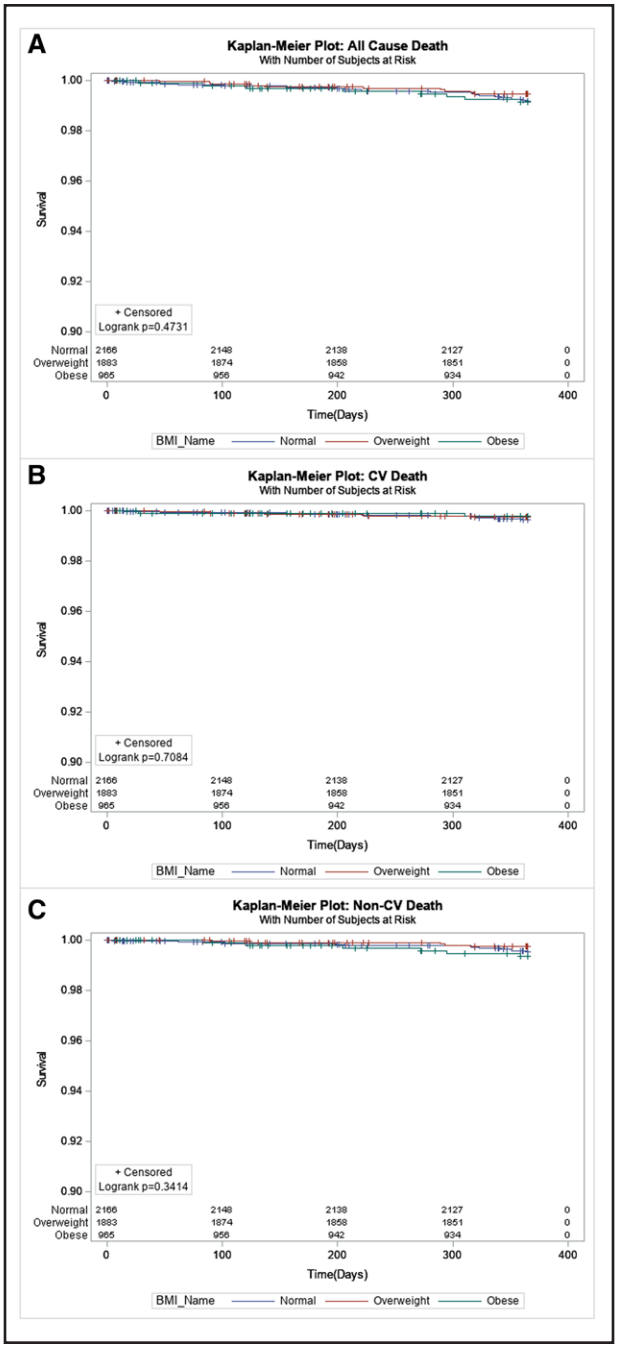

Figure 4. Mortality outcomes.
A, Kaplan-Meier plot for all-cause death. **B**, Kaplan-Meier plot for cardiovascular death. **C**, Kaplan-Meier plot for noncardiovascular death. BMI indicates body mass index; and CV, cardiovascular.

study but could explain the observed results, including atherosclerotic plaque volume, plaque composition, pericoronary inflammation, and/or endothelial dysfunction.

While we found discordance between anatomic and hemodynamically significant stenosis among patients with obesity, we observed agreement between physiologically significant (FFR_{CT}≤0.80) stenoses and clinical outcomes across BMI groups. This aligns with prior work that has shown that hemodynamic significance, even in nonobstructive CAD, may serve as a better prognostic indicator of future cardiovascular events than clinical risk scores or an anatomic assessment of CAD alone.[21] Our findings suggest that these results also hold true in the obese population and that the incorporation of physiological or hemodynamic significance is needed to optimize the evaluation of CAD and guide management in patients with obesity.

Prior work has shown that obesity can affect the diagnostic performance of noninvasive testing,[31] which could presumably lead to differences in clinical management and outcomes among patients with obesity. However, the interpretability of CCTA was high and the rejection rate for FFR_{CT} was low across all BMI groups suggesting that increased body size did not significantly impact the diagnostic yield. Additionally, we found that patients with obesity were significantly less likely to undergo any downstream testing compared with individuals with a normal or overweight BMI, including invasive coronary angiography, despite having a similar proportion of patients with physiologically significant or ischemia-inducing disease based on FFR_{CT}. Increasing recognition of the importance of physiologically significant disease on CCTA, even in the absence of obstructive CAD, may better identify individuals at risk for future adverse cardiovascular events, particularly among individuals with obesity in whom alternate noninvasive methods may have a lower diagnostic yield as a result of increased body size.

Limitations

In addition to the many strengths of this study, we also acknowledge several limitations. The ADVANCE registry represents an international real-world population, but it remains an observational analysis with the associated limitations thereof and did not enroll with the goal of ensuring an equal number of patients in each BMI cohort. Although patients with obesity comprised only 19% of the total study population, this is still one of the highest enrollments of individuals with obesity in a CCTA study and confirms the feasibility of this diagnostic approach in this population. This is important since other means of noninvasive imaging, such as stress echocardiography or myocardial perfusion imaging with single-photon emission computed tomography, may be significantly limited by artifact due to increased body habitus. Additionally, all clinical management decisions following enrollment and the initial CCTA were left to the discretion of the local physicians, including the decision to submit the CCTA for FFR_{CT}, and thus are reflective of current clinical practice but may be influenced by referral bias. Not all patients had a V/M assessment completed. The patients who were enrolled during the early stages of the trial with use of version 1.0 of the CT analysis software did not have a V/M assessment performed, while those who enrolled after 2.0 utilization all had a V/M assessment. While this is a subset of the final population, there was no selection

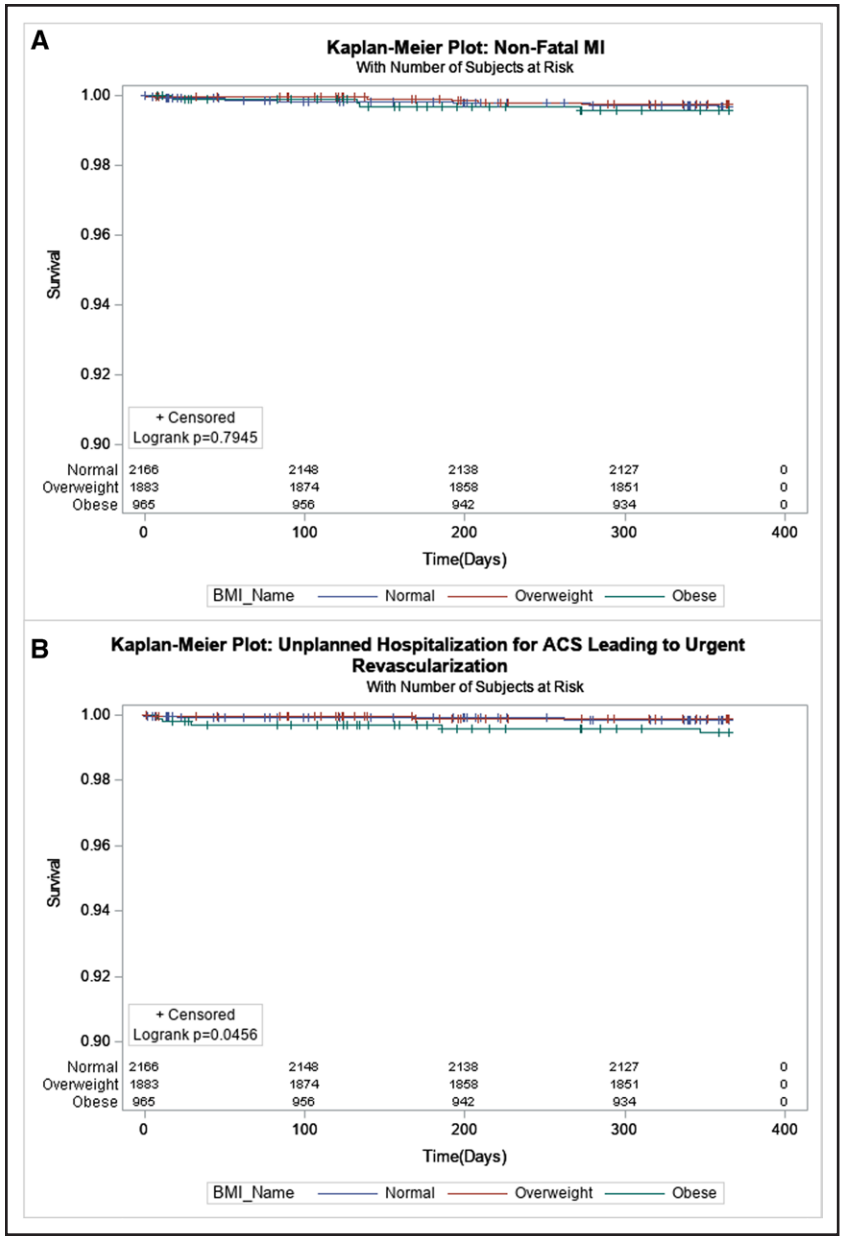

Figure 5. Nonfatal outcomes.
A, Kaplan-Meier plot for nonfatal MI. **B**, Kaplan-Meier plot for unplanned hospitalization for ACS leading to urgent revascularization. ACS indicates acute coronary syndrome; BMI, body mass index; and MI, myocardial infarction.

bias influencing which patients underwent V/M assessment beyond the timing of enrollment. Additionally, the differences observed in the V/M ratio, while statistically significant, were numerically very small, and additional analyses are needed to fully understand the clinical significance of these differences, particularly in light of the low event rate in this population. Clinical use of the V/M ratio for the prediction of microvascular disease requires further study, including correlation with quantitative positron emission tomography, cardiac magnetic resonance imaging, or invasive coronary flow reserve measures. The patients in ADVANCE represent a relatively low-risk cohort with low rates of adverse events. In this setting, outcome differences between groups may not be detectable. Additionally, among the CDC obesity subclasses where the number of patients within each class was small, observed differences in events should be viewed as hypothesis-generating and require further testing and replication in a larger population. Finally, as an observational registry analysis, causation cannot be assessed, and there are likely multiple factors, including processes of care, baseline comorbidities, and anatomic coronary differences, that play a role in patient outcomes. However, we used an adjusted analysis to try to minimize the confounding contribution of these factors.

Conclusions

In this secondary analysis of the ADVANCE registry, patients with obesity were younger but had a higher burden of comorbidities. While patients with obesity were less likely to have anatomically obstructive CAD, they had

Table 4. Clinical Outcomes

		Unadjusted			Adjusted		
	Total events	HR	95% CI	*P* value	HR	95% CI	*P* value
MACE composite	62						
Normal BMI (ref)	28						
Overweight BMI	17	0.70	0.38–1.27	0.24	0.87	0.32–2.32	0.78
Obese BMI	17	1.37	0.75–2.51	0.30	2.00	0.40–9.98	0.40
All-cause death	37						
Normal BMI (ref)	18						
Overweight BMI	10	0.64	0.30–1.38	0.25	1.54	0.40–5.94	0.53
Obese BMI	8	1.01	0.44–2.31	0.99	5.62	0.60–52.93	0.13
Cardiovascular death	15						
Normal BMI (ref)	8						
Overweight BMI	5	0.72	0.24–2.19	0.56	1.16	0.16–8.17	0.88
Obese BMI	2	0.57	0.12–2.67	0.47	0.90	0.02–44.77	0.96
Noncardiovascular death	22						
Normal BMI (ref)	10						
Overweight BMI	5	0.57	0.20–1.68	0.31	1.65	0.24–11.36	0.61
Obese BMI	6	1.36	0.49–3.74	0.55	15.81	0.86–291.47	0.06
Nonfatal MI	16						
Normal BMI (ref)	7						
Overweight BMI	5	0.82	0.26–2.59	0.74	0.30	0.05–1.67	0.17
Obese BMI	4	1.29	0.38–4.41	0.68	0.19	0.01–4.30	0.30
Unplanned revascularization	10						
Normal BMI (ref)	3						
Overweight BMI	2	0.77	0.13–4.58	0.77	0.84	0.04–18.74	0.91
Obese BMI	5	3.75	0.90–15.70	0.07	5.54	0.13–238.30	0.37

BMI indicates body mass index; HR, hazard ratio; MACE, major adverse cardiovascular events; and MI, myocardial infarction.

a similar degree of hemodynamically significant CAD, as assessed by the FFR_{CT} and similar rates of adverse events. Given the lower coronary volume-to-mass ratio observed in patients with obesity, an exclusively anatomic assessment of CAD stenosis may underestimate the burden of physiologically significant disease among individuals with obesity.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S6

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