

ORIGINAL RESEARCH

Identifying High-Risk Obese Individuals Without Diabetes for GLP-1RA Therapy Using Coronary CTA



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ABSTRACT

BACKGROUND The SELECT trial demonstrated that semaglutide reduced major adverse cardiovascular events among individuals with cardiovascular disease (CVD) and overweight/obesity without diabetes. We hypothesized that coronary artery disease (CAD) detected by coronary computed tomography angiography (CCTA) identifies individuals with similar cardiovascular risk.

OBJECTIVES The aim of the study was to evaluate the association between CAD severity by CCTA and cardiovascular outcomes among individuals resembling The SELECT (Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes) trial population but without known CVD.

METHODS We included individuals aged ≥ 45 years with body mass index ≥ 27 kg/m² undergoing CCTA at 2 centers. Exclusions: prior myocardial infarction, revascularization, stroke, diabetes, end-stage kidney disease, or malignancy. CAD severity was categorized as absent (0%), nonobstructive (1%-49%), or obstructive ($\geq 50\%$). Extensive nonobstructive CAD was defined as plaque in all coronary arteries. Cox modeling assessed the association between CAD and the composite outcome of cardiovascular death, myocardial infarction, or stroke.

RESULTS Among 5,173 individuals, 53% were male, and 68% and 62% had hypertension and dyslipidemia, respectively. Individuals with obstructive CAD had a 71% higher risk of events (adjusted HR: 1.71; 95% CI: 1.21-2.42; $P = 0.002$) vs those with no CAD. At 4 years, event risks were 7.8% for obstructive CAD and 7.7% for extensive nonobstructive CAD, comparable to SELECT's control arm (9.7%). Applying SELECT's relative rate reduction of 20%, the number needed to treat was 66 for obstructive and 67 for extensive nonobstructive CAD, comparable to SELECT's 56.

CONCLUSIONS Obstructive or extensive nonobstructive CAD by CCTA identifies overweight/obese individuals without diabetes and no prior CVD as being at elevated cardiovascular risk, suggesting potential benefit from glucagon-like peptide-1 receptor agonist therapy. (JACC Adv. 2025;4:101995) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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**ABBREVIATIONS
AND ACRONYMS****BMI** = body mass index**CAD** = coronary artery disease**CAD-RADS** = Coronary Artery
Disease Reporting and Data
System**CCTA** = coronary computed
tomography angiography**CVD** = cardiovascular disease**GLP-1RA** = glucagon-like
peptide-1 receptor agonist**ICD** = International
Classification of Diseases**MI** = myocardial infarction**NNT** = number needed to treat**MGB** = Mass General Brigham

Over 50% of the world's population is predicted to be overweight or obese by 2035, a threshold already surpassed in the United States, where about 74% meet these criteria.¹⁻³ Obesity imposes a significant financial burden, with \$260.6 billion spent yearly on obesity-related medical expenditures.^{4,5} Obesity also contributes to other cardiovascular risk factors such as dyslipidemia, diabetes, and hypertension.⁶

In 2024, the U.S. Food and Drug Administration approved Wegovy (semaglutide) as the first weight loss medication to reduce life-threatening cardiovascular disease (CVD) events, specifically in adults with CVD and either obesity or overweight. This approval was based on the SELECT trial that demonstrated that semaglutide, a glucagon-

like peptide-1 receptor agonist (GLP-1RA), reduces the rate of major adverse cardiovascular events (cardiovascular death, myocardial infarction [MI], or stroke) by approximately 20% compared with placebo.⁷

The potential for CVD prevention from semaglutide could be further expanded if the SELECT findings could extend to obese individuals who have not experienced a cardiovascular event but who have an elevated baseline CVD risk, similar to the SELECT population. Coronary computed tomography angiography (CCTA) can identify the presence, severity, and extent of coronary artery disease (CAD).⁸⁻¹⁰ Unlike traditional risk scores, CCTA provides direct visualization and quantification of the burden of coronary atherosclerosis, making it a robust tool for identifying individuals at higher risk of adverse cardiovascular outcomes.^{11,12} We hypothesized that overweight/obese individuals identified as high risk by CCTA may have a sufficiently high rate of cardiovascular events that they would derive a potential benefit from GLP-1RA. Therefore, we aimed to evaluate the association between CAD severity identified by CCTA and long-term cardiovascular outcomes among individuals without known coronary heart disease who otherwise resemble the SELECT trial population.

METHODS

STUDY DESIGN. The Mass General Brigham (MGB) CCTA registry is a retrospective cohort comprising approximately 27,978 individuals aged 18 years or older, clinically referred for CCTA, primarily for symptom evaluation, at Brigham and Women's Hospital and Massachusetts General Hospital between

2006 and 2021 (Supplemental Figure 1). Only the first CCTA was included in the analysis for individuals with multiple studies. The MGB Institutional Review Board approved the study with a waiver of informed consent.

STUDY POPULATION. In line with the SELECT trial population, we included individuals aged 45 years or older with a body mass index (BMI) of 27 kg/m² or higher and who did not have diabetes. In contrast to the SELECT trial, which included individuals with established CVD, we included individuals without a prior history of MI, percutaneous coronary intervention, coronary artery bypass grafting, or stroke. Similarly to SELECT, we excluded individuals with stage 5 chronic kidney disease (estimated glomerular filtration rate <15 mL/min/1.73 m²), prior renal transplant, ongoing renal replacement therapy, or a diagnostic International Classification of Diseases (ICD) code for malignant neoplasms, except non-melanoma skin cancer.

IMAGING AND CLINICAL ASSESSMENTS. CCTA was performed using a range of 64-slice or higher multi-detector computed tomography scanners, adhering to institutional protocols and the Society of Cardiovascular Computed Tomography guidelines. Both prospective gating with axial acquisition and retrospective gating with helical acquisition techniques were employed. Image interpretation followed Society of Cardiovascular Computed Tomography standards and was conducted by Core Cardiovascular Training Statement level III-trained cardiologists or radiologists. The presence and severity of CAD were assessed using the Coronary Artery Disease Reporting and Data System (CAD-RADS)¹³ classification, which categorized the severity of stenosis in the worst segment as follows: 1) no CAD (CAD-RADS 0); 2) non-obstructive CAD (<50% stenosis; CAD-RADS 1-2); and 3) obstructive CAD (≥50% stenosis; CAD-RADS 3-5).

To further identify whether extensive non-obstructive CAD might be associated with increased risk, we evaluated the extent of plaque among participants with nonobstructive CAD. The extent of disease was quantified by the number of coronary vessels with nonobstructive plaques, including the left main, left anterior descending, left circumflex, and right coronary arteries. Each vessel was assigned a score of 0 or 1 based on the absence or presence of plaque. As a result, the extent of disease ranged from 0 to 4. Extensive nonobstructive CAD was defined as a score of 4.

CLINICAL DATA. Demographic information, including age, sex, race, ethnicity, and vital status from the Social Security Administration, was obtained through

the MGB Research Patient Data Registry and Enterprise Data Warehouse. Clinical data such as diagnostic and procedural codes, laboratory results, imaging reports, clinical notes, and medication history were also sourced from these repositories. Overweight (BMI ≥ 27 kg/m²) and obesity (BMI ≥ 30 kg/m²) were defined using the most recent BMI prior to the CCTA scan or an obesity diagnosis based on ICD codes before the procedure. Cause of death was determined using ICD-coded data from the Massachusetts Office of Vital Statistics and the Centers for Disease Control and Prevention National Death Index, supplemented by a manual review of electronic health records. Cardiovascular risk factors and medical diagnoses at the time of CCTA were identified using ICD-9, ICD-10, and Current Procedural Terminology codes and laboratory data. Smoking status within the year of CCTA was assessed using a validated natural language processing¹⁴ tool and was categorized as never, former, or current smoking. Medication records for lipid-lowering therapies, spanning 2 years before and 1 year after CCTA, were extracted from electronic prescription records within the MGB Enterprise Data Warehouse.

OUTCOME. Participants were followed up from the time of CCTA for the composite outcome of cardiovascular death, nonfatal MI, or stroke, mirroring the primary endpoint in SELECT. Cardiovascular mortality was classified using ICD-coded causes of death derived from death certificates. Nonfatal MI and stroke were identified using validated methodologies based on ICD codes in the primary discharge diagnosis position. Participants who died from causes not included in the composite event were censored at the time of death.¹⁵

STATISTICAL ANALYSIS. We compared participant characteristics at the time of CCTA between the 3 CAD severity groups: no CAD, nonobstructive CAD, and obstructive CAD. Categorical variables were summarized as frequencies and percentages, and their distributions were compared using chi-square or Fisher exact tests. Continuous variables were summarized as median (first and third quartiles, Q1-Q3), and their distribution was compared using the Mann-Whitney *U* test.

In time-to-first event analyses, we compared the cause-specific cumulative risk of the composite event between the 3 CAD severity groups. In unadjusted analyses, we estimated cumulative risks by using the Kaplan-Meier estimator, and we estimated cause-specific HRs with 95% CIs for obstructive vs no CAD and nonobstructive vs no CAD with the use of a Cox proportional hazards model with CAD severity as a

fixed factor. In adjusted analyses, we accounted for age, sex, hypertension, dyslipidemia, current smoking, and baseline statin use. We estimated the cumulative risks and the cause-specific HRs with the use of a multivariable Cox proportional hazards model. We used cause-specific Cox proportional-hazards models, censoring deaths from noncardiovascular causes at the time of occurrence to align with the SELECT trial methodology and focus on the composite major adverse cardiovascular events endpoint.^{7,16,17} Listwise deletion was used for the model analysis. Participants were followed from the date of their index CCTA (time zero) until the first major adverse cardiovascular event, noncardiovascular death (censored), loss to follow-up, or study end. The multicollinearity was assessed via Spearman rank correlation, and the proportional hazards assumption was verified using Schoenfeld residuals. There was no evidence of assumption violations.

In unadjusted analyses, we reported the absolute risks $S_0(t^*)$ of the composite event in each CAD severity group at 1 milestone timepoint t^* : 4 years. Absolute 4-year event risks were estimated to align with the SELECT trial's primary Kaplan-Meier analysis through 48 months (mean follow-up: 3.3 years). To estimate the potential benefit from semaglutide therapy, we used the HR of 0.80 for semaglutide vs placebo observed in the SELECT trial for the composite event. We calculated what these absolute risks would be if the participants were treated with semaglutide. We further estimated an absolute rate reduction and the number needed to treat (NNT) in each CAD severity group. We compared these quantities to their counterparts estimated in the SELECT trial at the same milestone timepoint.⁷ All analyses were conducted with Stata MP version 18 (StataCorp).

RESULTS

Among 27,978 individuals in the MGB CCTA Registry, 5,173 (18.5%) overweight and obese individuals met our selection criteria and were followed for a median follow-up of 5.8 years (Q1-Q3: 3.9-8.5 years) from the index CCTA. Among the 5,173 included individuals, 2,762 (53.4%) were male, the median age was 57 years (Q1-Q3: 50-65), 3,500 (67.7%) had hypertension, and 3,222 (62.3%) had dyslipidemia. Regarding coronary CAD severity, 1,838 (35.5%) had no CAD, 2,239 (43.3%) had nonobstructive CAD, and 1,096 (21.2%) had obstructive CAD. Baseline characteristics stratified by CAD status are summarized in [Table 1](#). Male and older participants were more likely to have obstructive CAD ($P < 0.001$) ([Table 1](#)). Cardiovascular risk factors, including hypertension (80.5%),

TABLE 1 Baseline and Demographics by CAD Group

	All Patients (N = 5,173)	No CAD (n = 1,838, 35.5%)	Nonobstructive CAD (n = 2,239, 43.3%)	Obstructive CAD (n = 1,096, 21.2%)	P Value
Age, y, median (IQR)	57 (50-65)	51 (45-58)	59 (52-66)	63 (56-70)	<0.001
Female, n (%)	2,411 (46.6%)	1,133 (61.6%)	950 (42.4%)	328 (29.9%)	<0.001
Race, n (%)					<0.001
White	4,154 (80.3%)	1,303 (70.9%)	1,874 (83.7%)	977 (89.1%)	
Black	339 (6.6%)	203 (11.0%)	107 (4.8%)	29 (2.7%)	
Hispanic	132 (2.6%)	73 (4.0%)	45 (2.0%)	14 (1.3%)	
Asian	114 (2.2%)	53 (2.9%)	42 (1.9%)	19 (1.7%)	
Other	434 (8.4%)	206 (11.2%)	171 (7.6%)	57 (5.2%)	
BMI (kg/m ²), median (IQR)	31.1 (28.7-35); n = 4,368	31.6 (28.7-35.8); n = 1,527	31.1 (28.7-35); n = 1,942	30.4 (28.4-33.5); n = 899	<0.001
BMI ≥40 kg/m ² , n (%)	433 (8.4%)	185 (10.1%)	189 (8.4%)	59 (5.4%)	<0.001
Smoking status, n (%)					<0.001
Nonsmoker	3,315 (64.1%)	1,290 (70.2%)	1,416 (63.2%)	609 (55.6%)	
Past smoker	1,066 (20.6%)	270 (14.7%)	498 (22.2%)	298 (27.2%)	
Current smoker	792 (15.3%)	278 (15.1%)	325 (14.5%)	189 (17.2%)	
Hypertension, n (%)	3,500 (67.7%)	1,048 (57.0%)	1,570 (70.1%)	882 (80.5%)	<0.001
Dyslipidemia, n (%)	3,222 (62.3%)	919 (50.0%)	1,442 (64.4%)	861 (78.6%)	<0.001
Heart failure, n (%)	533 (10.3%)	157 (8.5%)	258 (11.5%)	118 (10.8%)	0.007
Atrial fibrillation, n (%)	897 (17.3%)	235 (12.8%)	448 (20.0%)	214 (19.5%)	<0.001
CKD, n (%)	253 (4.9%)	55 (3.0%)	116 (5.2%)	82 (7.5%)	<0.001
Statin use	2,382 (47.6%)	491 (28.4%)	1,136 (51.7%)	755 (69.7%)	<0.001

BMI = body mass index; CAD = coronary artery disease; CKD = chronic kidney disease.

dyslipidemia (78.6%), and current smoking (17.2%), were more prevalent among individuals with obstructive CAD ($P < 0.001$).

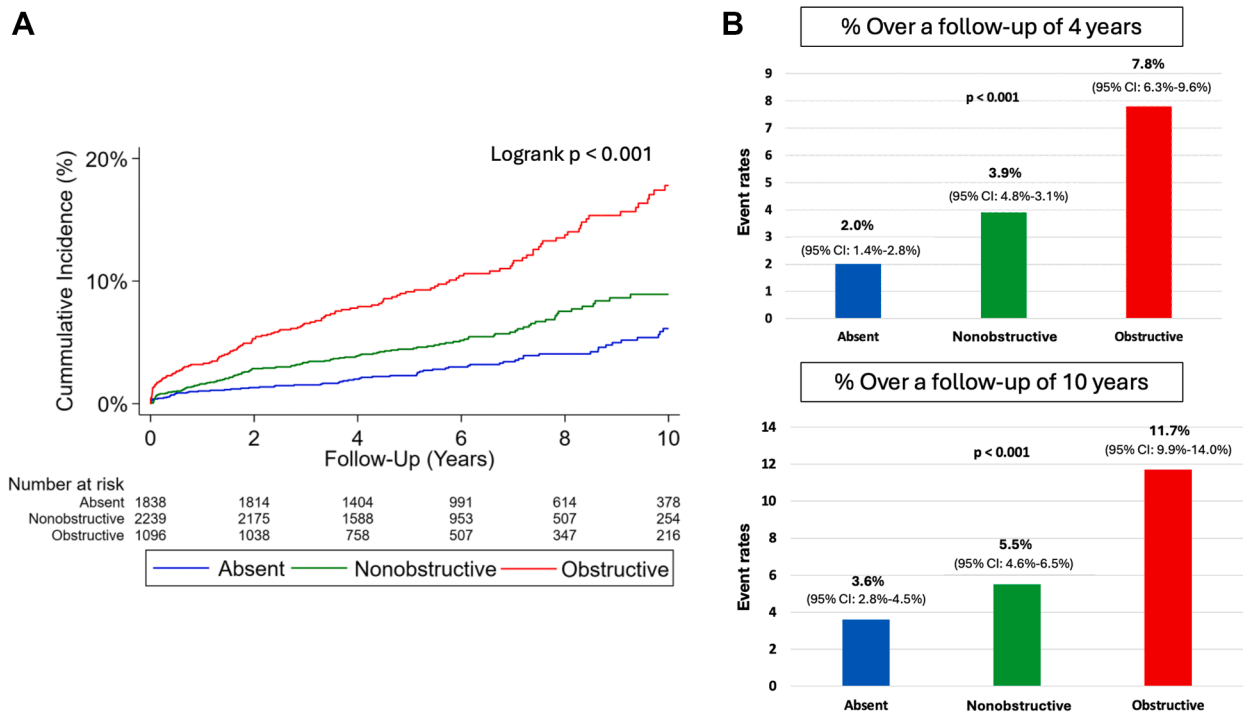
ASSOCIATION BETWEEN CAD SEVERITY AND THE COMPOSITE OUTCOME OF CARDIOVASCULAR DEATH, MI, OR STROKE. Over a 10-year follow-up, the composite outcome of cardiovascular death, MI, or stroke occurred in 3.6% of individuals without CAD, 5.5% of individuals with nonobstructive CAD, and 11.7% of individuals with obstructive CAD. In unadjusted analyses, individuals with obstructive CAD had a higher rate of the composite outcome (HR: 3.47; 95% CI: 2.58-4.67; $P < 0.001$) than those without CAD. After adjusting for age, sex, hypertension, dyslipidemia, current smoking, and statin use at baseline, these associations remained significant (adjusted HR: 1.71; 95% CI: 1.21-2.42; $P = 0.002$) (Figure 1).

When stratifying individuals with nonobstructive disease by the extent of CAD, event risk over a 10-year follow-up increased incrementally with the number of affected vessels: 4.6% for 1-vessel CAD, 4.9% for 2-vessel CAD, 5.9% for 3-vessel CAD, and 8.8% for four-vessel CAD. Similarly, Kaplan-Meier

cumulative incidence curves revealed a stepwise increase in the incidence of major adverse cardiovascular events with more extensive vessel involvement (Figure 2). In an unadjusted analysis, the presence of extensive nonobstructive CAD was significantly associated with the composite outcome (HR: 3.01; 95% CI: 1.84-4.92; $P < 0.001$) when compared with individuals with no CAD. However, after adjusting for traditional cardiovascular risk factors, these findings were no longer significant (adjusted HR: 1.47; 95% CI: 0.86-2.49; $P = 0.16$) (Supplemental Table 3).

When evaluating these outcomes using a milestone timepoint of 4 years, the incidence of the composite outcome of cardiovascular death, MI, or stroke increased with increasing CAD severity and extent. Event risks were 2% for no CAD, 3.9% for nonobstructive CAD, and 7.8% for obstructive CAD, with the latter being comparable to the 9.7% event risk inferred from the control arm of SELECT at the same timepoint. Among individuals with extensive nonobstructive CAD, the corresponding event risk was 7.7%, while for less extensive nonobstructive CAD, the event risk was 3.4%.

FIGURE 1 Cardiovascular Death, Myocardial Infarction, or Stroke by Coronary Artery Disease Severity Over 10-Year Follow-Up



(A) Kaplan-Meier curves show the 10-year cumulative incidence of the composite outcome (cardiovascular death, myocardial infarction, or stroke) stratified by CAD severity on CCTA: no CAD (blue), nonobstructive CAD (green), and obstructive CAD (red) (log-rank $P < 0.001$). (B) Bar charts display corresponding event risk at 4 years: 2.0% (no CAD), 3.9% (nonobstructive), and 7.8% (obstructive); and at 10 years: 3.6%, 5.5%, and 11.7%, respectively ($P < 0.001$), illustrating a stepwise increase in risk with greater CAD severity. CAD = coronary artery disease; CCTA = coronary computed tomography angiography.

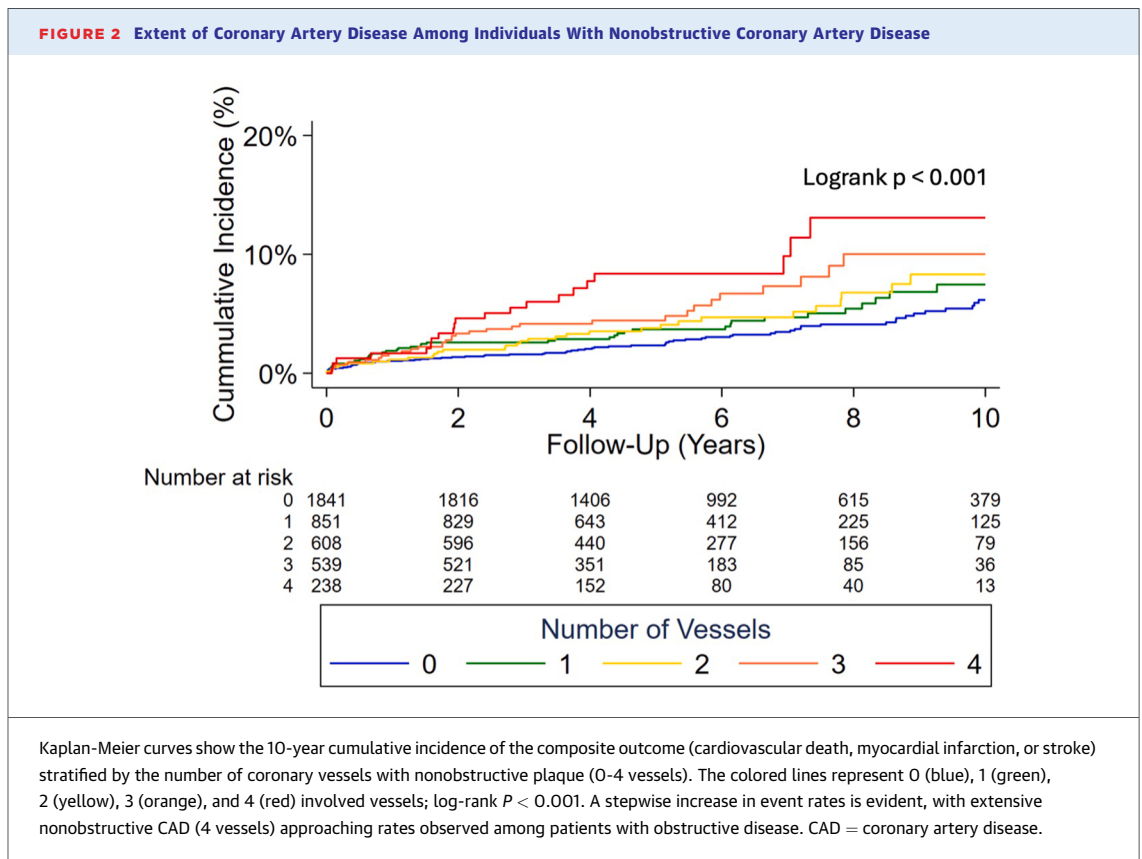
NUMBER NEEDED TO TREAT ANALYSIS. Applying the 20% relative rate reduction from the SELECT trial to the observed 4-year event risk in the obstructive CAD group (7.8%) yielded an estimated NNT of 66. This NNT aligns with the 56 inferred in the SELECT trial for preventing 1 event with semaglutide over the same 4-year timepoint (**Central Illustration**). Similarly, among individuals with extensive non-obstructive CAD, the estimated NNT was 67 based on the 4-year event risk of 7.7%. However, among individuals with less extensive nonobstructive CAD, the estimated NNT was 149 based on the 4-year event risk of 3.4% (**Supplemental Table 1**).

DISCUSSION

In this study, we examined the association between CAD severity, assessed by CCTA, and cardiovascular outcomes among overweight or obese individuals without prior CVD or diabetes. We found that patients with obstructive CAD or those with extensive nonobstructive CAD had an event risk of 7.8% and

7.7%, respectively, approaching the 9.7% event risk observed in the SELECT trial control arm at the same milestone timepoint of 4 years.⁷ By focusing on the same composite major adverse cardiovascular events—cardiovascular death, MI, or stroke—as the SELECT trial, we were able to model the potential predicted benefit of GLP-1RA therapies in a "SELECT-like" CCTA population with a similar cardiovascular risk profile as individuals in SELECT but without established clinical CVD at baseline.

We observed that individuals with obstructive CAD ($\geq 50\%$ stenosis) detected by CCTA had a significantly higher cumulative incidence of events compared with those who had no CAD. However, it is now well recognized that the amount of plaque can further stratify the risk of CVD events,^{9,13,18} especially for individuals with nonobstructive CAD. Accordingly, we also evaluated the association of CAD extent, defined by the number of vessels involved, with outcomes among individuals with nonobstructive CAD. Our results showed that only patients with the most extensive disease had a high



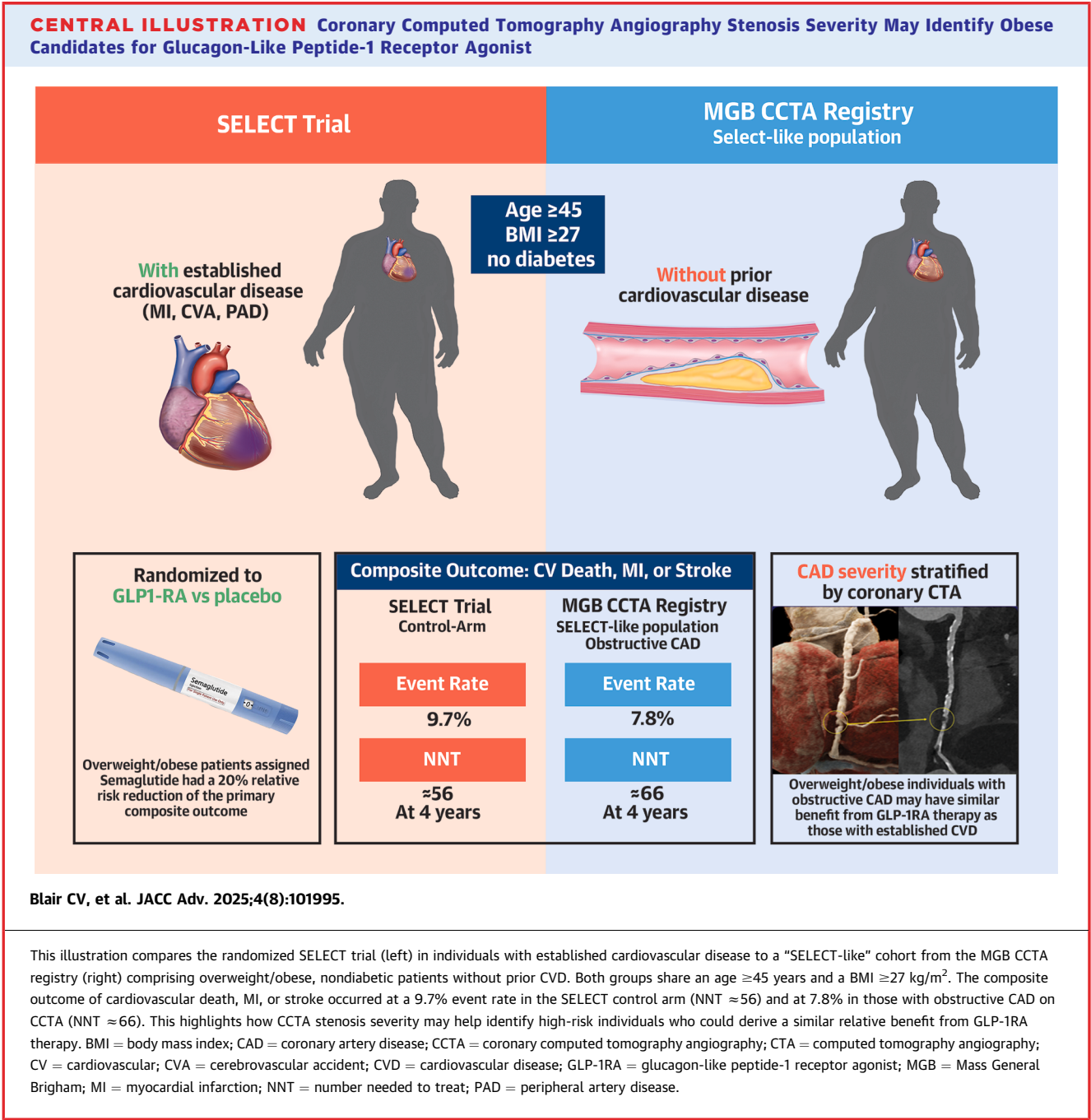
event probability comparable to the control group of the SELECT trial.⁷

Our findings suggest that patients with obstructive CAD and extensive nonobstructive CAD who meet other SELECT inclusion criteria but who have not yet experienced a clinical cardiovascular event may benefit from GLP-1RA treatment. This finding is also supported by the estimated NNTs predicted here in comparison to SELECT: 66 for obstructive CAD and 67 for extensive nonobstructive CAD (with four-vessel involvement) in our study, compared with 56 in SELECT at the same milestone timepoint of 4 years.

A strength of our study is the long follow-up period, enabling us to provide 10-year event risk and supporting the concept that the benefit of prevention efforts, such as treatment with GLP-1RA, may extend well beyond the short follow-up period of most clinical trials. Thus, our results support the likelihood that GLP-1RA analogs could provide more significant benefits over time. The benefits of GLP-1RAs may be even greater when considering their other effects. For example, recent findings with tirzepatide, a dual gastric inhibitory polypeptide/GLP-1RA, reported a reduced risk of cardiovascular death or worsening heart failure and improved health status in patients with obesity and heart failure with preserved ejection

fraction.¹⁹ Tirzepatide has also been shown to reduce sleep apnea,²⁰ a condition that can also promote cardiovascular risk. Moreover, semaglutide has been associated with a significant decrease in the progression to diabetes in SELECT⁷ as well as a reduction in pain among patients with obesity and knee osteoarthritis.²¹ GLP-1RA analogs lower systemic inflammation as evidenced by the reduction of hs-CRP by 38% compared to the placebo arm in the SELECT trial.⁷ A recent study among individuals with type 2 diabetes suggested that GLP-1RAs may have favorable changes on plaque composition by reducing lipid-rich necrotic cores, decreasing inflammatory cell infiltration, and increasing fibrous cap thickness.²² Furthermore, emerging data suggests benefits in patients with autoimmunity. A phase 3 clinical trial is testing if tirzepatide given to patients with obesity and psoriasis, a chronic immune-mediated inflammatory skin disorder associated with excess cardiovascular risk, improves psoriasis disease severity as compared to placebo.²³

Although patients without established CVD are typically less likely to be on statins than those who had a prior cardiovascular event,^{24,25} our study had a high prevalence of baseline statin therapy among individuals with obstructive CAD (~70%). Despite



this high use of statin therapy, significant residual cardiovascular risk persisted, emphasizing the need for additional therapeutic strategies. Such data also aligns with SELECT, in which 90% of participants were on lipid-lowering therapy, with the semaglutide treatment group still demonstrating a significant reduction in major adverse cardiovascular events. Therapies targeting nonlipid pathways, such as inflammation, metabolic dysfunction, and obesity, as

in this case with GLP-1RAs, could play a major role in mitigating the residual risk among otherwise appropriately treated patients.^{26,27}

Limited prior studies have demonstrated the efficacy of cardiac computed tomography for risk stratification in potential candidates for GLP-1RA treatment.^{8,11,28,29} Recently, Razavi et al³⁰ reported that coronary calcium measurement could guide the use of semaglutide for comprehensive

cardiovascular-kidney-metabolic risk reduction, emphasizing the value of imaging in optimizing therapy allocation. However, our study is the first to evaluate the relationship between CAD detected by CCTA and major cardiovascular outcomes in overweight and obese individuals without diabetes or prior CVD. Similar to the study by Razavi et al, we found that atherosclerosis imaging can provide an effective method to identify higher-risk individuals with overweight or obesity who may benefit from GLP-1RA therapy.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS. As with other advances in therapies with proven efficacy on cardiovascular risk, a progressive evolution is seen in applying treatments that have been proven in high-risk populations to patient populations with a decreasing gradient of cardiovascular risk, for example, statin use initially in secondary and subsequently in primary prevention. The striking prevalence of overweight/obesity as well as GLP-1RA-specific issues, including their cardiovascular risk reduction efficacy, their cost, supply issues, and popular interest in using these agents for more cosmetic than medical reasons, all combine to argue that more precise cardiovascular risk assessment is needed to identify patients who would benefit the most and warrant use of GLP-1RAs. Direct imaging of atherosclerosis can identify subgroups of patients with high cardiovascular risk who have not yet experienced a cardiovascular event, an approach now used in several ongoing clinical trials.³¹ However, no current trials are evaluating the efficacy of GLP-1RA agents using cardiovascular imaging for risk enrichment. Our results suggest that future trials may benefit from including individuals with obstructive CAD or extensive nonobstructive CAD without clinical CVD in evaluating GLP-1RAs, other GLP-1-related therapies, of which many are in development, and other weight loss interventions. Moreover, the absence of CAD on CCTA identifies patients with lower cardiovascular risk and could support focusing on intensive lifestyle modification over early pharmacotherapy with GLP-1RAs. Future advanced imaging techniques, such as quantitative coronary plaque analysis and perivascular fat attenuation index,³² could provide additional insights regarding plaque burden, composition, and inflammation. Such tools could provide better opportunities to assess risk, especially for therapies targeting plaque reduction or lowering inflammation.

While the data presented here suggests broader GLP-1RA use in other patients with increased cardiovascular risk without known clinical CVD events,

access to these therapies remains limited due to high costs and limited insurance coverage. Ensuring equitable access and affordability remains a significant challenge for our health care system, particularly for low-income populations³³⁻³⁵; CCTA may offer a means of detecting patients who would benefit the most from treatment while perhaps also having an impact on available GLP-1RA supply.

STUDY LIMITATIONS. This study is observational and may be limited by potential residual confounding. For example, patients referred for CCTA may be symptomatic or have a family history or other risk factors for CAD, and hence, a higher level of cardiovascular risk than the general population. However, prior studies have shown that the amount and severity of CAD—rather than symptoms—is most strongly associated with outcomes.^{36,37} While patients referred for CCTA who are found to have CAD are more likely to be treated with preventive therapies, the use of such treatments (such as the high level of statin use in our population) would be expected to attenuate risk and thus potentially reduce the impact of GLP-1RA use in the patients studied here. In fact, in SELECT, baseline medical therapy, including statins, hypertensive medications, and antiplatelet agents, was high. This supports the plausibility of comparing our “SELECT-like” cohort to the control arm of the SELECT trial. Even though we excluded individuals with prior MI or stroke, 10% of participants had prevalent heart failure and 17% had atrial fibrillation at baseline, which may influence both risk profiles and the generalizability of our results to other populations. To assess the robustness of our findings, we conducted sensitivity analyses stratified by BMI category and by sex, consistent with subgroup evaluations in the SELECT trial (Supplemental Tables 4 and 5).

Our CCTA registry was derived from a large U.S. registry encompassing 2 major medical centers. The findings may not be fully generalizable to other populations due to the smaller proportion of under-represented race and ethnicity, as most of our study population self-identified as White. Our study was primarily based on stenosis severity, and the number of vessels with plaque was used to estimate CAD extent, as plaque burden, segment involvement score, or quantitative plaque analysis were not available in our dataset due to the larger size of our cohort. In the future, detailed plaque burden quantification through segment involvement score, coronary artery calcium scoring, or quantitative coronary plaque analysis may provide additional insights regarding selecting high-risk individuals for GLP-1RA treatment.^{38,39}

CONCLUSIONS

Our findings demonstrate a significant association between the extent and severity of CAD detected by CCTA with adverse cardiovascular outcomes among overweight and obese individuals without prior CVD or diabetes, who resemble the SELECT trial population. These findings have implications for the use of CCTA for identifying high-risk overweight or obese individuals who may benefit from GLP-1RA therapy.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: CCTA assessment of stenosis severity and extent can stratify cardiovascular risk in overweight and obese, nondiabetic patients without prior CVD. Identification of obstructive or extensive nonobstructive CAD on CCTA may help clinicians recognize those most likely to derive benefit from early GLP-1RA therapy, while individuals without CAD may choose, through shared decision-making, to prioritize aggressive lifestyle strategies.

TRANSLATIONAL OUTLOOK: CCTA offers a noninvasive method to detect the presence, extent, and severity of coronary plaque. Integrating data from CCTA findings to guide patient management decisions could improve the allocation of various pharmacological interventions. Future research should explore how other imaging techniques—such as quantitative coronary plaque analysis or the fat attenuation index—can be combined with other risk factors to further personalize risk assessment and improve patient outcomes.

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APPENDIX For supplemental tables and figures and the STROBE statement, please see the online version of this paper.