Cardiovascular Diabetology

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Prognostic Value of Coronary CT Angiography Among Patients With and Without Diabetes: The Mass General Brigham CCTA registry

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Abstract

Background This study aimed to assess the relationship between coronary CT angiography detected coronary artery disease (CAD) and long-term cardiovascular outcomes among individuals with and without diabetes mellitus (DM).

Methods A retrospective cohort study of patients undergoing CCTA at two medical centers between 2006 and 2024. Patients with prior CAD, advanced kidney disease, or malignancy were excluded. DM was defined by diagnostic codes or elevated hemoglobin A1c. CCTA findings were categorized as no CAD, nonobstructive CAD (1–49% stenosis), or obstructive CAD (≥ 50% stenosis). The primary outcome was a composite of cardiovascular death (CVD) or myocardial infarction (MI).

Results Among 22,377 patients (median age 56 [IQR 47–65]; 45% women), 3,245 (14.5%) had diabetes. Individuals with diabetes were older and had more cardiovascular risk factors. Obstructive CAD was more frequent in patients with diabetes (33% vs. 19%), whereas no CAD was less common (23% vs. 42%). Over a median follow-up of 6 years (IQR 3.9–9.5), the primary outcome occurred more than twice as often among those with diabetes (7.8% vs. 3.1%; $P < 0.001$). Event rates increased with CAD severity and remained higher among individuals with diabetes across all categories. After adjustment, obstructive CAD remained significantly associated with the primary outcome in both groups (DM: HR 2.9 [95% CI 1.8–4.6], $P < 0.001$; non-DM: HR 2.7 [95% CI 2.1–3.4]), $p < 0.001$).

Conclusions Among patients undergoing CCTA, CAD was more frequent and severe in those with diabetes, and the risk of CVD or MI increased with CAD severity, approximately doubling in each category when diabetes was present.

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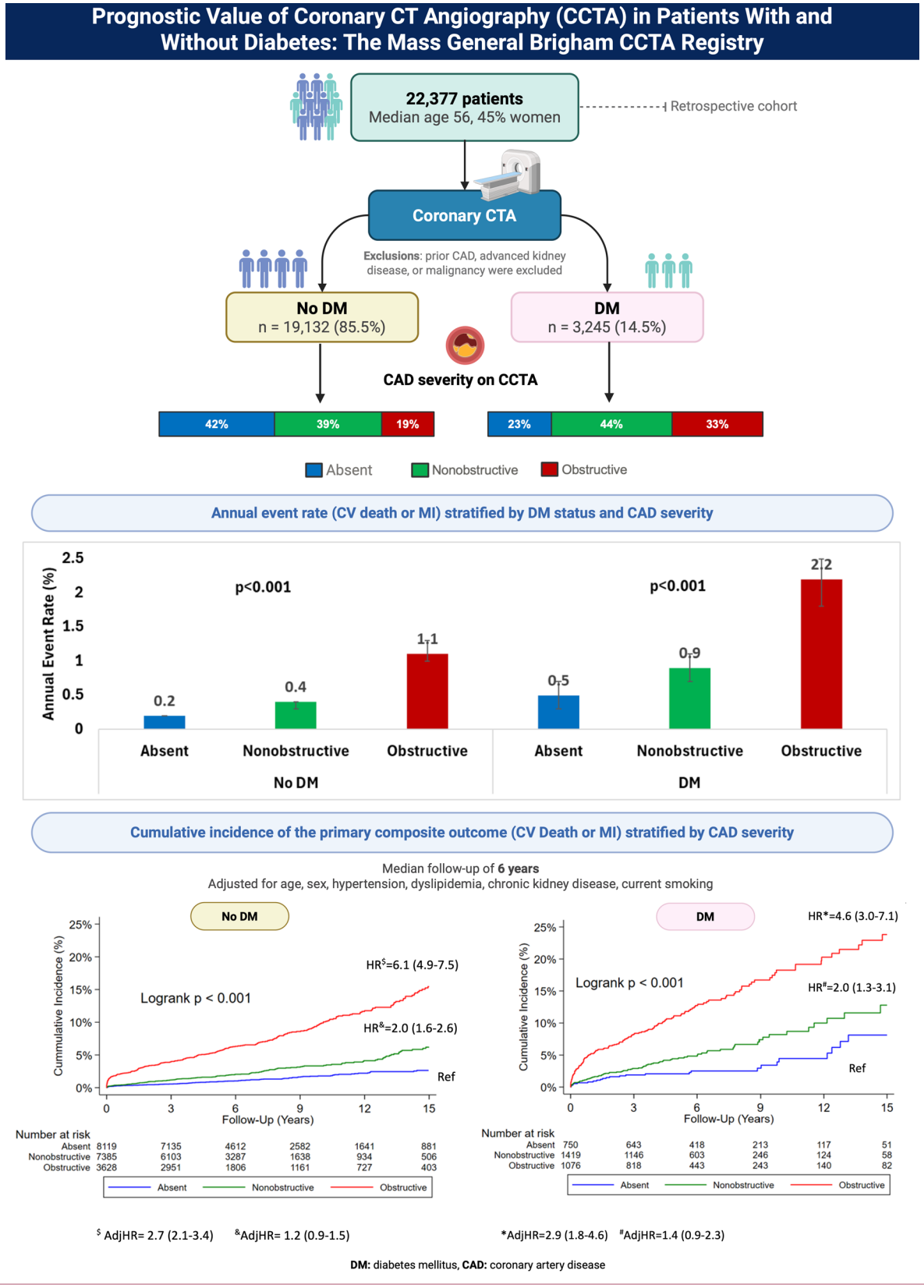
Graphical Abstract



What is already known?
Diabetes mellitus (DM) is associated with an increased burden of coronary artery disease (CAD) and higher rates of cardiovascular events. Coronary computed tomography angiography (CCTA) enables a noninvasive assessment of the presence and severity of CAD.
What does this study add?
In this large contemporary CCTA registry, patients with DM had a higher prevalence and severity of CAD and experienced substantially higher rates of cardiovascular death or myocardial infarction. Importantly, across all categories of CAD severity, patients with DM exhibited approximately a two-fold higher risk compared with those without DM.
What are the clinical implications?
These findings support the role of CCTA for refined risk stratification among individuals with DM and highlight that diabetes acts as a risk modifier across the full spectrum of CAD. Identification of CAD by CCTA may help guide more intensive preventive strategies in this high-risk population.

Introduction

Diabetes mellitus (DM) is a significant cardiovascular risk factor, with its global prevalence and associated burden steadily rising [1, 2]. Coronary artery disease (CAD) continues to be the primary cause of morbidity and mortality in individuals with DM [3–6].

Coronary computed tomography angiography (CCTA) plays a pivotal role in the diagnosis of CAD, evaluation of disease severity, risk stratification, treatment monitoring, and guiding therapeutic decision-making across a broad range of clinical scenarios [7–10].

Coronary CT angiography (CTA) and coronary artery calcium scoring have consistently shown a greater burden of disease among patients with DM compared with those who do not have DM [11, 12]. Coronary plaque has been proposed as a marker to identify diabetic patients at increased risk for future adverse cardiovascular events [13]. Furthermore, among individuals with DM presenting with stable chest pain, a CCTA strategy was associated with fewer adverse CV outcomes than a functional testing strategy [14]. However, among asymptomatic patients with diabetes, routine testing with CCTA vs. standard national guidelines-based optimal diabetes care was not associated with a reduction in events [15]. Given mixed results of these aforementioned studies, there is a need to identify the prevalence and severity of CAD, and its associated outcomes, among contemporary patients with DM referred for CCTA. Such information is particularly important given the increased use of CCTA in evaluating patients with CP [16], the increasing prevalence of DM, and the recent introduction of various DM therapies that can improve cardiovascular outcomes.

Accordingly, this study aimed to evaluate the association between CCTA-detected coronary artery disease (CAD) and long-term cardiovascular outcomes among individuals with and without DM.

Methods

Study population

The Mass General Brigham (MGB) Coronary Computed Tomography Angiography (CCTA) registry is a retrospective cohort of patients who were clinically referred for CCTA at two major medical centers - Brigham and Women's Hospital and Massachusetts General Hospital in Boston, MA- between 2006 and 2024 as previously described [17]. This study included adults aged 18 and older without a prior history of coronary artery disease (CAD), such as myocardial infarction (MI), percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG). Exclusion criteria consisted of two factors: (1) severe kidney dysfunction, which was defined as stage 5 chronic kidney disease (estimated glomerular filtration rate < 15 mL/min/m2), prior renal transplant, or those receiving renal replacement therapy; or (2) the presence of a diagnostic International Classification of Diseases (ICD) code for a malignant neoplasm during the covariate assessment window, except for non-melanoma skin cancer.

In the current study diabetes was defined as two or more ICD-9 or ICD-10 diagnosis codes on distinct dates before and up to 30 days after CCTA or a single hemoglobin A1c > 6.5% for men or women older than 50 or two hemoglobin A1c > 6.5% at least 300 days apart for women of child-bearing age 18–50. The study was approved by the MGB Institutional Review Board with a waiver of informed consent.

CCTA acquisition, interpretation, and data extraction

CCTA imaging was performed using a variety of 64-slice or higher multidetector CT scanners, adhering to institutional protocols and the Society of Cardiovascular Computed Tomography (SCCT) guidelines. Both retrospective helical and prospective axial gating techniques were employed. Pre-scan administration of nitroglycerin and beta blockers was used as indicated.

Scans were visually interpreted by COCATS level III cardiologists or radiologists with equivalent training, following SCCT guidelines. Structured reports were generated and stored within the electronic health record system.

Plaque presence and luminal stenosis degree were extracted from reports using a validated natural language processing (NLP) approach based on the open-source Canary NLP platform [18]. In this registry, this method demonstrated an accuracy of over 95% (sensitivity 90.3%

and specificity 98.4%) when compared to manual adjudication by cardiologists [19]. Findings were categorized according to the Coronary Artery Disease Reporting and Data System 2.0 (CAD-RADS) [20] as follows: Absent plaque, Non-obstructive plaque: 0–49% stenosis (CAD-RADS 1–2), Obstructive plaque: ≥50% stenosis (CAD-RADS 3–5).

The extent of disease was further evaluated by the number of coronary vessels with plaque, including the left main, left anterior descending, left circumflex, and right coronary arteries.

Clinical data

Patient demographics (age, sex, race/ethnicity), vital status from the Social Security Administration, and clinical data (including diagnostic and procedural codes, laboratory results, imaging data, clinical notes, and medication history) were retrieved from the Mass General Brigham (MGB) Research Patient Data Registry (RPDR) and Enterprise Data Warehouse (EDW). Cause of death was determined through ICD-coded data from the Massachusetts Office of Vital Statistics and the CDC National Death Index, supplemented by manual review of the electronic health record. Cardiovascular risk factors and medical diagnoses at the time of CCTA were extracted using ICD-9, ICD-10, and Current Procedural Terminology (CPT) codes, as well as laboratory values (detailed in the Supplemental Material). Smoking status in the year of CCTA was determined using a validated natural language processing (NLP) tool [21]. Prescription data for lipid-lowering medications, covering the two years prior to and one-year post-CCTA, was obtained from electronic prescription records in the MGB EDW.

Outcomes

The primary outcome was defined as a composite cardiovascular death (CVD) or nonfatal myocardial infarction (MI). Cardiovascular mortality was classified based on ICD-coded causes of death from death certificates (Supplementary Material). Acute MI was identified using codes in the principal discharge diagnosis position, following previously validated methodologies [22]. Additional outcomes that were evaluated were all-cause death, ischemic stroke and coronary revascularization (> 90 days after CCTA). Further details are provided in the Supplementary Material and in our prior work [17].

Statistical analysis

Baseline categorical characteristics were reported as frequencies (percentages) and analyzed with chi-square tests of associations or Fisher exact tests, while baseline numerical characteristics were reported as median (interquartile range) and analyzed with Mann-Whitney U tests. For survival analysis, patients were censored at date of death or date of querying vital statistics. Furthermore, patients without cardiovascular death were labeled as not experiencing cardiovascular death. Kaplan-Meier curves were compared with log-rank tests, while the primary outcome of cardiovascular death or acute myocardial infarction were analyzed with hazard ratios (HRs) and their 95% confidence intervals.

Univariable and multivariable Cox proportional hazards regressions were analyzed to assess the association of CAD severity with cardiovascular death or acute myocardial infarction outcome, as well as the individual outcomes as secondary outcomes. For multivariable Cox regression models, multicollinearity was checked with Spearman rank correlation and proportional hazard assumptions checked with Schoenfeld residuals, as well as being adjusted for the following covariates: sex, hypertension, dyslipidemia, diabetes, current smoking, and chronic kidney disease. When proportional hazard assumption was violated, accelerated-failure time (AFT) model with Weibull was used to assess the association of CAD with the outcome. Outcomes from the AFT models were reported as time ratios (TR) with corresponding 95% confidence intervals, where a $TR > 1$ indicated a longer time to the outcome and a $TR < 1$ indicated a shorter time to the outcome. AFT hazard behavior was analyzed with p, where $p > 1$ the hazard increases with time and $p < 1$ hazard decreases with time. AFT scale parameter, sigma, was reported with $sigma > 1$ representing more variability in survival times and $sigma < 1$ representing less variability in survival times. The proportional hazards assumption was violated for the primary outcome among patients without diabetes; therefore, an AFT model with Weibull distribution was used in this subgroup. CAD (plaque) categories were reported as frequencies and percentages, while primary composite outcome was reported as hazard ratios and 95% confidence intervals for both unadjusted and adjusted models. Adjusted models used the same adjusted covariates as described in the main analysis. Two-tailed tests with an alpha value of 0.05 were considered statistically significant and analyses were performed using Stata Now/ MP Version 19.5 (StataCorp, College Station, TX).

Results

Among 22,377 eligible patients (median age 56 [IQR 47–65]; 45% women), 3,245 (14.5%) had DM. Baseline characteristics are presented in Table 1. Patients with DM were older and had a higher prevalence of cardiovascular risk factors. Obstructive CAD was more common among those with DM (33% vs. 19%), while no CAD was less frequent (23% vs. 42%), $p < 0.001$. Furthermore, patients with diabetes had a greater number of coronary arteries with plaque compared with those without diabetes ($p < 0.001$). Involvement of ≥ 3 coronary arteries was

Table 1 Baseline characteristics stratified by diabetes mellitus status

Characteristic	All Patients (*n* = 22,377)	Diabetes (*n* = 3,245, 14.5%)	No Diabetes (*n* = 19,132, 85.5%)	*p*
Age, median (IQR)	56 (47–65)	59 (52–67)	56 (47–65)	**< 0.001**
Female, n (%)	10,008 (44.7%)	1,474 (45.4%)	8,534 (44.6%)	0.39
Race, n (%)				**< 0.001**
White	17,251 (77.1%)	2,102 (64.8%)	15,149 (79.2%)	
Black	1,566 (7.0%)	386 (11.9%)	1,180 (6.2%)	
Hispanic	627 (2.8%)	144 (4.4%)	483 (2.5%)	
Asian	841 (3.8%)	147 (4.5%)	694 (3.6%)	
Other	2,091 (9.3%)	466 (14.4%)	1,625 (8.5%)	
BMI, median (IQR)	28.34 (24.95–32.74); *n* = 11,062	31.82 (27.96–36.92); *n* = 2,157	27.65 (24.47–31.71); *n* = 8,905	**< 0.001**
BMI ≥ 40, n (%)	798 (7.2%); *n* = 11,062	336 (15.6%); *n* = 2,157	462 (5.2%); *n* = 8,905	**< 0.001**
HBA1C, median (IQR)	5.60 (5.30–6.10); *n* = 7,489	6.70 (6.10–7.80); *n* = 2,099	5.50 (5.20–5.70); *n* = 5,390	**< 0.001**
HBA1C ≥ 6.5, n (%)	1,302 (17.4%); *n* = 7,489	1,258 (59.9%); *n* = 2,099	44 (0.8%); *n* = 5,390	**< 0.001**
Smoking Status, n (%)				**< 0.001**
Non-Smoker	14,760 (66.0%)	1,944 (59.9%)	12,816 (67.0%)	
Past Smoker	3,835 (17.1%)	681 (21.0%)	3,154 (16.5%)	
Current Smoker	3,782 (16.9%)	620 (19.1%)	3,162 (16.5%)	
Hypertension, n (%)	11,801 (52.7%)	2,742 (84.5%)	9,059 (47.4%)	**< 0.001**
Dyslipidemia, n (%)	10,617 (47.4%)	2,572 (79.3%)	8,045 (42.1%)	**< 0.001**
Hypercholesterolemia, n (%)	4,132 (18.5%)	1,138 (35.1%)	2,994 (15.7%)	**< 0.001**
Heart Failure, n (%)	2,105 (9.4%)	539 (16.6%)	1,566 (8.2%)	**< 0.001**
Atrial Fibrillation, n (%)	3,351 (15.0%)	600 (18.5%)	2,751 (14.4%)	**< 0.001**
TIA, n (%)	709 (3.2%)	182 (5.6%)	527 (2.8%)	**< 0.001**
Stroke, n (%)	889 (4.0%)	212 (6.5%)	677 (3.5%)	**< 0.001**
CKD, n (%)	1,138 (5.1%)	340 (10.5%)	798 (4.2%)	**< 0.001**
ESRD, n (%)	29 (0.1%)	6 (0.2%)	23 (0.1%)	0.30
Pre-CCTA Medication Use				
Statin Therapies	6,658 (33.5%)	1,727 (55.1%)	4,931 (29.5%)	**< 0.001**
Anticoagulant Therapies	1,525 (7.7%)	337 (10.8%)	1,188 (7.1%)	**< 0.001**
Antiplatelet Therapies	4,860 (24.5%)	1,047 (33.4%)	3,813 (22.8%)	**< 0.001**
Blood Pressure Lowering Therapies	8,255 (41.5%)	1,871 (59.7%)	6,384 (38.1%)	**< 0.001**
Lipid Lowering Therapies	6,835 (34.4%)	1,763 (56.2%)	5,072 (30.3%)	**< 0.001**
Insulin	394 (1.8%)	354 (10.9%)	NA	**< 0.001**
SGLT2i	185 (0.8%)	147 (4.5%)	38 (0.2%)	**< 0.001**
GLP-1 RA	283 (1.3%)	220 (6.8%)	63 (0.3%)	**< 0.001**
Medication 1 Year After				
Statin Therapies	9,535 (48.0%)	2,196 (70.0%)	7,339 (43.8%)	**< 0.001**
eGFR, median (IQR)	89.98 (76.73-101.89); *n* = 15,406	87.28 (72.60-100.64); *n* = 2,769	90.52 (77.45–102.20); *n* = 12,637	**< 0.001**
Number of Vessels with plaque				**< 0.001**
0	8,870 (39.6%)	750 (23.1%)	8,120 (42.4%)	
1	3,954 (17.7%)	551 (17.0%)	3,403 (17.8%)	
2	3,128 (14.0%)	515 (15.9%)	2,613 (13.7%)	
3	3,498 (15.6%)	690 (21.3%)	2,808 (14.7%)	
4	2,927 (13.1%)	739 (22.8%)	2,188 (11.4%)	
CAD Category				**< 0.001**
No plaque or stenosis	8,869 (39.6%)	750 (23.1%)	8,119 (42.4%)	
Nonobstructive	8,804 (39.3%)	1,419 (43.7%)	7,385 (38.6%)	
Obstructive	4,704 (21.0%)	1,076 (33.2%)	3,628 (19.0%)	

BMI: body mass index; CAC: coronary artery calcium; CAD: coronary artery disease; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; GLP-1 RA: glucagon-like peptide-1 receptor agonist; HbA1c: glycated hemoglobin; IQR: interquartile range; Lp(a): lipoprotein(a); SGLT2i: sodium–glucose cotransporter-2 inhibitor; TIA: transient ischemic attack

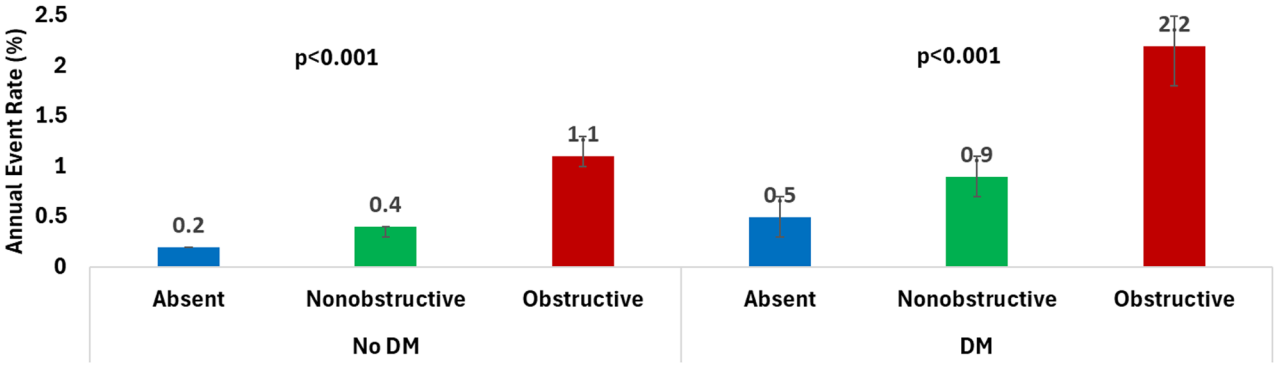


Fig. 1 Annual event rate stratified by DM status and CAD severity

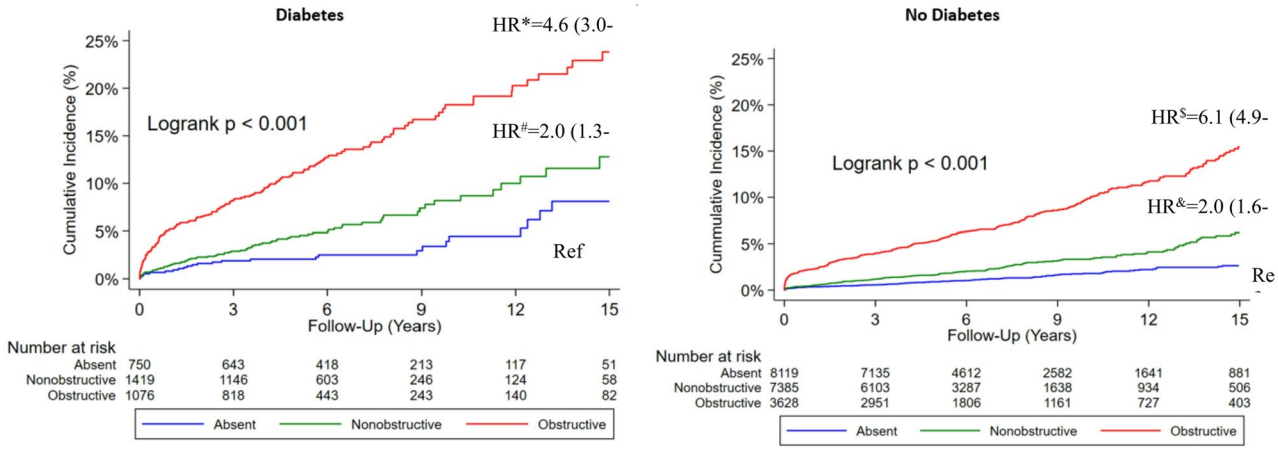


Fig. 2 Cumulative incidence of the primary composite outcome (CV Death or MI) stratified by CAD severity

nearly twice as common among individuals with diabetes versus those without (44.1% vs. 26.1%).

Baseline characteristics of patients with DM according to CAD severity are presented in Supplemental Table 1. Patients with more severe CAD were older, had a higher prevalence of most cardiovascular risk factors, were less likely to be female, and had significantly higher HbA1c levels.

Over a median follow-up of 6.0 years (IQR 3.9–9.5), the primary outcome occurred more often among patients with DM (7.8%) than those without (3.1%; $p < 0.001$).

Throughout the follow-up period, individuals with either diabetes mellitus (DM) or CAD experienced higher rates of the primary outcome, as illustrated in Fig. 1. In addition, for both patients with and without DM, there was a graded increase in risk according to CAD severity. Notably, across all categories of CAD severity, patients with DM exhibited higher event rates. Among individuals with both DM and obstructive CAD, the annual rate of cardiovascular death or myocardial infarction (MI) was 2.2%, compared with only 0.2% among those without DM or CAD.

Similarly, the cumulative incidence of the composite outcome increased with increasing CAD severity and was consistently higher in DM across all CAD categories (Fig. 2, Supplemental Fig. 1). After adjustment (Table 2; Fig. 2), obstructive CAD was significantly associated with the primary outcome in both groups (DM: HR 2.9, 95% CI 1.8–4.6; non-DM: HR 2.7, 95% CI 2.1–3.4). Nonobstructive CAD showed a modest elevation which did not reach statistical significance (DM: HR 1.4, 95% CI 0.9–2.3; non-DM: HR 1.2, 95% CI 0.9–1.5). Interestingly, among patients without detectable plaque, the presence of diabetes mellitus was associated with a significantly increased risk of the primary outcome (HR 2.5, 95% CI

Table 2 Multivariable cause-specific proportional hazards model for the primary (CVD or nonfatal MI) among patients with and without DM

A.

Parameter	Diabetes mellitus		Without diabetes mellitus	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Absent	Ref	--	Ref	--
Nonobstructive CAD	1.43 (0.90–2.28)	0.13	1.18 (0.92–1.50)	0.19
Obstructive CAD	2.90 (1.84–4.56)	**< 0.001**	2.67 (2.09–3.41)	**< 0.001**

Figure 2. Part B. Multivariable Cox model for prediction of the primary (CVD or MI) composite outcome for patients without Diabetes using AFT model with Weibull Distribution

Parameter	Primary composite outcome	
	Time Ratio (95% CI)	*P*-value
Absent	Ref	--
Nonobstructive CAD	0.83 (0.59-1.17)	.28
Obstructive CAD	0.24 (0.17-0.34)	**<.001**
Age	0.94 (0.93-0.95)	**<.001**
Female	1.03 (0.81-1.31)	.79
Hypertension	0.63 (0.48-0.82)	**.001**
Dyslipidemia	0.73 (0.57-0.92)	**.010**
Chronic Kidney Disease	0.28 (0.20-0.39)	**<.001**
Current Smoker	0.43 (0.33-0.57)	**<.001**
P	0.43 (0.33-0.57)	**<.001**
Sigma	1.40 (1.30-1.51)	**<.001**

P denotes the Weibull shape (power) parameter of the accelerated failure time (AFT) model, describing the time dependence of the baseline hazard ($P < 1$ indicates a decreasing hazard over time).

CAD: coronary artery disease, *CVD*: cardiovascular death; *HR*: hazard ratio, *CI*: confidence interval

Model adjusted for age, sex, hypertension, dyslipidemia, chronic kidney disease, current Smoking

1.6–3.9; adjusted HR 1.7, 95% CI 1.1–2.7). Similar patterns were observed for the individuals outcomes of cardiovascular death or MI (Supplemental Fig. 2).

In the diabetic subgroup, increasing extent of coronary artery disease, as reflected by the number of vessels involved, was associated with a stepwise increase in the risk of the composite outcome of cardiovascular death or myocardial infarction. Compared with patients with no CAD, the risk progressively increased with 1 vessel (HR 1.92, 95% CI 1.15–3.20; $p = 0.013$), 2 vessels (HR 2.32, 95% CI 1.40–3.85; $p = 0.001$), 3 vessels (HR 3.19, 95% CI 2.01–5.07; $p < 0.001$), and 4 vessels (HR 5.13, 95% CI 3.29–7.99; $p < 0.001$), demonstrating a clear dose–response relationship.

In addition, the results of the accelerated failure time (AFT) model were consistent with those of the Cox proportional hazards analysis in both direction and clinical interpretation. Specifically, greater severity of CAD was associated with an increased hazard of cardiovascular death or myocardial infarction in the Cox model and a corresponding shorter time to these events in the AFT model.

Supplemental Fig. 3 presents the cumulative incidence of the additional outcomes stratified by diabetes status and CAD severity. Overall, the incidence of these outcomes was generally higher among patients with diabetes. Increasing CAD severity was associated with a higher rate of coronary revascularization in both individuals with and without diabetes, with rates being the highest for those with obstructive disease. In contrast, associations with all-cause mortality were modest, reaching significance in non-diabetic patients with obstructive CAD, while no statistically significant relationship was observed between CAD severity and ischemic stroke in either group.

Discussion

This large real-world contemporary CCTA registry demonstrated three key findings.

First, diabetes mellitus was associated with a markedly higher prevalence and severity of CAD on CCTA. Second, for each category of CAD severity, adverse cardiovascular events occurred more than twice as often among patients with diabetes compared with those without diabetes. Third, the combination of diabetes and obstructive CAD identified the highest-risk subgroup, with an annual rate of cardiovascular death or MI of approximately 2.2%, versus 0.2% among patients without either condition. Importantly, after multivariable adjustment, obstructive CAD remained an independent predictor of outcomes in both patients with and without DM.

The observed higher prevalence and severity of CAD on CCTA among patients with diabetes is consistent with prior studies in both symptomatic and asymptomatic populations [12, 23–29]. Notably, in our cohort, the vast majority of patients with diabetes (77%) demonstrated evidence of CAD on CCTA, and one-third had obstructive disease, underscoring the substantial atherosclerotic burden in this population.

The observation of worse outcomes among patients with diabetes and CCTA-detected CAD, as well as among those with diabetes compared with individuals who did not have DM, is consistent with prior literature [12, 23]. Diabetes is a known risk factor for the development and progression of coronary atherosclerosis—and is also a causal risk factor for developing coronary heart disease related events. However, multiple studies have shown that in the contemporary era, diabetes may not exert as high of a risk [2, 15, 30, 31]. Our analysis provides granular, contemporary, real-world data from clinically indicated CCTAs, demonstrating that across all levels of CAD severity, event rates were higher among patients with diabetes than among those without, with outcomes worsening progressively with increasing stenosis severity. Notably, in contrast to a prior study by Blanke et al. [23] where patients with diabetes without plaque did not experience increased risk, our cohort showed higher event rates even in this subgroup. Such differences may be attributable to heterogeneity in patient populations, analytical approaches, underlying risk profiles, and progressive improvements in CCTA technology, interpretation, and clinical use over time. Our findings support current guidelines that recommend more aggressive lipid lowering therapies for patients with diabetes, even in the absence of plaque.

Interestingly, in our cohort, nonobstructive CAD among patients with diabetes was associated with significantly higher annual event rates compared with patients with diabetes and no plaque. However, after adjustment for confounders, only a modest and statistically non-significant excess risk remained relative to patients with diabetes and no plaque, whereas statistical significance persisted when compared with patients without diabetes and without plaque. This observation is somewhat discordant with the findings of several prior studies [12, 23, 28, 32]. The discrepancy may be explained by differences in CAD severity - potentially reflecting milder disease in our cohort - as well as possibly by more comprehensive adjustment for confounders. In addition, we used a robust and hard outcome of CV death or MI, which may have less variability that outcomes that include unstable angina or coronary revascularization. Alternatively, increased awareness and more intensive preventive management of patients with nonobstructive CAD in contemporary clinical practice may have attenuated their risk, particularly following studies demonstrating that CT-based identification of subclinical atherosclerosis can improve outcomes among patients with diabetes [14]. This is further supported by the high prevalence of preventive therapies use in our cohort.

In this context, it is noteworthy that the FACTOR-64 randomized trial [15] which enrolled asymptomatic patients with diabetes, found that routine CCTA screening followed by CCTA-guided therapy did not reduce mortality or major adverse cardiac events compared with standard care over four years, despite identifying a high prevalence of subclinical CAD and prompting more intensive risk-factor management. The absence of significant benefit in that study may be explained by the high baseline quality of care and aggressive preventive management in both cohorts, the unexpectedly low event rates. In contrast, in the PROMISE substudy by Sharma et al. [14], symptomatic patients with diabetes randomized to an initial CCTA strategy had significantly lower rates of cardiovascular death or myocardial infarction compared with those undergoing functional stress testing, whereas no difference was observed among non-diabetic patients. The observed benefit of CCTA in that context may reflect greater preventive therapies and selective use of downstream invasive angiography.

Potential mechanistic explanations for the greater risk observed among patients with diabetes across all degrees of CAD on CCTA include a higher overall plaque burden and a greater prevalence of high-risk plaque features that are more prone to rupture, as well as more extensive endothelial dysfunction [24, 32–34]. In addition, diabetes-related metabolic, inflammatory, and pro-thrombotic pathways promote accelerated atherosclerosis and plaque vulnerability, resulting in worse outcomes even for comparable anatomic findings [24, 33, 34]. Furthermore, autonomic neuropathy and silent ischemia may contribute by delaying symptom recognition and timely treatment [35]. Furthermore, among patients without significant epicardial CAD, DM is associated with coronary microvascular dysfunction, often reflected by impaired coronary flow reserve (CFR), even in the absence of obstructive disease [36, 37]. Reduced CFR, as demonstrated in numerous studies of populations with diabetes, is a powerful predictor of myocardial ischemia, adverse cardiovascular outcomes, and heart failure [36–38].

Further supporting our findings that patients with diabetes remain at increased cardiovascular risk even in the absence of clinically apparent atherosclerosis and may therefore benefit from more aggressive preventive strategies - a prespecified subgroup analysis of the VESALIUS-CV trial demonstrated that intensive LDL-C lowering with evolocumab reduces the risk of first major cardiovascular events in high-risk patients with diabetes but without known significant atherosclerosis. Among 3,655 patients without prior myocardial infarction or stroke, obstructive disease, evolocumab achieved substantial LDL-C reduction (median ~ 52 vs. 111 mg/dL) and was associated with significant reductions in both 3-point MACE (5.0% vs. 7.1%; HR 0.69) and 4-point MACE (7.6% vs. 10.5%; HR 0.69) over a median follow-up of 4.8 years. Notably, a reduction in all-cause mortality was also observed (HR 0.76) [39].

Limitations

Several limitations of our study should be acknowledged. First, as with all observational registry studies, residual confounding cannot be excluded despite multivariable adjustment for clinical and imaging variables. Second, the study population comprised patients without prior CAD who were referred for clinically indicated CCTA, which may introduce selection bias and limit generalizability to asymptomatic or screening populations, as well as to patients with established CAD. Third, data regarding diabetes duration, glycemic control, and anti-hyperglycemic medication use were not uniformly available, precluding evaluation of their impact on outcomes. Fourth, downstream management-including initiation or intensification of preventive therapies-was not systematically recorded and may have influenced event rates. Finally, plaque quantification was not available in this large cohort, and analyses were based on clinical reads regarding the presence and severity of stenosis.

Conclusions

In this contemporary, real-world CCTA registry, diabetes mellitus was associated with a markedly higher prevalence and severity of coronary artery disease, as well as with substantially higher long-term rates of

cardiovascular death and myocardial infarction. Event rates increased progressively with greater CAD severity and were consistently higher among patients with diabetes across all CCTA-defined categories of disease, underscoring the adverse prognostic impact of diabetes even in the presence of nonobstructive or even minimal or no—plaque. These findings highlight the value of CCTA for refined risk stratification in patients with diabetes and the need to further optimize and intensify preventive and therapeutic strategies in this high-risk group.

Abbreviations

AFT	Accelerated failure time
BMI	Body mass index
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CAD	RADS–Coronary Artery Disease Reporting and Data System
CCTA	Coronary computed tomography angiography
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CP	Chest pain
CPT	Current Procedural Terminology
CV	Cardiovascular
CVD	Cardiovascular death
DM	Diabetes mellitus
EDW	Enterprise Data Warehouse
eGFR	Estimated glomerular filtration rate
ESRD	End–stage renal disease
GLP	1 RA–Glucagon–like peptide–1 receptor agonist
HbA1c	Glycated hemoglobin
HR	Hazard ratio
ICD	International Classification of Diseases
IQR	Interquartile range
MI	Myocardial infarction
MGB	Mass General Brigham
NLP	Natural language processing
PCI	Percutaneous coronary intervention
RPDR	Research Patient Data Registry
SGLT2i	Sodium–glucose cotransporter–2 inhibitor

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-026-03193-1.

Supplementary Material 1

Author contributions

Study conception and design: AS, RB, DMH.CCTA report phenotyping and natural language processing development, implementation, and validation: ANB, DMH, AS, SAB, DWB, RC.Statistical analysis: SAB.Figure preparation: SAB, ASData collection and study coordination: DMH, AS, SAB, CVB, RB, RC, MO, ASi.Manuscript drafting: AS.Project Supervision: RB.Data interpretation and critical revision of the manuscript for important intellectual content: RC, ANB, DWB, MP, BNW, JH, CVB, NMM, ASi, VB, MTL, MS, AA, KN, CPC, SH, MDC, BG.Final approval of the manuscript: All authors.

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Data availability

The data underlying this study are derived from the Mass General Brigham institutional databases and contain sensitive patient information. Due to ethical and legal restrictions, the datasets are not publicly available. De-identified data may be made available from the corresponding author upon reasonable request and subject to institutional review board approval and data use agreements.

Declarations

Competing interests

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