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Long-Term Prognostic Utility of Coronary CT Angiography in Stable Patients With Diabetes Mellitus

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CME Objective for This Article: After reading this article the reader should be able to: 1) develop a deeper understanding of the prognostic value of coronary CTA in patients with stable chest pain both with and without diabetes; 2) highlight the extent and burden of coronary artery disease found amongst patients with diabetes mellitus presenting for coronary CTA; and 3) examine the differences in risk associated with atherosclerosis amongst diabetics at 2 versus 5 years follow up.

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ABSTRACT

OBJECTIVES The goal of this study was to determine the long-term prognostic value of coronary computed tomography angiography (CTA) among patients with diabetes mellitus (DM) compared with nondiabetic subjects.

BACKGROUND The long-term prognostic value of coronary CTA in patients with DM is not well established.

METHODS Patients enrolled in the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) registry with 5-year follow-up data were identified. The extent and severity of coronary artery disease (CAD) were analyzed at baseline coronary CTA and in relation to outcomes between diabetic and nondiabetic patients. CAD according to coronary CTA was defined as none (0% stenosis), nonobstructive (1% to 49% stenosis), or obstructive (≥50% stenosis). Time to death (and in a subgroup, time to major adverse cardiovascular event) was estimated by using multivariable Cox proportional hazards models.

RESULTS A total of 1,823 patients were identified as having DM with 5-year clinical follow-up and were propensity-matched to 1,823 patients without DM (mean age 61.8 ± 10.9 years; 54.4% male). Patients with DM did not exhibit a heightened risk of death compared with the propensity-matched nondiabetic subjects in the absence of CAD on coronary CTA (risk-adjusted hazard ratio [HR] of DM: 1.32; 95% confidence interval [CI]: 0.78 to 2.24; $p = 0.296$). Patients with DM were at increased risk of dying compared with nondiabetic subjects in the setting of nonobstructive CAD (in the propensity-matched cohort: HR, 2.10; 95% CI: 1.43 to 3.09; $p < 0.001$) with a mortality risk greater than nondiabetic subjects with obstructive disease ($p < 0.001$). In a risk-adjusted hazard analysis among patients with DM, both per-patient obstructive CAD and nonobstructive CAD conferred an increase in all-cause mortality risk compared with patients without atherosclerosis on coronary CTA (nonobstructive disease—HR: 2.07; 95% CI: 1.33 to 3.24; $p = 0.001$; obstructive disease—HR: 2.22; 95% CI: 1.47 to 3.36; $p < 0.001$).

CONCLUSIONS Among patients with DM, nonobstructive and obstructive CAD according to coronary CTA were associated with higher rates of all-cause mortality and major adverse cardiovascular events at 5 years, and this risk was significantly higher than in nondiabetic subjects. Importantly, patients with DM without CAD according to coronary CTA were at a risk comparable to that of nondiabetic subjects. (J Am Coll Cardiol Img 2016;9:1280–8)

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CI = confidence interval

CTA = computed tomography angiography

DM = diabetes mellitus

MACE = major adverse cardiovascular event(s)

HR = hazard ratio

LM = left main

The prevalence of diabetes mellitus (DM) is increasing rapidly due to a growing obesity epidemic and an aging Western population (1). Incremental cardiovascular risk associated with DM over the short term has been documented in both single-center studies and through the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) registry (2). In addition, it has been shown that coronary stenosis confers additive risk prediction beyond both calcium scoring and nonobstructive disease on coronary computed tomography angiography (CTA) over short- to intermediate-term follow-up (3).

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To date, the prognostic value of CTA in patients with DM over the long term has not been well elucidated, with current knowledge limited to small single-center studies (4,5). In addition, the relative risk of patients with DM with both nonobstructive and obstructive disease on coronary CTA compared with nondiabetic subjects over the long term is unknown. We accordingly performed an analysis to determine the long-term prognostic value of coronary CTA among patients with DM compared with nondiabetic subjects in a large, prospective, multicenter international coronary CTA registry (CONFIRM).

MATERIALS AND METHODS

The CONFIRM registry is a prospective, international, multicenter registry designed to evaluate the relationship of coronary atherosclerosis and clinical risk factors to adverse outcomes among patients who have undergone at least 64-slice clinically indicated coronary CTA. The rationale and design of CONFIRM have been reported previously (6). For the present analysis, the primary study cohort comprised patients included in the CONFIRM registry with 5-year follow-up (all-cause mortality) and DM but no history of known coronary artery disease (CAD) (myocardial infarction or revascularization before the scan date). A subgroup analysis was also performed among patients with 5-year major adverse cardiovascular event (MACE) follow-up. For comparison, a propensity-matched cohort of patients without DM or a history of known CAD who also had 5-year follow-up were identified.

TABLE 1 Demographic and Baseline Clinical Characteristics

	Patients With DM (n = 1,823)	Nondiabetic Subjects (n = 1,823)	p Value
Age, yrs	61.7 ± 11.2	61.8 ± 10.9	0.944
Male	986 (54.1)	992 (54.4)	0.842
BMI (n = 5,566; 2,003), kg/m^2	28.8 ± 5.9	27.1 ± 4.5	<0.001
Cardiac risk factors			
Hypertension	1,384 (75.9)	1,373 (75.3)	0.671
Dyslipidemia	1,192 (65.4)	1,182 (64.8)	0.728
Smoking	391 (21.6)	385 (21.1)	0.808
Family history of coronary artery disease	677 (37.7)	667 (36.6)	0.731
History of PAD	57 (7.7)	45 (6.6)	0.417
Chest pain			0.002 (overall)
No chest pain	389 (24.2)	486 (30.2)	<0.001
Noncardiac chest pain	291 (18.1)	272 (16.9)	0.352
Atypical chest pain	547 (34.1)	496 (30.8)	0.046
Typical chest pain	379 (23.6)	358 (22.2)	0.348

Values are mean ± SD or n (%).
DM = diabetes mellitus; PAD = peripheral arterial disease.

CLINICAL EVALUATION AND CARDIAC RISK FACTOR DEFINITIONS. Patient symptoms were assessed before undergoing coronary CTA and defined using Diamond and Forrester criteria (7) according to the American College of Cardiology guidelines for chest pain assessment (8). Pre-test cardiovascular risk was defined using the Morise score (9). The presence of

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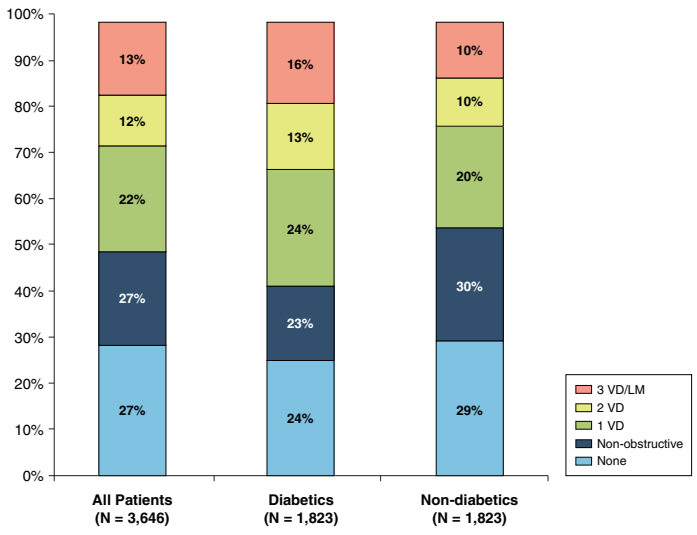
cardiac risk factors was also prospectively assessed before the coronary CTA. DM was defined according to a previous diagnosis made by a physician (using a fasting glucose threshold of 126 mg/dl) and/or use of insulin or oral hypoglycemic agents. Systemic arterial hypertension was defined as a documented history of high blood pressure or treatment with antihypertensive medications. Dyslipidemia was defined as known but untreated dyslipidemia or current treatment with lipid-lowering medications. A positive smoking history was defined as current smoking or cessation of smoking within 3 months of testing. Family history of premature coronary heart disease was determined by patient query. Symptom presentation was classified into 1 of 4 categories: typical angina, atypical angina, noncardiac pain, or asymptomatic.

DATA ACQUISITION, IMAGE RECONSTRUCTION, AND CTA ANALYSIS. Coronary CTA scanners used in the CONFIRM registry and data acquisition for CTA have been described in detail previously (10). Standardized protocols for image acquisition, as defined by the Society of Cardiovascular Computed Tomography, were used at all participating sites. Image interpretation was uniformly performed at each site according to the society's guidelines (11) by experienced observers with level III (or equivalent) accreditation and/or board certification in cardiovascular computed tomography. Each site applied standard anatomic segmental analysis for image interpretation. All segments were coded for the presence and severity of coronary stenosis and were scored as normal (0% luminal stenosis), nonobstructive (1% to 49% luminal stenosis), or obstructive (≥50% luminal stenosis). Stenoses were assessed on a per-patient and per-vessel (left main [LM]; left anterior descending, left circumflex, and right coronary artery) basis.

FOLLOW-UP. The primary endpoint was time to death from all causes. The secondary endpoint was time to occurrence of major adverse cardiac event (MACE), defined as death, myocardial infarction, unstable angina, or late coronary revascularization (>90 days) in a subgroup of 973 patients with DM for whom this information was available.

Follow-up procedures were approved by all study centers' institutional review boards. Death status for non-U.S. centers was gathered by using clinical visits, telephone contacts, and questionnaires sent by mail; all reported events were verified by hospital records or direct contact with a patient's attending physician. Death status for U.S. centers was ascertained either by query of the Social Security Death Index or by direct physician and/or patient contact.

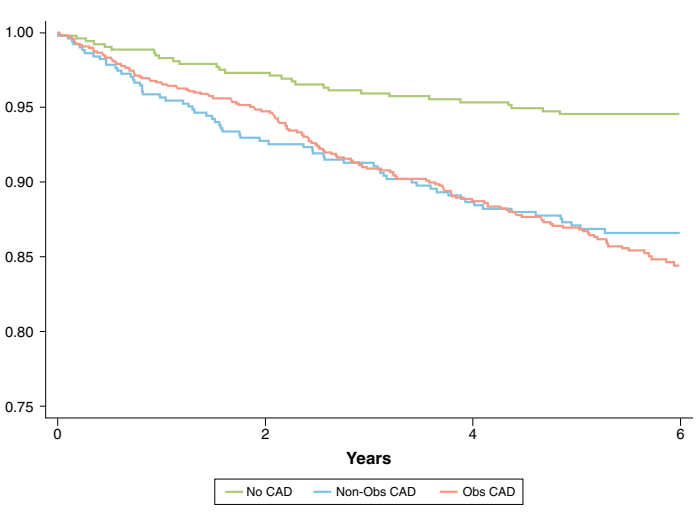
FIGURE 1 Extent and Severity of CAD on CTA in a Propensity-Matched Cohort of Nondiabetic Subjects and Patients With DM



Disease extent and severity on coronary computed tomography angiography (CTA) across propensity-matched patients with diabetes mellitus (DM) and nondiabetic subjects ($p < 0.001$). CAD = coronary artery disease; LM = left main; VD = vessel disease.

STATISTICAL ANALYSIS. Stata version 14.0 (Stata Corp., College Station, Texas) was used for all statistical analyses. Categorical variables are presented as frequencies (percentages) and continuous variables

FIGURE 2 Risk-Adjusted Kaplan-Meier Curve for Survival on the Basis of CAD Severity (None, Nonobstructive, or Obstructive) Among Patients With DM



Adjusted Kaplan-Meier curve for survival on the basis of CAD severity among patients with DM and nondiabetic subjects. **(A)** Risk adjusted. Obs = obstructive; other abbreviations as in Figure 1.

TABLE 2 Risk-Adjusted HR for All-Cause Mortality Among Patients With DM According to Extent of CAD

	HR*	95% CI	p Value
No CAD	1.00		
Nonobstructive CAD	2.09	1.34–3.27	0.001
1-Vessel obstructive CAD	1.79	1.13–2.85	0.013
2-Vessel obstructive CAD	2.61	1.61–4.23	<0.001
3-Vessel/LM obstructive CAD	2.61	1.63–4.20	<0.001

*Risk-adjusted for age, sex, hypertension, dyslipidemia, family history, and current smoking.

CAD = coronary artery disease; CI = confidence interval; DM = diabetes mellitus; HR = hazard ratio; LM = left main.

as mean ± SD. Time to death from all causes and death rates as well as time to MACE and MACE rates were calculated using univariable Cox proportional hazards models. In each case, the proportional hazards assumption was assessed using Schoenfeld residuals. Patients with early revascularization were censored from the prognosis analyses for the MACE endpoint. Overall survival and MACE-free survival among stenosis groups are presented using Kaplan-Meier survival curves and compared using the log-rank test.

For comparison versus the group with DM, a propensity score was developed from the predicted probabilities of a multivariable logistic regression model predicting DM from age, sex, hypertension, dyslipidemia, smoking history, and family history. A total of 1,823 patients with DM were matched to 1,823 nondiabetic subjects on the basis of this propensity score using the Mahalanobis nearest-neighbor matching algorithm with a caliper <0.001 (12). In all matched patients, the balancing property was satisfied.

Univariable Cox models were then used to compare mortality risk between patients with DM and propensity-matched nondiabetic subjects. Within both the diabetic and nondiabetic groups, mortality risk was assessed by using multivariable Cox models with adjustment for age, sex, hypertension, dyslipidemia, family history, and current smoking; the resulting hazard ratios (HRs) and 95% confidence intervals (CIs) are reported. A 2-tailed p value <0.05 is considered statistically significant.

TABLE 3 Relative Risk for All-Cause Mortality in Patients With DM Compared With Propensity-Matched Nondiabetic Subjects Stratified According to Extent and Severity of CAD

	HR for Patients With DM Versus Nondiabetic Subjects	95% CI	p Value
No CAD DM	1.31	0.78–2.22	0.310
Nonobstructive CAD DM	2.09	1.43–3.06	<0.001
Obstructive CAD DM	1.95	1.46–2.61	<0.001
1-Vessel obstructive CAD DM	1.48	0.95–2.29	0.080
2-Vessel obstructive CAD DM	2.45	1.36–4.40	0.003
3-Vessel/LM obstructive CAD DM	2.31	1.35–3.94	0.002

Abbreviations as in Table 2.

RESULTS

STUDY POPULATION. From the long-term cohort of the CONFIRM registry, 5-year follow-up data were available in 12,086 patients; 1,823 patients were identified as having DM and no known prior CAD (mean age 62 ± 11 years; 54% male; mean follow-up 5.2 ± 1.6 years). A propensity-matched cohort of 1,823 patients (mean age 62 ± 11 years; 54% male; mean follow-up 5.5 ± 1.4 years) was selected from 8,407 patients without DM or known CAD and with complete age, sex, and stenosis information. Patient demographic characteristics and symptom status are presented in Table 1.

PREVALENCE OF CAD. Overall, 443 (24%) of 1,823 patients with DM had no evidence of CAD on coronary CTA. Nonobstructive CAD was present in 425 (23%) patients and obstructive CAD in 955 (52%) patients (1-, 2-, and 3-vessel/LM disease in 433 [24%], 239 [13%], and 283 [16%] patients, respectively) (Figure 1). Among the 1,823 nondiabetic subjects, 531 (29%) had no evidence of CAD on coronary CTA. Nonobstructive CAD was present in 554 (30%) patients and obstructive CAD in 738 (40%) patients (1-, 2-, and 3-vessel/LM disease in 366 [20%], 182 [10%], and 190 [10%] patients).

CLINICAL OUTCOMES. Death occurred in 382 (10.5%) of 3,646 patients (136 [7.5%] nondiabetic subjects; 246 [13.5%] patients with DM), with an annualized mortality rate of 0.020 per person-year (95% confidence interval [CI]: 0.018 to 0.022) overall, 0.027 (95% CI: 0.024 to 0.031) in patients with DM, and 0.014 (95% CI: 0.012 to 0.016) in nondiabetic subjects. The absence of CAD according to coronary CTA was associated with a low overall annual mortality rate of 0.010 (95% CI: 0.008 to 0.013). In a risk-adjusted hazard analysis, both per-patient obstructive and nonobstructive CAD conferred an increase in all-cause mortality risk compared with patients without atherosclerosis on coronary CTA in patients with DM (nonobstructive disease—HR: 2.07; 95% CI: 1.33 to 3.24; p = 0.001; obstructive disease—HR: 2.22; 95% CI: 1.47 to 3.36; p < 0.001).

Kaplan-Meier all-cause mortality curves stratified according to the presence and severity of coronary CTA findings in patients with DM are shown in Figure 2. In a risk-adjusted hazard analysis based on the extent of CAD, a worsened all-cause mortality

prognosis was identified with a greater number of coronary vessels with obstructive CAD in the DM population (Table 2). Importantly, risk-adjusted mortality was increased among patients with nonobstructive CAD compared with patients without evidence of CAD (p = 0.001).

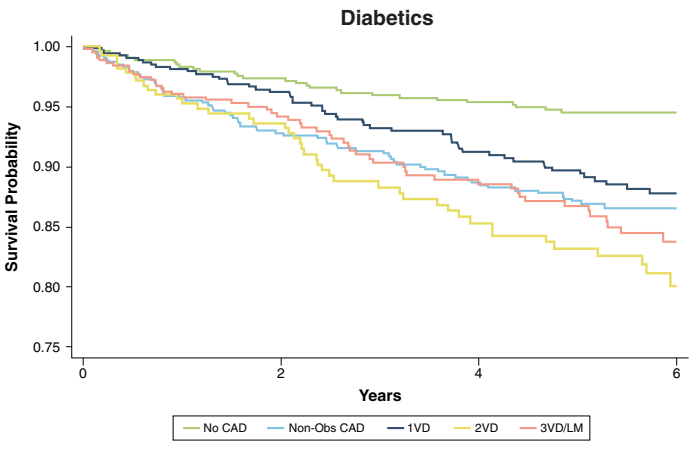
RELATIVE RISK IN DM PATIENTS VERSUS NONDIABETIC SUBJECTS. Patients with DM exhibited no heightened risk of death compared with nondiabetic subjects in the absence of CAD on coronary CTA (p = 0.310). The risk of all-cause mortality was increased for patients with DM compared with nondiabetic subjects for both nonobstructive (HR: 2.10; 95% CI: 1.43 to 2.09; p < 0.001) and obstructive disease, with a poorer prognosis in patients with increasing severity of CAD (Table 3). The presence of nonobstructive disease conferred a particularly poor prognosis in patients with DM, with no significant difference in survival observed among diabetic patients with nonobstructive CAD compared with those with 1-vessel CAD (p = 0.403), 2-vessel CAD (p = 0.257), or 3-vessel/LM CAD (p = 0.232) (Figure 3).

MACE OCCURRENCE IN THE COHORT WITH DM. Follow-up data on occurrence of MACE were available in 973 of 1,823 patients with DM. When early revascularization was censored, MACE (inclusive of late revascularization) occurred in 209 (32%) patients, with 71 (11%) patients experiencing myocardial infarction. The absence of CAD according to coronary CTA was associated with a lower annualized MACE rate of 0.013 (95% CI: 0.008 to 0.021) compared with the overall annual MACE rate for the entire cohort of 0.068 (95% CI: 0.059 to 0.077). In a risk-adjusted Cox analysis, both per-patient obstructive and nonobstructive CAD conferred an increase in MACE risk over those without atherosclerosis on coronary CTA (nonobstructive disease—HR: 4.95; 95% CI: 2.85 to 8.59; p < 0.001; obstructive disease—HR: 10.51; 95% CI: 6.12 to 18.06; p < 0.001). Kaplan-Meier curves for MACE-free survival stratified according to the presence and severity of coronary CTA findings are illustrated in Figures 4A and 4B, respectively. In a risk-adjusted hazard analysis based on the extent of CAD, a dose-response relationship between the number of coronary vessels exhibiting obstructive CAD and MACE occurrence was noted (Table 4). In addition, the worsened prognosis associated with extent of CAD held true across symptom status and type (Table 5).

DISCUSSION

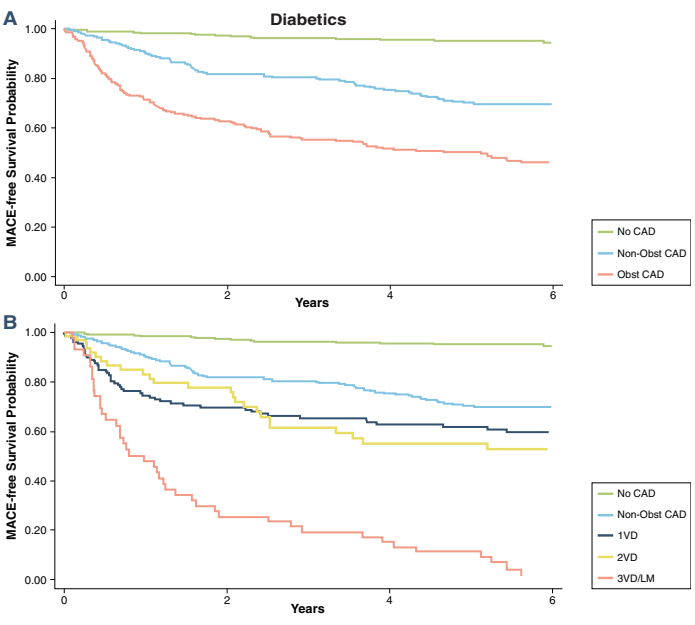
To the best of our knowledge, our analysis represents the largest evaluation of the long-term prognostic value of coronary CTA-identified CAD in patients with DM. The main findings of our analysis are that when propensity-matched to nondiabetic subjects, those with DM without atherosclerosis have a similar

FIGURE 3 Risk-Adjusted Kaplan-Meier Curve for All-Cause Mortality



Risk-adjusted Kaplan-Meier curve for survival on the basis of CAD severity (none, nonobstructive, and 1-, 2- or 3-vessel/left main disease) among patients with DM. Obs = obstructive; other abbreviations as in Figure 1.

FIGURE 4 Risk-Adjusted Kaplan-Meier Curve for Event-Free Survival Stratified According to CAD



(A) CAD presence assessed as none, nonobstructive, or obstructive disease. **(B)** CAD severity assessed as none, nonobstructive, and 1-, 2- or 3-vessel/left main disease among patients with DM. Obs = obstructive; other abbreviations as in Figure 1.

TABLE 4 Risk-Adjusted HR for MACE Among Patients With DM and Nondiabetic Subjects According to Extent of CAD

	HR*	95% CI	p Value
Diabetic patients			
No CAD	1.00		
Nonobstructive CAD	5.12	2.95–8.88	<0.001
1-Vessel obstructive CAD	8.15	4.57–14.53	<0.001
2-Vessel obstructive CAD	9.03	4.77–17.11	<0.001
3-Vessel/LM obstructive CAD	24.76	13.48–45.51	<0.001
Nondiabetic subjects			
No CAD	1.00		
Nonobstructive CAD	1.34	0.81–2.23	0.252
1-Vessel obstructive CAD	3.90	2.31–6.61	<0.001
2-Vessel obstructive CAD	4.47	2.39–8.36	<0.001
3-Vessel/LM obstructive CAD	4.30	2.22–8.35	<0.001

*Risk-adjusted for age, sex, hypertension, dyslipidemia, family history, and current smoking.

MACE = major adverse cardiovascular event; other abbreviations as in Table 2.

prognosis; however, their survival probability according to coronary CTA is significantly worse in the setting of any atherosclerotic disease. In fact, patients with DM with nonobstructive CAD have a significantly worsened survival than those without atherosclerosis and is comparable to patients with DM with 1-vessel obstructive disease and to nondiabetic subjects with multivessel obstructive CAD. Our results emphasize that the anatomic findings of CAD according to coronary CTA confers important long-term prognostic information, permitting accurate risk stratification of these patients.

The impact of nonobstructive disease in patients with DM at long-term follow-up is much more profound than in previous analyses from the same registry at 2.3 years (2,3,5,6), which have consistently shown that obstructive disease confers a greater incremental risk than nonobstructive disease across many patient populations. There are many potential explanations for this observation. It is a widely held perception that vulnerable plaques often result in MACE during a period of only modest plaque size and luminal encroachment, supported by historical data that up to two-thirds of acute coronary syndromes occur in this setting (13). This belief developed from several retrospective studies which showed that in patients who underwent invasive angiography months to years in advance of myocardial infarction, the culprit lesion was most commonly angiographically mild (13–17). Longer follow-up may therefore provide adequate time for plaque progression and rapid luminal encroachment, resulting in the development of both symptoms and potentially MACE. Another explanation may be that post-CTA revascularization of those patients with obstructive CAD resulted in improved clinical outcomes. Although this mechanism remains possible, angiographic-guided revascularization of patients with DM has not been shown to improve clinical outcomes compared with medical therapy alone (18). The exact cause for the apparent merging of clinical outcomes of those patients with nonobstructive disease and those with single-vessel obstructive disease cannot be stated with certainty; however, our data strongly suggest that nonobstructive disease is of significant long-term prognostic importance in patients with DM.

Another important observation from our analysis is that patients with DM without plaque had a comparable risk of both MACE and death compared with nondiabetic subjects without CAD according to coronary CTA. In addition, although a common assumption would be that only a small percentage of patients with DM do not have CAD, in our cohort of >1,800 patients, approximately 1 in 4 had no computed tomographic evidence of CAD. The comparable clinical outcomes among patients with DM and nondiabetic subjects without CAD, as well as the

TABLE 5 Annualized MACE Event Rates (95% CIs) Among Patients With DM and Nondiabetic Subjects Stratified According to Symptom Type and Disease Severity

	Asymptomatic	Nonanginal Chest Pain	Atypical Angina	Typical Angina
Nondiabetic patients				
Normal	0.009 (0.004–0.022)	0.028 (0.013–0.062)	0.011 (0.005–0.025)	0.006 (0.001–0.040)
Nonobstructive	0.022 (0.013–0.035)	0.012 (0.004–0.037)	0.018 (0.010–0.035)	0.053 (0.024–0.118)
Obstructive	0.60 (0.038–0.093)	0.061 (0.033–0.114)	0.100 (0.062–0.160)	0.0127 (0.085–0.192)
p Value	<0.001	0.0198 (0.10)	<0.001	<0.001
Patients with DM				
Normal	0.013 (0.005–0.031)	0.006 (0.001–0.042)	0.014 (0.006–0.032)	0.006 (0.001–0.042)
Nonobstructive	0.054 (0.034–0.085)	0.073 (0.039–0.135)	0.043 (0.025–0.075)	0.087 (0.050–0.154)
Obstructive	0.164 (0.120–0.224)	0.075 (0.041–0.135)	0.120 (0.082–0.175)	0.245 (0.164–0.365)
p Value	<0.001	0.009	<0.001	<0.001

Abbreviations as in Tables 1 and 4.

significantly worsened prognosis of patients with DM with nonobstructive disease comparable to nondiabetic subjects with multivessel obstructive disease, warrant further investigation. This paradox may inform future trials to determine the potential role of aggressive therapy for atherosclerosis prevention in the diabetic population. The potential benefit of aggressive medical therapy was recently highlighted by the FACTOR-64 Trial (19). Patients in FACTOR-64 had medical care optimized in advance of enrollment with an event rate that was substantially lower than realized in our cohort. Although there are almost certainly many factors that may help explain this discordance, it highlights the potential differences between standard and regulated optimal medical care. The CONFIRM registry represents a broad, global, real-world registry with medical therapy managed at the discretion of the individual practitioner.

STUDY LIMITATIONS. Although this study involved a large, multicenter international cohort, inherent referral biases remain that plague any real-world registry. Our study findings are derived from a cohort of patients who underwent imaging rather than from a cohort of stable patients with DM and suspected CAD who may or may not be referred clinically for further testing. Although risk factor ascertainment was carefully and prospectively performed, the downstream treatment of patients in our cohort remains unknown. Potential downstream treatment biases may have altered the rates of MACE on the basis of the baseline CAD extent and severity. Finally, not all patients had MACE-related follow-up, which is lowered further owing to the required censoring of early revascularization procedures.

CONCLUSIONS

Coronary CTA-identified atherosclerotic disease, both nonobstructive and obstructive in nature, confers important long-term prognostic information in patients with DM. Importantly, patients with DM without atherosclerosis according to coronary CTA have a comparable prognosis to nondiabetic subjects, but in the setting of both nonobstructive and obstructive disease, they have a significantly worsened prognosis.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Both nonobstructive and obstructive CAD according to coronary CTA confers an increased long-term risk of MACE and mortality in patients with DM. Importantly, the risk in these patients is comparable to those with nonobstructive disease and obstructive coronary disease. In addition, patients with DM without atherosclerosis on coronary CTA have a good long-term prognosis that is comparable to that of nondiabetic subjects.

TRANSLATIONAL OUTLOOK: Coronary CTA uniquely provides important long-term risk stratification of patients with DM. The role of coronary CTA to stratify therapy according to presence or absence and extent of CAD needs further assessment.

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