Cardiometabolic Risk is Associated With Atherosclerotic Burden and Prognosis: Results from the Partners Coronary Computed Tomography Angiography Registry

Short Title: CAD Prognosis by Cardiometabolic Risk

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Word count: 3,964

Disclosures: Dr. Hoffmann reports research support from Siemens Medical Systems. Dr. Rybicki reports research support from Toshiba Medical Systems.
Abstract.

Objective: Our purpose was to evaluate coronary artery disease (CAD) prevalence and prognosis according to cardiometabolic (CM) risk.

Research Design and Methods: Registry of all patients without prior CAD referred for coronary computed tomography angiography (CCTA). Patients were stratified by groups of increasing CM risk factors (hypertension, low HDL, hypertriglyceridemia, obesity, and dysglycemia) as: patients without type 2 diabetes mellitus (T2DM) with <3 or ≥3 CM risk factors, patients with T2DM not requiring insulin or those with T2DM requiring insulin. Patients were followed for a primary endpoint of major adverse cardiovascular events (MACE) composed of unstable angina, late coronary revascularization, myocardial infarction, and cardiovascular mortality.

Results: Among 1118 patients (mean age 57±13 years) followed for a mean 3.1 years, there were 21 (1.9%) cardiovascular deaths and 13(1.2%) myocardial infarctions. There was a stepwise increase in the prevalence of obstructive CAD with increasing CM risk, from 15% in those without diabetes and <3 CM risk factors to as high as 46% in patients with type 2 diabetes requiring insulin (p<0.001). Insulin exposure was associated with the highest adjusted hazard of MACE (HR = 3.29, 95% CI 1.28-8.45, p=0.01), while both T2DM without insulin (HR=1.35, p=0.3) and ≥3 CM risk factors without T2DM (HR=1.48, p=0.3) were associated with a similar rate of MACE.

Conclusion: Patients without diabetes who have multiple metabolic risk factors have a similar prognosis and burden of CAD as those with T2DM not requiring insulin. Among patients with diabetes, the need for insulin therapy is associated with greater burden of CAD as well as worse prognosis.
Keywords: cardiodiabetology, cardiovascular epidemiology, imaging

Abbreviations:

CCTA = coronary computed tomography angiography

CM = cardiometabolic

HDL = high density lipoprotein

MACE = major adverse cardiovascular events

SIS = segment involvement score

SSS = segment stenosis score

T2DM: type 2 diabetes mellitus

USA = unstable angina
Standard risk assessment guidelines regard type 2 diabetes mellitus (T2DM) as a coronary heart disease risk equivalent(1; 2). Although a subgroup of patients with T2DM may have minimal coronary artery disease (CAD)(3), coronary heart disease is the most common cause of death in patients with T2DM. Moreover, the presence of T2DM is associated with a poorer prognosis after a myocardial infarction (MI) (4) As a result, the American Diabetes Association recommends primary prevention measures for CAD in all patients with T2DM, and particularly intensive secondary prevention among those with T2DM and CAD(5).

However, there is insufficient data to suggest that patients without T2DM who have cardiometabolic (CM) risk factors, such as obesity, dysglycemia, atherogenic dyslipidemia or hypertension, should be treated as aggressively as patients with T2DM. While such patients have been termed to be at increased CM risk(6-8), not all of them will have the same extent of anatomical CAD and risk of cardiovascular disease(5; 9). Therefore, improved methods for CAD detection and risk assessment could be useful in improving patient outcome.

Nuclear myocardial perfusion imaging has been shown to be useful in risk stratification among individuals with T2DM(10), although in the contemporary era of widespread medical therapy, such testing did not lead to improvement in cardiovascular outcomes among asymptomatic patients with T2DM. (11) Furthermore, in comparison to patients without T2DM, a shorter “warranty period” (i.e. favorable prognosis with normal results) has been found(12; 13) possibly reflecting the fact that patients with T2DM are more likely to have diffuse coronary atherosclerosis and accelerated disease progression. More recently, the use of cardiac computed tomography angiography (CCTA) has been evaluated among patients with T2DM and showed greater burden of disease in comparison to patients without T2DM as well as worse prognosis.(14; 15) However, these studies have been limited to all-cause mortality and did not
examine patients without T2DM with CM risk factors. Therefore the aim of this study was to evaluate the association between CM risk factors and prognosis, and to determine whether differences in prognosis can be explained by CCTA findings.

**Methods**

**Study population**

This study examined data from all consecutive subjects, 18 years or older, who underwent a clinical CCTA at the Massachusetts General Hospital or the Brigham and Women’s Hospital from 2004 - 2011 with available data on baseline clinical risk factors. All scans were performed using a 64 detector (or newer generation) scanner. We excluded patients with prior known CAD (defined as prior percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), or MI). The study was approved by the local Institution Review Board.

**CCTA Exam Acquisition and Interpretation**

CCTA scans were performed according to established guidelines(16; 17) and institutional protocol at the time of the scan. All CCTA exams were categorized as having no (0%), non-obstructive (<50%), or obstructive (≥50%) CAD. Vessels smaller than 2 mm were not included. The 18 segment model proposed by the American Heart Association,(17) was used to categorize the presence and severity of CAD for each segment. Extent of CAD was also assessed by the number of vessels with CAD [left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA)] as 1-vessel, 2-vessel and 3-vessel/left main (LM) disease. Additionally, a binary CCTA finding of high-risk coronary anatomy was defined as LM or two or three vessel proximal obstructive coronary disease involving the LAD.(18) More detailed analysis of the extent and severity of the CAD were performed using previously validated scores:
• Segment involvement score (SIS): the sum of the number of segments with CAD, which ranges from 0 to 17.(19)

• Segment severity score (SSS): each segment receives a value according the amount of disease present in that vessel (0: no CAD, 1: non-obstructive CAD, 2: 50 – 70% stenosis, 3: > 70% stenosis). The final score is the sum of each individual score, and ranges from zero to 51.(20)

Cardiometabolic Risk factors

Review of all clinical data prior to the CCTA was used to verify the presence or absence of risk factors.(1; 21) Hypertension was defined as a systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, or diagnosis/treatment of hypertension. Obesity was defined as body mass index ≥30 kg/m^2. Hypertriglyceridemia was defined as triglycerides ≥150 mg/dL. Low high density lipoprotein cholesterol (HDL) was defined as <40 mg/dL (male) or HDL < 50 mg/dL (women). T2DM was defined by a hemoglobin A1C (HbA1c) ≥6.5% (45 mmol/mol) (22), two fasting glucose levels ≥126 mg/dL, or diagnosis/treatment of T2DM. Dysglycemia was defined as HbA1C ≥5.7% (39 mmol/mol) and <6.5% (45 mmol/mol) or fasting glucose level 100 – 125 mg/dL without a known diagnosis of T2DM.(22) Insulin requiring T2DM was defined according to the presence of exogenous insulin, excluding where used for sliding scale purposes only. All patient clinic notes were reviewed to determine the duration (years) of diagnosed T2DM. Smoking was defined as current (tobacco products used within the last month), former or never. Family history of premature CAD was defined as any first-degree family member with a history of clinical CAD prior to age 60.
For each patient, we determined the total number of CM risk factors present, as clustering of these common risk factors have been recognized as the key contributors to the pathogenesis of both T2DM and cardiovascular disease. We used the following CM risk factors: 1) obesity; 2) low HDL; 3) hypertriglyceridemia; 4) hypertension; and, 5) dysglycemia. All patients were verified as having T2DM or not by past medical history and lab testing. BMI was used as a measure of central adiposity (instead of waist circumference), although these two measures have consistently been shown to be highly correlated and have similar predictive value for future onset of diabetes or clinical CV disease. This method is consistent with the recommendations of the American Association of Clinical Endocrinologists and the World Health Organization, both of which include BMI as a means of defining CM risk.

**Cardiovascular Outcomes**

All patient charts were reviewed by two cardiologists who were blinded to CCTA results for adjudication of cardiovascular events. In order to ensure that events outside of our healthcare network are captured, a standardized questionnaire was mailed to each patient in a manner similar to prior studies. In addition, patients had the option of completing a web-based version of the questionnaire via the REDCap (Research Electronic Data Capture) system, which is encrypted, secure, and HIPAA compliant. For patients who did not reply to the questionnaire upon repeated mailings, scripted phone interviews were performed based on the questionnaire. In order to avoid erroneous diagnoses from self-reported events, all self-reported events were verified via outside medical record review by two cardiologists, blinded to CTA results with discordant events adjudicated by consensus.
The primary endpoint was major adverse cardiovascular events (MACE) composed of myocardial infarction, late coronary revascularization, unstable angina, and cardiovascular mortality. In addition, we further evaluated the combined end-point of only cardiovascular mortality and non-fatal MI to avoid inherent bias of softer outcomes (e.g. angina, coronary revascularization). As a secondary endpoint, we evaluated all-cause mortality. Diagnosis of MI was confirmed by two of three: chest pain or equivalent symptom complex; positive cardiac biomarkers; ECG changes typical of MI.(31) Time to the first coronary revascularization procedure (PCI or CABG) was evaluated. Early revascularizations (≤90 days post CCTA) were removed from survival analysis to minimize verification bias.(32-34) That is, patients with ≥50% stenosis by CCTA are likely to undergo invasive angiography and revascularization early after the CCTA, whereas late revascularizations are less likely to be associated with the CCTA and more associated with CAD progression and prognosis. Unstable angina without revascularization (USA) was defined as chest pain or chest pain equivalent with dynamic electrocardiogram (ECG) changes such as ST depression or T wave inversion but without abnormal cardiac biomarkers and characterized by: 1) rest symptoms; 2) new onset angina (less than 2 months duration); or, 3) increasing duration or severity of previously stable anginal symptoms.(35)

Deaths were confirmed by the Social Security Death Index. For all patients who died, the cause of death was obtained from the National Death Index as well as the Massachusetts Department of Vital Statistics, if applicable. In addition, other pertinent clinical records (e.g. death notes, autopsy findings, hospice notes) related to the cause of death were reviewed. Using all available data, the causes of deaths were adjudicated by two cardiologists blinded to the CTA results with cardiovascular mortality defined as a primary cause of acute MI,
atherosclerotic coronary vascular disease, congestive heart failure, valvular heart disease, arrhythmic heart disease, stroke, or other structural or primary cardiac cause of death.

**Statistical analysis**

Continuous variables are reported as mean +/- standard deviation. Categorical variables are reported as counts and proportions. Continuous variables were compared between groups using analysis of variance techniques. Median segment scores were compared between groups using the Kruskal-Wallis test. Categorical variables were compared using chi-squared test or Fisher’s exact test, where appropriate. Univariable and stepwise multivariable logistic regression was used to assess the association between covariates and the presence of obstructive CAD (defined as above). For purposes of multivariable logistic regression for variables associated with obstructive CAD only, missing HbA1c (HbA1c was available in 78% of patients with T2DM) was imputed based on linear regression of HbA1c with available fasting glucose levels for patients without HbA1c as has been previously validated.(36; 37) The Kaplan Meier method was used to assess event-free survival for the various outcomes of interest (as defined above). To account for baseline differences in patient characteristics for patients with T2DM who are treated or not treated with exogenous insulin, a propensity weighted analysis was conducted. In order to adjust for these baseline differences, we used a two-step process(38; 39) of first evaluating a priori all variables associated with insulin therapy in a logistic model and including those baseline characteristics with a p-value below 0.10 in a final propensity score, which represented a summary statistic for prediction of treatment with insulin therapy. Secondly, we included the propensity score in a propensity weighted Cox-proportional hazards model for prediction of MACE. Such an approach controls for confounding due to baseline differences in each cohort in addition to the effect of non-randomized treatment allocation to statin therapy.
Univariable and multivariable propensity weighted Cox proportional hazards models were constructed to compare risk between strata. Predictors with a \( p < 0.10 \) in univariable analysis were included in the propensity weighted multivariable model. All statistics were performed using Stata version 12.1 (Statacorp, College Station, TX).

**Results**

**Patient population**

1,148 patients met inclusion criteria, of which 10 patients (0.9%) had no available outcomes follow-up and 20 patients (1.7%) had un-interpretable CTA, leaving 1,118 patients available for analysis (Table 1). The most common indication for referral was chest pain symptoms in 641 (57%) followed by abnormal stress testing in 278 (25%) and pre-operative assessments in 66 (6%) of patients.

There were 483 (43%) patients without T2DM with <3 CM risk factors, and 187 (17%) patients without T2DM and ≥3 CM risk factors. Among the remaining 451 (40%) patients with T2DM, 367 did not require insulin and 84 were were insulin requiring.

Over a mean follow-up of 3.1 years, there were 46 (4.1%) all-cause deaths, 21 (1.9%) cardiovascular deaths, 13 (1.2%) MI, 13 (1.2%) unstable angina without revascularization, and 34 (3.1%) late coronary revascularizations.

**Baseline Characteristics**

As expected, significant differences in prevalence of baseline risk factors occurred across CM risk groups (Table 1). Hemoglobin A1c was progressively higher across groups of increased CM risk (\( p < 0.001 \)).
Prevalence, Severity, andExtent of CAD Across Cardiometabolic Risk

Across a spectrum of increasing CM risk, there was increasing prevalence of any CAD from 51% among those with no T2DM and <3 CM risks, to 60% among those with no T2DM and ≥3 CM risks, to 71% among those with T2DM not requiring insulin, to 80% among those with T2DM requiring insulin (p<0.001). Although statistically significant differences occurred (p<0.001), the prevalence of non-obstructive CAD was numerically similar across all patient groups, ranging from 36% to 42% to 41% to 33%. Finally, obstructive CAD was markedly increased according to CM risk, ranging from 15 to 46% (p<0.001). When considering extent of disease, SIS and SSS both increased significantly across groups of increasing CM risk (Figure 1).

In logistic regression models to identify predictors of obstructive CAD across the entire population (Figure 2), CM risk factors and T2DM exhibited a strong and significant association with obstructive CAD. Typical angina was also associated with obstructive disease (OR = 1.6, p = 0.03). A stepwise increase in association with obstructive CAD was seen with low HDL (OR=0.98 for each 1 mg/dL increase, p<0.001), dysglycemia (OR=1.34 for each 1% (11 mmol/mol) increase in HbA1c, p<0.001), hypertriglyceridemia (OR=1.55, p=0.004), and hypertension (OR=3.50, p<0.001). The OR for obesity was not significant (OR=1.14, p=0.3). Diabetes was a significant univariable predictor of obstructive CAD (OR=2.34 for patients with T2DM not requiring insulin and OR=4.79 for T2DM requiring insulin, p<0.001 for both). In the absence of diabetes, the presence of ≥ 3 CM risk factors was not associated with a numeric increase in the odds of obstructive CAD (univariable OR=1.21, p=0.4) but was associated with increased SIS and SSS (Figure 1).
**Propensity Score for Insulin Use**

Significant baseline characteristics associated with insulin use among patients with diabetes included age, male gender, low HDL cholesterol, hypertriglyceridemia, hypertension, higher BMI, and years diagnosed with T2DM. In the final propensity model for insulin use, the c-statistic was 0.91, p<0.001.

**Cardiovascular Outcomes Across Cardiometabolic Risk**

As shown on Supplemental Figure 1, patients with T2DM requiring insulin exhibited the highest annualized risk of cardiovascular death or MI (3.1%), whereas patients without T2DM and <3 CM risk factors exhibited the lowest risk (0.3%; p<0.001). Patients without T2DM and ≥3 CM risk factors had an equivalent annualized rate of cardiovascular death or MI as compared with patients with T2DM not requiring insulin (0.7% versus 1.1%; p = 0.2). Similar results were found when we assessed annualized risk of all-cause mortality (Supplemental figure 2).

When each CM risk group was stratified by severity of CAD, we found that increased stenosis by CCTA was associated with increased MACE (Figure 3 top panel), although differences in cardiovascular death and MI (Figure 3, bottom panel) and all-cause mortality (Supplemental figure 2) were less pronounced.

To evaluate whether early revascularizations (occurring < 90 days post CCTA) influenced prognosis, we compared revascularization rates by metabolic group. Those with T2DM requiring insulin had a significantly increased rate of early revascularization (16% p < 0.001) but other groups did not differ significantly from one another (p= 0.3): 5.0% for those
without T2DM and <3 CM risk factors, 5.6% for those with ≥3 CM risks, and and 7.6% for those with T2DM not requiring insulin.

When restricted to patients with T2DM, those not requiring insulin and without stenosis by CCTA had the greatest long-term event-free survival while patients requiring insulin had an unfavorable prognosis that was further worsened in the presence of stenosis by CCTA (Figure 4, top panel).

In patients without T2DM, the poorest survival occurred in patients with both ≥3 CM risk factors and significant stenosis (Figure 4, bottom panel). Notably, patients with significant stenosis and lower CM risk (<3 CM risk factors) had similar outcomes as patients with ≥3 CM risk factors and no stenosis (p=0.3).

To further examine the association between CM risk, CAD severity and prognosis, we constructed several univariable and multivariable Cox regression models for combined MACE (Supplemental Figure 3). In univariable Cox models, diabetes, extent of CAD, presence of high-risk anatomy, and smoking were associated with risk of combined MACE and cardiac death or MI. In addition, the presence of diabetes was also strongly associated with combined MACE (HR=2.55, p<0.001) and cardiac death or MI (HR=2.89, p=0.004). A significant interaction (p-interaction = 0.008) occurred for diabetes and insulin use.

The final propensity weighted multivariable Cox regression model adjusted for age, smoking, propensity score for insulin use, and high-risk anatomy. In this model, age, current smoking, increasing CM risk category, and high risk CCTA were independently associated with adverse events (Supplemental Figure 3). Analysis according to number of CM risks demonstrated that among those with T2DM, the presence of three additional CM risks was
associated with increased risk for MACE (HR=1.98, p = 0.035). Among patients without T2DM, the presence of 4 or more CM risks was borderline significantly associated with MACE(HR=2.47, p = 0.052) independent of age (HR=1.03, p = 0.049) and high-risk CAD(HR=7.20, p<0.001).

A finding of high risk CAD by CCTA significantly increased the propensity weighted multivariable hazard ratios for MACE in each group with increased CM risk (Supplemental Figure 4). Similar trends were obtained from the univariate and multivariable models for CV death and MI in addition to all-cause mortality (data not shown).

Discussion

Our study demonstrates that that across categories of increasing cardiometabolic risk, there is a graded, dose-dependent association with the presence, extent, and severity of CAD as well as adverse cardiovascular prognosis. A particularly important finding is that among patients without T2DM, the presence of multiple CM risk factors is increasingly associated with risk of future cardiovascular events. Furthermore, among patients without T2DM, CM risk appears to modify the association between obstructive CAD and adverse prognosis, such that the presence of obstructive CAD most strongly impacts patients with higher CM risk. (Figure 3) Finally, among patients with T2DM (already at “high CM risk”), insulin use identifies a subgroup with a worse prognosis. Collectively, these results suggest CM risk is strongly associated with both CAD and cardiac events, and may be an important risk factor in CAD pathogenesis and prognosis before the onset of frank T2DM.

Our findings that patients with T2DM requiring insulin have a greater risk of events has also been shown by Berman et al.(40) who showed that individuals with T2DM requiring insulin
have higher cardiac mortality, particularly if they also have an abnormal adenosine myocardial perfusion imaging study, when the annual cardiac mortality was 9%. However, our study had a lower event rate in this group (3% annual rate of cardiovascular death or MI), reflecting the lower risk associated with patients that undergo CCTA versus MPI. Moreover, while our study excluded all patients with prior CAD, nearly half of the patients with diabetes in the study by Berman et al underwent prior coronary revascularization.(40)

The mechanism underlying the higher event rate of patients with T2DM requiring insulin is not known. Some have hypothesized that direct harmful effects of insulin therapy on endothelial dysfunction (41) could account for poorer long-term prognosis, independent of epicardial disease severity. Alternatively, the use of insulin may serve as a marker for patients with more prolonged duration of diabetes, worse CM risk status, and who are more likely to have hyperglycemia. In turn, hyperglycemia leads to increased inflammation and oxidative stress as well as trapping of pro-atherogenic particles in the vascular endothelium.(42) These mechanisms also account for the increased instability of atherosclerotic plaque among patients with T2DM(43), potentially explaining the higher event rate observed in patients with T2DM on insulin. While recently it has been shown that patients with T2DM with stenosis in at least two coronary vessels have a significantly lower risk of death or myocardial infarction when treated with CABG versus PCI(44), the optimal treatment for individuals with non-obstructive disease has not been defined in prospective studies and warrants further investigation.

Prior studies have demonstrated that patients with increased cardiometabolic risk have higher prevalence of CAD and worse prognosis. Investigators from the Multi-Ethnic Study of Atherosclerosis (MESA) demonstrated that T2DM and metabolic syndrome are associated with higher prevalence of nonzero coronary arterial calcium (CAC) score and higher CAC. (9)
Recently, Wong et al also demonstrated that T2DM and the metabolic syndrome are associated with a higher rate of CAC progression and adverse cardiovascular outcomes (45). Extending these observations, it has also been shown that the absence of CAC identifies patients at low risk: Malik et al showed that even among patients with T2DM or the metabolic syndrome, the absence of CAC was associated with a favorable prognosis (3); similar findings have also been found by Raggi et al. (46)

Our findings extend the results of these prior studies utilizing CAC. While these prior studies have focused on coronary calcifications in predominantly asymptomatic populations, our study is among the first to investigate the association of CM risk across patients with T2DM and patients without T2DM with CCTA, a more sensitive test for coronary plaque, which also can assess for coronary stenosis. Recent important studies by Rana(14) and Hadamitzky(15) demonstrated that CCTA has prognostic utility among patients with T2DM, although these studies utilized an endpoint of all-cause mortality and were unable to evaluate glycemic status or distinguish differences according to insulin use. Our analysis specifically evaluated the endpoint of cardiovascular mortality and non-fatal MI. Importantly, these prior studies and our analysis demonstrate that CCTA identities a subgroup of patients (those with no CAD) with an excellent prognosis in spite of guideline recommendations for consideration as being “high risk” by virtue of a diagnosis of T2DM. However since the proportion of patients with T2DM requiring insulin that have normal studies (i.e. no plaque and no stenosis) was only 20%, the yield of testing in this group may be low (i.e. number needed to scan to identify 1 normal study is 5).

Finally we show that HbA1c has utility not only to define glucose intolerance and diabetes as CM risk factors, but as a predictor of increasing severity of CAD. Specifically, we found a 34% increase in odds of obstructive CAD per 1% (11 mmol/mol) increase in HbA1C
Interestingly, however, increasing HbA1C was not associated with worse prognosis. This finding is in keeping with prior randomized trials which showed aggressive control of hyperglycemia among patients with T2DM reduced microvascular complications such as retinopathy but was not associated with benefit in cardiovascular outcomes, perhaps due to off-target effects of insulin therapies.(47) Specifically, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial(48), the cardiovascular mortality rate of the intensive glucose lowering group (0.8% per year) was not significantly different from the standard therapy controls (0.6% per year). Notably, these event rates were comparable to the overall CV mortality rate in our study (0.8% per year among all those with T2DM). However, our finding is exploratory, as HbA1C assessment was cross-sectional and its association with risk may be influenced by disease-specific therapy.

The results of our study must be viewed in context with its design. Our study was retrospective, thus limiting full ascertainment of some risk factors for all patients who underwent CCTA. Thus, our sample size was reduced in order to include only patients with completely available data for all risk factors. Additionally, we did not use measures of central adiposity such as waist:hip ratio but rather used BMI. BMI is highly correlated(23) with and has similar predictive value for future onset of diabetes(24) or clinical CV disease(25) as waist-hip ratio. Also, we did not obtain follow-up creatinine in order to assess for contrast nephropathy, as the rate of this complication is exceedingly low in clinical practice. For instance, among patients with T2DM referred for CT angiography for pulmonary embolus (a study which requires a higher dose of contrast than coronary CT; 120 mL versus 70 mL), there was no clinical case of renal failure although 4% of patients experienced an increase in creatinine of unknown clinical significance.(49) Because contrast nephropathy after CCTA is a rare event even among patients...
with T2DM(50), we followed SCCT guidelines for performance of CCTA, which do not recommend any active surveillance for this rare event.(16) Finally, the present study only includes patients who underwent CTA and thus these results can only be generalized to individuals who do not have contraindications for intravenous contrast and those with no history of prior CAD. In addition, this study involved patients clinically referred for CTA at tertiary care referral centers, who may therefore represent an inherently higher risk group of patients. While not the focus of our study, it is well known that anatomic measures of coronary stenosis, whether by CCTA or invasive angiography, only have a modest correlation with physiologic tests which are designed to detect ischemia.(51) Furthermore, although anatomic stenosis(52; 53) and extent of CAD(54) have been shown to predict outcomes, many adverse CV events occur in the setting of plaque rupture at sites of previously <50% luminal stenosis(55) demonstrating that anatomy alone does not exclusively determine prognosis. Nevertheless, as has been demonstrated in prior research,(52; 53) anatomical markers of plaque and stenosis do provide important prognostic data. Notwithstanding these limitations, we demonstrate a strong and independent association of CM risk, CAD extent, and prognosis, suggesting that across a diverse spectrum of baseline cardiometabolic risk, CCTA may stratify clinically important risk.

**Conclusion**

In conclusion, our study shows that CCTA identifies patients across a spectrum of baseline CM risk factors with differential CAD prevalence and prognosis at 3.1 years follow-up. Patients without T2DM with increased CM risk have a similar prognosis as patients with T2DM but not requiring insulin. On the other hand, among patients with T2DM, the need for insulin
therapy identifies individuals with greater burden of CAD and worse prognosis. While use of CCTA to more effectively stratify patients without T2DM but with increased cardiometabolic risk and those with overt diabetes warrants additional investigation, our findings suggest that integrating data on CM risk factors together with data on CAD presence and severity may have an important role in efficient allocation of aggressive preventive therapies.

**Disclosures.** Dr. Hoffmann reports research support from Siemens Medical Systems. Dr. Rybicki reports research support from Toshiba Medical Systems.

**Acknowledgements. Author contributions.** EH was involved in all steps of this study and is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. RB and MSB were involved in data collection, study design, and reviewing/editing the manuscript. DO, MP, PM, and JH assisted in data collection. RS, MS, QT, KN, FR, TB, MDC reviewed/edited the manuscript. BG, UH, SA assisted in study design and reviewed/edited the manuscript.

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**Figure 1.** Increasing prevalence / extent (SIS, left panels) and severity (SSS, right panels) of CAD according to number of CM criteria (top panels) and stratified by CM risk (lower panels). Boxes represent the 25\(^{th}\) (lower box), 50\(^{th}\) (middle bar) and 75\(^{th}\) % (top box). Whiskers represent upper and lower adjacent values. CM Risks include obesity, low HDL, hypertriglyceridemia, hypertension, and hemoglobin A1C >5.7% (39 mmol/mol). T2DM = Type 2 Diabetes Mellitus. CAD = coronary artery disease; CM = cardiometabolic; SIS = segment involvement score; SSS = segment stenosis score; T2DM = type 2 diabetes mellitus. * = p<0.05 when compared to the next lower CM risk group.

**Figure 2.** Predictors of obstructive coronary disease by logistic regression. CM Risks include obesity, low HDL, hypertriglyceridemia, hypertension, and hemoglobin A1C >5.7% (39 mmol/mol). CM = cardiometabolic; HbA1c = hemoglobin A1c; T2DM = Type 2 Diabetes Mellitus.

**Figure 3.** Top panel: Annualized rate of combined adverse cardiovascular events including cardiovascular death, non-fatal myocardial infarction, unstable angina, and late revascularization according to coronary artery disease (CAD) classification by CTA and Cardiometabolic risk category. Bottom panel: Annualized cardiovascular death and non-fatal myocardial infarction. CM Risks include obesity, low HDL, hypertriglyceridemia, hypertension, and hemoglobin A1C >5.7% (39 mmol/mol). CM = cardiometabolic; T2DM = Type 2 Diabetes Mellitus.

**Figure 4.** Univariate Kaplan-Meier survival curves for event free survival from cardiovascular death or myocardial infarction for patients with T2DM (top panel) and patients without T2DM (bottom panel) according to presence or absence of >50% stenosis on CTA and cardiometabolic (CM) risk category. CM Risks include obesity, low HDL, hypertriglyceridemia,
hypertension, and hemoglobin A1C >5.7% (39 mmol/mol). CM = cardiometabolic; T2DM = Type 2 Diabetes Mellitus.

**Supplemental Figure 1.** Annualized rate of adverse events according to Cardiometabolic (CM) risk category. CM Risks include obesity, low HDL, hypertriglyceridemia, hypertension, and hemoglobin A1C >5.7% (39 mmol/mol). CM = cardiometabolic; T2DM = Type 2 Diabetes Mellitus.

**Supplemental Figure 2.** Annualized incidence of all-cause mortality according to coronary artery disease (CAD) classification by CTA and Cardiometabolic risk category. CM Risks include obesity, low HDL, hypertriglyceridemia, hypertension, and hemoglobin A1C >5.7% (39 mmol/mol). CM = cardiometabolic; T2DM = Type 2 Diabetes Mellitus.

**Supplemental Figure 3.** Cox proportional hazard model for cardiovascular major adverse combined events (MACE: unstable angina, late coronary revascularization, non-fatal MI, cardiovascular death). CM Risks include obesity, low HDL, hypertriglyceridemia, hypertension, and hemoglobin A1C >5.7% (39 mmol/mol). CM = cardiometabolic; T2DM = Type 2 Diabetes Mellitus.

**Supplemental Figure 4.** Adjusted hazard ratio for major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, unstable angina, and late coronary revascularization) according to cardiometabolic risk and CTA finding. Hazard adjusted for age, insulin use, and propensity score for insulin. CM Risks include obesity, low HDL, hypertriglyceridemia, hypertension, and hemoglobin A1C >5.7% (39 mmol/mol). CM = cardiometabolic; T2DM = Type 2 Diabetes Mellitus.
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<th>≥3 CM Risks</th>
<th>T2DM no insulin</th>
<th>T2DM on insulin</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1118</td>
<td>483</td>
<td>184</td>
<td>367</td>
<td>84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, years</td>
<td>57(13)</td>
<td>54(13)</td>
<td>54(13)</td>
<td>60(12)</td>
<td>61(11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% Male</td>
<td>645(58)</td>
<td>283(59)</td>
<td>108(59)</td>
<td>211(57)</td>
<td>43(51)</td>
<td>0.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>628(56)</td>
<td>150(31)</td>
<td>133(72)</td>
<td>270(74)</td>
<td>75(89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>low HDL</td>
<td>412(37)</td>
<td>71(15)</td>
<td>125(68)</td>
<td>169(46)</td>
<td>47(56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>330(30)</td>
<td>56(12)</td>
<td>113(61)</td>
<td>119(32)</td>
<td>42(50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity</td>
<td>467(42)</td>
<td>83(17)</td>
<td>136(74)</td>
<td>192(52)</td>
<td>56(67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dysglycemia, without T2DM</td>
<td>314(28)</td>
<td>175(36)</td>
<td>139(76)</td>
<td>0(0)</td>
<td>0(0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Current</td>
<td>121(11)</td>
<td>45(9)</td>
<td>28(15)</td>
<td>41(11)</td>
<td>7(8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Former</td>
<td>338(30)</td>
<td>122(25)</td>
<td>54(29)</td>
<td>137(37)</td>
<td>25(30)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>659(59)</td>
<td>316(65)</td>
<td>102(55)</td>
<td>189(51)</td>
<td>52(62)</td>
<td></td>
</tr>
<tr>
<td>Family History</td>
<td>595(53)</td>
<td>276(57)</td>
<td>103(56)</td>
<td>170(46)</td>
<td>46(55)</td>
<td>0.02</td>
</tr>
<tr>
<td>Years with T2DM</td>
<td>1.5(4)</td>
<td>0(0)</td>
<td>0(0)</td>
<td>2(3)</td>
<td>11(10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reason for CCTA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonanginal Chest Pain</td>
<td>92(8)</td>
<td>34(7)</td>
<td>15(8)</td>
<td>32(9)</td>
<td>11(13)</td>
<td>0.3</td>
</tr>
<tr>
<td>Atypical Angina</td>
<td>441(39)</td>
<td>199(41)</td>
<td>77(42)</td>
<td>136(37)</td>
<td>29(35)</td>
<td>0.4</td>
</tr>
<tr>
<td>Typical Angina</td>
<td>108(10)</td>
<td>42(9)</td>
<td>24(13)</td>
<td>34(9)</td>
<td>8(10)</td>
<td>0.4</td>
</tr>
<tr>
<td>Prior equivocal stress test</td>
<td>85(8)</td>
<td>33(7)</td>
<td>15(8)</td>
<td>30(8)</td>
<td>7(8)</td>
<td>0.9</td>
</tr>
<tr>
<td>Prior positive stress test</td>
<td>193(17)</td>
<td>69(14)</td>
<td>34(18)</td>
<td>73(20)</td>
<td>17(20)</td>
<td>0.7</td>
</tr>
<tr>
<td>Other clinical referral</td>
<td>66(6)</td>
<td>32(7)</td>
<td>8(4)</td>
<td>21(6)</td>
<td>5(6)</td>
<td>0.8</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30(7)</td>
<td>27(4)</td>
<td>34(7)</td>
<td>31(7)</td>
<td>34(8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>6.1(1)</td>
<td>5.6(0.3)</td>
<td>5.7(0.3)</td>
<td>6.5(1.1)</td>
<td>7.9(1.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 1. Baseline demographics according to cardiometabolic risk. BMI = body mass index (kg/m²); CM = cardiometabolic; DM = diabetes mellitus; HbA1c = hemoglobin A1c; HDL = high density lipoprotein; T2DM = type 2 diabetes mellitus.
Increasing prevalence / extent (SIS, left panels) and severity (SSS, right panels) of CAD according to number of CM criteria (top panels) and stratified by CM risk (lower panels). Boxes represent the 25th (lower box), 50th (middle bar) and 75th % (top box). Whiskers represent upper and lower adjacent values. CM Risks include obesity, low HDL, hypertriglyceridemia, hypertension, and hemoglobin A1C >5.7% (39 mmol/mol). T2DM = Type 2 Diabetes Mellitus. CAD = coronary artery disease; CM = cardiometabolic; SIS = segment involvement score; SSS = segment stenosis score; T2DM = type 2 diabetes mellitus. * = p<0.05 when compared to the next lower CM risk group.
Predictors of obstructive coronary disease by logistic regression. CM Risks include obesity, low HDL, hypertriglyceridemia, hypertension, and hemoglobin A1C >5.7% (39 mmol/mol). CM = cardiometabolic; HbA1c = hemoglobin A1c; T2DM = Type 2 Diabetes Mellitus.
Top panel: Annualized rate of combined adverse cardiovascular events including cardiovascular death, non-fatal myocardial infarction, unstable angina, and late revascularization according to coronary artery disease (CAD) classification by CTA and Cardiometabolic risk category. Bottom panel: Annualized cardiovascular death and non-fatal myocardial infarction. CM Risks include obesity, low HDL, hypertriglyceridemia, hypertension, and hemoglobin A1C >5.7% (39 mmol/mol). CM = cardiometabolic; T2DM = Type 2 Diabetes Mellitus.
Univariate Kaplan-Meier survival curves for event free survival from cardiovascular death or myocardial infarction for patients with T2DM (top panel) and patients without T2DM (bottom panel) according to presence or absence of >50% stenosis on CTA and cardiometabolic (CM) risk category. Log-rank p-value < 0.001 between groups for top and bottom figure. CM Risks include obesity, low HDL, hypertriglyceridemia, hypertension, and hemoglobin A1C >5.7% (39 mmol/mol). CM = cardiometabolic; T2DM = Type 2 Diabetes Mellitus.

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Annualized rate of adverse events according to Cardiometabolic (CM) risk category. CM Risks include obesity, low HDL, hypertriglyceridemia, hypertension, and hemoglobin A1C >5.7% (39 mmol/mol). CM = cardiometabolic; T2DM = Type 2 Diabetes Mellitus.
Annualized incidence of all-cause mortality according to coronary artery disease (CAD) classification by CTA and Cardiometabolic risk category. CM Risks include obesity, low HDL, hypertriglyceridemia, hypertension, and hemoglobin A1C >5.7% (39 mmol/mol). CM = cardiometabolic; T2DM = Type 2 Diabetes Mellitus.
Cox proportional hazard model for cardiovascular major adverse combined events (MACE: unstable angina, late coronary revascularization, non-fatal MI, cardiovascular death). CM Risks include obesity, low HDL, hypertriglyceridemia, hypertension, and hemoglobin A1C >5.7% (39 mmol/mol). CM = cardiometabolic; T2DM = Type 2 Diabetes Mellitus.
Adjusted hazard ratio for major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, unstable angina, and late coronary revascularization) according to cardiometabolic risk and CTA finding. Hazard adjusted for age, insulin use, and propensity score for insulin. CM Risks include obesity, low HDL, hypertriglyceridemia, hypertension, and hemoglobin A1C >5.7% (39 mmol/mol). CM = cardiometabolic; T2DM = Type 2 Diabetes Mellitus.

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