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CLINICAL INVESTIGATIONS

Relationship between carotid atherosclerosis and coronary artery calcification in asymptomatic diabetic patients: A prospective multicenter study

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Background: The value of screening sub-clinical atherosclerosis in asymptomatic patients with type 2 diabetes mellitus (T2DM) remains controversial.

Hypothesis: An integrated model incorporating carotid intima-media thickness (CIMT) and carotid plaque with traditional risk factors can be used to predict prevalence and severity of coronary artery calcification in asymptomatic T2DM patients.

Methods: A cohort of 262 asymptomatic T2DM patients were prospectively studied with carotid ultrasound to evaluate CIMT and carotid plaque and also a computed tomography coronary artery calcium (CT-CAC) scan.

Results: Carotid plaque was detected in 124 (47%) patients and mean CIMT was 0.75±0.14 mm. Two hundred (76%) patients had a CAC score >0, of whom 57 (22%) had severe coronary atherosclerosis (>400 Au). In this group, carotid plaque was present in 40 (70%) patients ($p<0.001$).

Univariable analysis revealed significant associations between non-zero CAC score and age ($p<0.001$), hypertension ($p=0.01$), gender ($p=0.003$) and duration of diabetes ($p=0.004$). Carotid plaque and mean CIMT were also significantly associated with non-zero CAC score (odds ratios [95% CI], 3.12 [1.66 -5.85] and 2.98 [0.24 -7.17], respectively). After adjusting for traditional risk factors, carotid plaque continued to be predictive of non-zero CAC score (2.59 [1.17 -5.74]) and CIMT was borderline significant ($p=0.05$). When analysed with binary logistical regression, the prevalence of carotid plaque significantly predicted severe CAC burden (CAC >400 Au; 3.26 [2.05 -5.19]). Upper CIMT quartiles showed a similar association (2.55 [1.33 -4.87]).

Conclusion: Carotid plaque is more predictive of underlying silent coronary atherosclerosis prevalence, severity and extent in asymptomatic T2DM patients.

KEYWORDS

Carotid Plaque, Intima-Media Thickness, Coronary Atherosclerosis, Cardiovascular Computed Tomography, Calcium Score, Diabetes

1 | INTRODUCTION

Diabetes mellitus (DM) is a major source of cardiovascular morbidity and mortality in developed and developing countries. Previous estimates of DM prevalence by the International Diabetes Federation have shown significant regional variability, with a large and increasing burden.[1,2] Currently, the worldwide prevalence of DM is estimated to be 382 million. This figure is predicted to rise to 592 million by the year 2035. DM currently affects 56.3 million people in Europe, and this is expected to rise to 68.9 million in 2035.[3]

The Global Registry of Acute Coronary Events (GRACE) registry shows that approximately 25% of patients with ST-segment elevation myocardial infarction, non–ST-segment elevation myocardial infarction, and unstable angina also have a history of DM.[4]

Patients with DM generally have a greater extent of atherosclerosis, with a higher prevalence of multivessel coronary artery disease (CAD), frequent silent myocardial ischemia, and infarction with a higher cardiac event rate compared with the non-DM population.[5,6] Furthermore, some studies suggest that DM patients without CAD have the same risk for future cardiac death as do non-DM patients with established CAD.[5,7] Once CAD manifests clinically, DM patients continue to have a worse prognosis compared with non-DM patients, both acutely after the event and during long-term follow-up.[8]

Historically, Framingham risk score and QRISK algorithms have been used for CAD risk prediction based on traditional risk factors such as age, sex, hypertension (HTN), serum cholesterol level, smoking, and family history of CAD.[9,10] However, these risk algorithms tend to underestimate the risk of cardiovascular disease in patients with type 2 diabetes mellitus (T2DM).[11]

Several noninvasive techniques have been used to identify subclinical atherosclerosis in asymptomatic patients: (1) carotid ultrasound to measure carotid intima-media thickness (CIMT), (2) coronary artery calcium (CAC) scan to quantify coronary calcification, and (3) computed tomography (CT) coronary angiography to evaluate total atherosclerotic burden.[6,12,13] CIMT has been widely used as a marker to identify subclinical atherosclerosis, as increased CIMT has been associated with a high prevalence of CAD and future cardiovascular events.[14,15]

The present study was designed to explore the potential role of CIMT and carotid plaque in the identification of DM patients at high risk for cardiovascular disease. Relationships were prospectively evaluated between CIMT/carotid plaques and the presence and extent of CAC when assessed noninvasively by multislice CT in asymptomatic diabetic patients.

2 | METHODS

2.1 | Patient Enrollment

We recruited 262 patients as part of the multicenter Progression of Coronary Atherosclerosis in Asymptomatic Diabetic Subjects: Evaluation of the Role of Computed Tomography Coronary Angiography and Novel Biomarkers of Vascular Inflammation and Endothelial Function (PROCEED) trial. This study was an observational, prospective study of asymptomatic T2DM patients from 3 National Health Service hospitals and a cardiovascular screening clinic in North West London, United Kingdom. All subjects underwent carotid ultrasonography and unenhanced noncontrast CT-CAC scan on the same day. Inclusion criteria were (1) established T2DM for ≥1 year with and without microvascular complications of DM (retinopathy, peripheral neuropathy, and/or microalbuminuria) and (2) no history of CAD. Exclusion criteria were (1) pregnant women, (2) atrial fibrillation, and (3) age <35 years.

All patients included in the study provided written informed consent before enrollment. This study is registered with http://www.ClinicalTrials.gov (NCT02109835). Ethical approval was obtained from National Research Ethics Service, United Kingdom (REC reference 11/LO/16/96).

All patients provided baseline demographic data. Clinical and laboratory data were obtained with patients' consent and included sex, age, ethnicity (self-reported; Mediterranean was classified as Caucasian), DM medications, duration of DM, smoking history, height, weight, waist and hip measurements, blood pressure, hyperlipidemia, presence of microvascular disease and type, family history of CAD, and glycated hemoglobin (HbA_{1c}), total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and creatinine levels.

2.2 | Carotid ultrasonography

Carotid ultrasonography was performed using a B-mode ultrasound system (11 L, GE Vivid E9; GE Healthcare, Wauwatosa, WI) as per the American Society of Echocardiography 2008 consensus statement.[16]

Intima-media thickness (IMT) is defined as the distance between the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface. The near and far walls were identified on a longitudinal display by 2 bright lines separated by hypoechogenic space. Patients were examined in the supine position with the head slightly extended to the opposite direction of the carotid artery being examined. Each carotid artery and segment was interrogated independently from continuous angles (anterior, lateral, and posterior). CIMT was measured using automated edge-detection software in the far wall of the distal common carotid artery 1 cm proximal to the carotid bulb, with 3- to 5-beat cine loop and optimized R-wave-gated still frames at each angle. Doppler recordings of the proximal segments of common, internal, and external carotid arteries were also recorded. A composite mean IMT was calculated from the mean IMTs measured from 3 angles on both sides. Maximal IMT was defined as the greatest wall thickness from the same segments imaged for the mean IMT.

The entire carotid system was surveyed bilaterally (3- to 5-beat cine loop from 3 different angles in each segment) for presence of plaque. Presence of carotid plaque was defined as a focal increase in thickness (>50%) of the surrounding CIMT.[17] All ultrasound measurements were made by 2 experienced doctors who were not aware of the CAC results.

2.3 | CT-CAC scanning

CAC scans were performed on a SOMATOM Definition Siemens Dual Source CT scanner (Siemens Medical Systems, Forchheim,

Germany). All patients underwent an unenhanced noncontrast scan to assess calcified plaque burden at the Cardiac Imaging and Research Centre, Wellington Hospital, London. Thirty-eight contiguous images were obtained with a scan of 200 ms, 3-mm slice thickness, 120-kVp tube energy, 152-mA tube current, and a rotation speed of 330 ms.

Images were reconstructed at 70% R-R interval phase for heart rates <70 bpm or 40% R-R phase for heart rates >70 bpm, using electrocardiogram triggering with a single breathhold. Coronary artery calcification was quantified using an Aquarius workstation (TeraRecon, Inc., San Mateo, CA) displaying all pixels with a density of >130 Hounsfield units (HU).[18–20] Calcifications were defined as a minimum of 2 pixels with an area of 0.52 mm^2 and density of >130 HU. Each high-density lesion in the epicardial coronary arteries was recorded, and the sum total of all the lesions identified resulted in the CAC score for the entire coronary system, as proposed by Agatston et al.[21] Agatston calcium scores (Au) were calculated to quantify the extent of CAC by a single experienced investigator blinded to the clinical data.

The CAC score was classified relative to CAD risk as no increase (0 Au), mildly increased (1–99 Au), moderately increased (100–400 Au), and severely increased (>400 Au).[18–20,22]

2.4 | Statistical analysis

Analysis was performed using SPSS statistical software version 21 (IBM Corp., Armonk, NY). All categorical variables were described as percentages, whereas continuous variables were expressed as mean (IQR). CIMT was considered as the mean of the 2 individual values (right and left CIMT) and greater IMT was the maximum of 2 sides. The analyses examined factors associated with coronary artery calcification, defined as a CAC score >0. As this was a binary outcome, all analysis was performed using logistical regression. Baseline characteristics were available for 262 patients. Data from 254 patients were available for further analysis.

The first stage in the analysis examined the separate association between each variable and each risk factor. Traditional risk factors were examined along with cardiac risk factors of interest. A second set of analyses examined whether there was any additional benefit of CIMT and carotid plaque over traditional risk factors for the prediction of coronary artery calcification. To achieve this, a multivariable analysis was performed with CIMT and carotid plaque in combination with traditional risk factors. To restrict the number of variables in this analysis, only traditional/other risk factors indicating a tendency for association in the univariable analyses ($P < 0.2$) were included.

A final set of analyses considered the outcome on a more detailed scale. Rather than simply the presence or absence of coronary artery calcification (defined as CAC > 0), CAC score was considered in 4 categories (0, 1–99, 100–400, and >400).[19,20,22] The associations between the cardiac risk factors and this revised outcome were examined, with each risk factor considered separately. To allow for the ordering of the CAC categories, ordinal logistical regression was used for the analysis. Logistical regression was also used to examine the variation of risk-factor associations by ethnicity (categorized as either Asian, Caucasian, or Afro-Caribbean).

A P value of <0.05 was used to indicate statistical significance.

3 | RESULTS

The mean age at assessment was 61.3 ± 8.7 years and mean body mass index was 29.4 ± 6.3 kg/m^2; 154 (59%) patients were male (Table 1). The South Asian population comprised 58% of the entire cohort, reflecting the high prevalence of DM in this ethnic group. Microvascular disease was present in 48% of the study population. Mean CIMT was 0.78 ± 0.14 mm and 0.74 ± 0.14 mm in patients with and without microvascular disease, respectively. However, there was no statistically significant difference noted ($P = 0.06$).

Two hundred (76%) patients had a CAC score >0, of which 57 (22%) had severe coronary artery calcification (CAC score >400 Au) and 20 (8%) had extensive coronary calcification with a CAC score of >1000 Au. Of the 200 subjects with a nonzero CAC score,

TABLE 1 Baseline characteristics of study population (N = 262)

Baseline characteristics	
Mean age, y	61.3 (35.5–82.6)
Male sex	59
BMI, kg/m^2	29.35 (18.0–58.5)
Ethnicity	
African	12.0
Asian	57.5
Caucasian	30.5
Duration of T2DM, y	13.71 (1–37)
Microvascular disease	47.5
Hyperlipidemia	69.2
HTN	74.0
HTN treatment	74.
Medications	
Statin use	72.1
Oral hypoglycemics + insulin therapy	27.5
Insulin only	6.1
Oral hypoglycemics only	65.2
Smoking	8.7
Family history of ischemic heart disease	43.4
Family history of premature ischemic heart disease	18.3
SBP, mm Hg	135.9 (90–180)
DBP, mm Hg	84.1 (60–110)
HbA_{1c}, mmol/mol	65.2 (35.5–143.7)
CAC score, Au	
>0	200 (74)
>400	57 (22)
>1000	20 (9)

Abbreviations: BMI, body mass index; CAC, coronary artery calcium; DBP, diastolic blood pressure; HbA_{1c}, glycated hemoglobin; HTN, hypertension; IQR, interquartile range; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus.

Data are presented as %, n (%), or mean (IQR).

106 (53%) also had concomitant carotid plaque. Interestingly, 40 (70%) patients with severe calcification and 15 (75%) with extensive calcification were associated with prevalence of a carotid plaque ($P < 0.001$).

Individual associations between each risk factor and nonzero CAC score were initially examined in a series of univariable analyses (Table 2). Statistically significant associations were identified between CAC and several traditional risk factors for CAD. The occurrence of CAC increased with age ($P < 0.001$), particularly when comparing patients age >60 years with patients age 35 to 50 years. CAC was also more common in males than females ($P = 0.003$) and in patients with HTN compared with those without ($P = 0.01$).

Of the "other" factors assessed, only the duration of T2DM was found to be significantly associated with CAC. A longer duration was associated with an increased likelihood of CAC ($P = 0.004$). Also, it is interesting to see that microvascular disease was not associated with increased CAC.

Mean CIMT (upper quartiles) and carotid plaque were significantly associated with CAC ($P = 0.003$ and $P < 0.001$, respectively). CAC was 3× more likely to be detected in the mean CIMT upper quartiles (50th–75th quartile and >75th quartile) than in the lower quartiles. No significant difference in the presence of CAC was found between the third and fourth quartiles. Although CAC scores increased with max-CIMT, this association did not reach statistical significance ($P = 0.21$). The presence of CAC was 3× more likely in patients with carotid plaque compared with those without.

Associations identified (as $P < 0.2$) in the univariable analysis were evaluated after adjusting for traditional risk factors by

TABLE 2 Predictors of CAC, univariable analysis

Variable	Category	CAC > 0, n (%)	OR (95% CI)	*P* Value
Traditional factors				
Age, y	35–50	13/23 (57)	1	<0.001
	51–60	66/100 (66)	1.49 (0.59-3.76)	
	>60	115/131 (88)	5.53 (2.08-14.7)	
Sex	F	68/102 (67)	1	0.003
	M	126/152 (83)	2.42 (1.34-4.37)	
Hyperlipidemia	N	57/80 (71)	1	0.19
	Y	137/174 (78)	1.49 (0.82-2.74)	
HTN	N	40/62 (65)	1	0.01
	Y	154/192 (80)	2.22 (1.19-4.18)	
Smoker	N	151/200 (76)	1	0.71
	Y	39/50 (78)	1.15 (0.55-2.42)	
Family history CAD	N	105/139 (76)	1	0.73
	Y	89/115 (77)	1.11 (0.62-1.99)	
Waist-hip ratio[a]	—	—	1.32 (0.89-1.97)	0.16
BMI[b]	—	—	0.85 (0.70-1.04)	0.11
Other factors				
Duration of DM[b]	—	—	1.34 (1.10-1.64)	0.004
HbA_{1c}[c]	—	—	1.03 (0.87-1.22)	0.76
Microvascular disease	N	98/133 (74)	1	0.29
	Y	96/121 (79)	1.37 (0.76-2.46)	
Cardiac factors				
Mean CIMT	1st quartile	43/64 (67)	1	0.003
	2nd quartile	38/58 (66)	0.93 (0.44-1.97)	
	3rd quartile	53/60 (88)	3.70 (1.43-9.51)	
	4th quartile	55/64 (86)	2.98 (0.24-7.17)	
Max CIMT	1st quartile	42/61 (69)	1	0.21
	2nd quartile	43/58 (74)	1.30 (0.58-2.88)	
	3rd quartile	49/62 (79)	1.71 (0.75-3.86)	
	4th quartile	54/64 (84)	2.44 (1.03-5.80)	
Carotid plaque	N	86/129 (67)	1	<0.001
	Y	106/123 (86)	3.12 (1.66-5.85)	

Abbreviations: BMI, body mass index; CAC, coronary artery calcium; CAD, coronary artery disease; CI, confidence interval; CIMT, carotid intima-media thickness; DM, diabetes mellitus; F, female; HbA_{1c}, glycated hemoglobin; HTN, hypertension; M, male; N, no; OR, odds ratio; Y, yes.

Data are presented as n (%).

[a] OR given for a 0.1-unit increase in predictor variable.

[b] OR given for a 5-unit increase in predictor variable.

[c] OR given for a 10-unit increase in predictor variable.

TABLE 3 Predictors of CAC after adjusting for traditional risk factors by multivariable analysis

Variable	Category	OR (95% CI)	*P* Value
Traditional factors			
Age, y	35–50	1	0.04
	51–60	1.32 (0.43-4.06)	
	>60	3.32 (1.01-10.9)	
Sex	F	1	0.002
	M	3.33 (1.56-7.12)	
Hyperlipidemia	N	1	0.97
	Y	1.01 (0.47-2.17)	
HTN	N	1	0.34
	Y	1.48 (0.66-3.29)	
Waist-hip ratio[a]	—	0.97 (0.59-1.62)	0.92
BMI[b]	—	1.07 (0.82-1.40)	0.61
Other factors			
Duration of DM[b]	—	1.33 (1.04-1.71)	0.03
Cardiac factors			
Mean CIMT	1st quartile	1	0.05
	2nd quartile	0.95 (0.36-2.47)	
	3rd quartile	4.57 (1.26-16.5)	
	4th quartile	2.20 (0.59-8.26)	
Max CIMT	1st quartile	1	0.83
	2nd quartile	0.81 (0.30-2.24)	
	3rd quartile	0.59 (0.18-1.88)	
	4th quartile	0.83 (0.22-3.14)	
Carotid plaque	N	1	0.02
	Y	2.59 (1.17-5.74)	

Abbreviations: BMI, body mass index; CAC, coronary artery calcium; CI, confidence interval; CIMT, carotid intima-media thickness; DM, diabetes mellitus; F, female; HTN, hypertension; M, male; N, no; OR, odds ratio; Y, yes.

[a] OR given for a 0.1-unit increase in predictor variable.

[b] OR given for a 5-unit increase in predictor variable.

multivariable analysis (Table 3). The association between carotid plaque and CAC continued to be significant ($P = 0.02$). However, the result for mean CIMT only reached borderline significance ($P = 0.05$). In agreement with the univariable analysis, the presence of CAC was most likely in the mean CIMT upper quartiles and in patients with carotid plaque. As in the univariable analysis, there was no evidence of an association between max CIMT and CAC ($P = 0.83$).

The final set of analyses used ordinal logistic regression to examine the associations between cardiovascular risk factors and CAC score when considered in 4 CAC severity categories. Table 4 shows the number of patients in each category and the odds ratio (OR) of being in the next-highest-severity category (eg, 1–100 Au rather than 0 Au) for each category relative to the odds in the baseline category.

Statistically significant associations with CAC severity were identified for both mean CIMT and the presence of carotid plaque. A higher mean CIMT quartile was associated with an increased severity of CAC. In the upper quartiles, 66% of patients had a CAC score of ≥100, compared with only 45% of those in the first quartile. The odds of a patient being in the next-highest severity category were 2.5× higher for the upper quartile compared with the lower quartile ($P = 0.004$).

Patients with carotid plaque were more likely to have severe CAC compared with those without. One-third of patients with carotid plaque had a CAC score of >400, compared with 13% of patients with no carotid plaque. The odds of being in the next-highest severity category were >3× higher for patients with carotid plaque compared with those without ($P < 0.001$).

3.1 | Ethnic variation

No statistically significant interaction was found between ethnicity and any of the factors examined (Table 5).

4 | DISCUSSION

This study found coronary artery calcification to be common in T2DM patients asymptomatic for CAD. Severe calcification was identified in one-quarter of patients, and extensive calcification in 1 in 10 patients. Our analyses revealed strong positive associations of coronary calcification with carotid plaque and mean CIMT.

4.1 | Relationship of nonzero CAC score with CIMT and carotid plaque

Carotid plaque and increased CIMT both were associated with the presence of coronary calcification. As the strongest predictor, carotid plaque also was associated with the presence of any CAC after adjusting for traditional cardiovascular risk factors. Although the upper 2 quartiles of mean CIMT were also related to the presence of coronary calcification when unadjusted for traditional risk factors, this association became weaker after adjustment. These findings are consistent with previously published trials comparing carotid and coronary atherosclerosis.[23–27]

There were no significant differences in the associations of risk factors with CAC when assessed by ethnic population, suggesting these relationships are independent of ethnicity.

4.2 | Relationship of severity and extent of CAC with mean CIMT and carotid plaque

The presence of carotid plaque and the quartile range of mean CIMT reliably predicted the severity and extent of CAC. However, the prognostic benefit of identifying a high CAC score in asymptomatic T2DM patients is uncertain, as further management decisions are contentious, particularly as this relates to revascularization. In contrast, the cardiovascular survival benefit of a lower CAC score is well accepted.

It is noteworthy that the upper 2 quartiles of mean CIMT were positively related to CAC severity, which is consistent with a previous study done by Kablak-Ziembicka et al.[28] Their study of 558 patients with suspected CAD demonstrated a positive correlation between increasing IMT and advanced CAD detected by coronary angiography.

In the current study, the presence of carotid plaque showed a strong and persistent relationship with extensive coronary artery calcification. These findings are consistent with a previous study by Oei et al.[29] Their study of 2013 patients found a linear and graded

TABLE 4 Associations of CIMT and carotid plaque with CAC severity analyzed by ordinal logistical regression

Variable	CAC 0 Au	CAC 1–99 Au	CAC 100–400 Au	CAC >400 Au	OR (95% CI)	*P* Value
Mean CIMT						
1st quartile	21 (33)	14 (22)	15 (23)	14 (22)	1	0.004
2nd quartile	20 (34)	13 (22)	16 (28)	9 (16)	0.85 (0.44-1.63)	
3rd quartile	7 (12)	18 (30)	25 (42)	10 (17)	1.60 (0.85-2.99)	
4th quartile	9 (14)	13 (20)	19 (30)	23 (36)	2.55 (1.33-4.87)	
Max CIMT						
1st quartile	19 (31)	17 (28)	12 (20)	13 (21)	1	0.10
2nd quartile	15 (26)	16 (28)	16 (28)	11 (19)	1.17 (0.61-2.25)	
3rd quartile	13 (21)	10 (16)	26 (42)	13 (21)	1.73 (0.91-3.29)	
4th quartile	10 (16)	15 (23)	21 (33)	18 (28)	2.05 (1.08-3.89)	
Carotid plaque						
N	43 (33)	36 (28)	33 (26)	17 (13)	1	<0.001
Y	17 (14)	22 (18)	44 (36)	40 (33)	3.26 (2.05-5.19)	

Abbreviations: CAC, coronary artery calcium; CI, confidence interval; CIMT, carotid intima-media thickness; N, no; OR, odds ratio; Y, yes.
Data are presented as n (%).

TABLE 5 Variation of risk-factor associations by ethnicity assessed by logistical regression

Variable Group	Variable	Interaction *P* Value
Traditional	Age	0.11
	Sex	0.23
	Hyperlipidemia	0.44
	HTN	0.63
	Smoker	0.86
	Family history of CHD	0.87
	Waist-hip ratio	0.13
	BMI	0.57
Other factors	Duration of DM	0.85
	HbA_{1c}	0.17
	Microvascular disease	0.78
Cardiac factors	Mean CIMT	0.56
	Max CIMT	0.80
	Carotid plaque	0.51

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CIMT, carotid intima-media thickness; DM, diabetes mellitus; HbA_{1c}, glycated hemoglobin; HTN, hypertension.

relationship between CAC and carotid plaque using CAC scans and carotid ultrasound.

The prevalence of severe coronary artery calcification was moderately high (22%) in our asymptomatic study population. This is consistent with the study by Anand et al, which demonstrated a high prevalence of severe CAC in an asymptomatic DM population in a similar North West London population.[30]

Although previous studies have reported the association of CAD with carotid plaque and CIMT, there are few prospective studies that have demonstrated this relationship in a DM population lacking CAD symptoms. The American College of Cardiology/American Heart Association guidelines for assessment of cardiovascular risk in asymptomatic intermediate risk group recommend use of CAC screening and carotid screening (IIa recommendation). It is therefore paramount to identify the subgroup of this population who are at risk of cardiovascular events.[31]

4.3 | Study limitations

As this study population was relatively small and observational in nature, the validity of any of the conclusions offered needs to be tested in a larger population before any revision of guidelines can be recommended. Although IMT was measured by 2 experienced doctors there may have been small differences in measurements due to variation between sonographers and between clinicians.

In this study, we evaluated the usefulness of CIMT measurement and carotid plaque detection in asymptomatic T2DM patients to identify high-risk patients. Because all the risk algorithms (eg, QRISK, Framingham, Reynolds, UKPDS) are meant to calculate risk estimates and not meant for detection of subclinical atherosclerosis, further studies are required to evaluate whether the addition of carotid ultrasound examination (for IMT and carotid plaque) to conventional risk algorithms will confer any additional benefits. Interestingly, Nambi et al demonstrated that CAD prediction could be significantly improved by adding CIMT measurement and carotid plaque information to the traditional risk factors.[12]

5 | CONCLUSION

This study supports the addition of noninvasive carotid ultrasound to current risk-estimation strategies to identify subclinical atherosclerosis in an asymptomatic but high-risk population of T2DM patients. Carotid ultrasound is currently not recommended routinely for asymptomatic DM patients. However, the findings from this study reiterate the advantages of incorporating carotid ultrasound into mainstream cardiovascular investigations to improve risk stratification in an asymptomatic DM population. Carotid ultrasound imaging has a significant advantage of not utilizing ionizing radiation. It is also widely available and, with the newer software available, easily reproducible.

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Conflicts of interest

The authors declare no potential conflicts of interest.

REFERENCES

1. International Diabetes Federation. *IDF Diabetes Atlas*. 4th ed. Brussels, Belgium: International Diabetes Federation; 2009.
2. International Diabetes Federation. *IDF Diabetes Atlas*. 5th ed. Brussels, Belgium: International Diabetes Federation; 2011.
3. Guariguata L, Whiting DR, Hambleton I, et al. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res Clin Pract*. 2014;103:137–149.
4. Franklin K, Goldberg RJ, Spencer F, et al; GRACE Investigators. Implications of diabetes in patients with acute coronary syndrome: the Global Registry of Acute Coronary Events. *Arch Intern Med*. 2004;164:1457–1463.
5. Hafner SM, Lehto S, Rönnemaa T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in non-diabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;339:229–234.
6. Anand DV, Lim E, Hopkins D, et al. Risk stratification in uncomplicated type 2 diabetes: prospective evaluation of the combined use of coronary artery calcium imaging and selective myocardial perfusion scintigraphy. *Eur Heart J*. 2006;27:713–721.
7. Grundy SM, Howard B, Smith S Jr, et al. Prevention Conference VI: Diabetes and Cardiovascular Disease: executive summary. Conference proceedings for healthcare professionals from a special writing group of the American Heart Association. *Circulation*. 2002;105:2231–2239.
8. Becker A, Bos G, de Vegt F, et al. Cardiovascular events in type 2 diabetes: comparison with non-diabetic individuals without and with prior cardiovascular disease. 10-year follow-up of the Hoorn Study. *Eur Heart J*. 2003;24:1406–1413.
9. Eichler K, Puhan MA, Steurer J, et al. Prediction of first coronary events with the Framingham score: a systematic review. *Am Heart J*. 2007;153:722–731.
10. Collins GS, Altman DG. Predicting the 10-year risk of cardiovascular disease in the United Kingdom: independent and external validation of an updated version of QRISK2. *BMJ*. 2012;21;344:e4181.
11. Coleman RL, Stevens RJ, Retnakaran R, et al. Framingham, SCORE, and DECODE risk equations do not provide reliable cardiovascular risk estimates in type 2 diabetes. *Diabetes Care*. 2007;30:1292–1293.
12. Nambi V, Chambless L, Folsom AR, et al. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. *J Am Coll Cardiol*. 2010;55:1600–1607.
13. Achenbach S, Moselewski F, Ropers D, et al. Detection of calcified and noncalcified coronary atherosclerotic plaque by contrast-enhanced, submillimeter multidetector spiral computed tomography: a segment-based comparison with intravascular ultrasound. *Circulation*. 2004;109:14–17.
14. Bauer M, Caviezel S, Teynor A, et al. Carotid intima-media thickness as a biomarker of subclinical atherosclerosis. *Swiss Med Wkly*. 2012;142:w13705.
15. Lee S, Cho GY, Kim HS, et al. Common carotid intima-media thickness as a risk factor for outcomes in Asian patients with acute ST-elevation myocardial infarction. *Can J Cardiol*. 2014;30:1620–1626.
16. Stein JH, Korcarz CE, Hurst RT, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine [published correction appears in *J Am Soc Echocardiogr*. 2008;21:376]. *J Am Soc Echocardiogr*. 2008;21:93–111.
17. Touboul PJ, Hennerici MG, Meairs S, et al. Mannheim carotid intima-media thickness consensus (2004–2006). An update on behalf of the advisory board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. *Cerebrovasc Dis*. 2007;23:75–80.
18. Shaw LJ, Raggi P, Schisterman E, et al. Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. *Radiology*. 2003;228:826–833.
19. Anand DV, Lim E, Darko D, et al. Determinants of progression of coronary artery calcification in type 2 diabetes role of glycemic control and inflammatory/vascular calcification markers. *J Am Coll Cardiol*. 2007;50:2218–2225.
20. Yerramasu A, Lahiri A, Venuraju S, et al. Diagnostic role of coronary calcium scoring in the rapid access chest pain clinic: prospective evaluation of NICE guidance. *Eur Heart J Cardiovasc Imaging*. 2014;15:886–892.
21. Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990;15:827–832.
22. Berman DS, Wong ND, Gransar H, et al. Relationship between stress induced myocardial ischemia and atherosclerosis measured by coronary calcium tomography. *J Am Coll Cardiol*. 2004;44:923–930.
23. Cohen GI, Aboufakher R, Bess R, et al. Relationship between carotid disease on ultrasound and coronary disease on CT angiography. *JACC Cardiovasc Imaging*. 2013;6:1160–1167.
24. Naqvi TZ, Mendoza F, Rafii F, et al. High prevalence of ultrasound-detected carotid atherosclerosis in subjects with low Framingham risk score: potential implications for screening for subclinical atherosclerosis. *J Am Soc Echocardiogr*. 2010;23:809–815.
25. Davis PH, Dawson JD, Mahoney LT, et al. Increased carotid intimal-medial thickness and coronary calcification are related in young and middle-aged adults: the Muscatine study. *Circulation*. 1999;100:838–842.
26. Sillesen H, Muntendam P, Adourian A, et al. Carotid plaque burden as a measure of subclinical atherosclerosis: comparison with other tests for subclinical arterial disease in the High Risk Plaque BioImage study [published correction appears in *JACC Cardiovasc Imaging*. 2013;6:131–132]. *JACC Cardiovasc Imaging*. 2012;5:681–689.
27. Jeevarethinam A, Venuraju S, Weymouth M, et al. Carotid intimal thickness and plaque predict prevalence and severity of coronary atherosclerosis: a pilot study. *Angiology*. 2015;66:65–69.
28. Kablak-Ziembicka A, Tracz W, Przewlocki T, et al. Association of increased carotid intima-media thickness with the extent of coronary artery disease. *Heart*. 2004;90:1286–1290.
29. Oei HH, Vliegenthart R, Hak AE, et al. The association between coronary calcification assessed by electron beam computed tomography and measures of extra coronary atherosclerosis: the Rotterdam Coronary Calcification Study. *J Am Coll Cardiol*. 2002;39:1745–1751.
30. Anand DV, Lim E, Raval U, et al. Prevalence of silent myocardial ischemia in asymptomatic individuals with subclinical atherosclerosis detected by electron beam tomography. *J Nucl Cardiol*. 2004;11:450–457.
31. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2010;122:2748–2764.

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