Usefulness of Carotid Plaques as Predictors of Obstructive Coronary Artery Disease and Cardiovascular Events in Asymptomatic Individuals With Diabetes Mellitus

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Carotid intima-media thickness (CIMT) measurement and carotid plaque detection by B-mode ultrasound are frequently used as surrogates to predict coronary artery disease (CAD). However, their systematic use in routine clinical management of asymptomatic patients with diabetes mellitus (DM) has not been studied. The aim of the study was to identify carotid parameters that predict cardiovascular events in patients with asymptomatic type 2 DM by evaluating the relation between carotid disease and CAD. This multicenter, observational, prospective study included 259 asymptomatic patients with type 2 DM followed-up for 34 months after measurement of CIMT and carotid plaque with carotid ultrasound, and CAD assessment with computed tomography coronary angiography. Statistically significant differences between patients with and without carotid plaque were found for coronary plaque >50% stenosis (59 vs 36, p = 0.02). Greater maximal CIMT was associated with an increased risk of coronary plaque >50% (odds ratio 1.21 [1.02, 1.44], p = 0.03) and >70% stenosis (odds ratio 1.23 [1.01, 1.50], p = 0.04) after adjusting for traditional risk factors. At 34-month follow-up, the occurrence of total major adverse cardiovascular event was estimated to be 7.1% (mean age 68 years, 6% male and 1.1% female) in the whole study population. The subgroup of patients with carotid plaque showed increased incidence of major adverse cardiovascular event compared with patients with no carotid plaque (p = 0.005). In conclusion, carotid plaque was a strong predictor of future cardiovascular events and may be a prognostic marker in asymptomatic patients with type 2 DM. Carotid plaque and maximal intima-media thickness were independently associated with obstructive CAD. **(Am J Cardiol 2018;121:910–916)**

Several noninvasive imaging techniques have been used to detect subclinical atherosclerosis in asymptomatic patients: (1) carotid ultrasonography (US) to measure carotid intima-media thickness (CIMT) and to detect carotid plaque, (2) coronary artery calcium scanning to quantify coronary artery calcification, and (3) computed tomography coronary angiography (CTCA) to evaluate total atherosclerotic burden.[1–3] CIMT has been widely used as a marker to identify subclinical atherosclerosis, as increased CIMT has been associated with a high prevalence of coronary artery disease (CAD) and future cardiovascular events.[4–6] A CIMT increment of 0.1 mm is reported to increase the risk of a myocardial infarction by 10% to 15% and stroke by 13% to 18% after adjustment for age and gender.[6] Carotid plaque has been reported to have similar prognostic power in predicting future cardiovascular events.[7–9] Previous studies in this area enrolled stable, low-risk patients who were not documented by CTCA. The present study was designed to explore the potential role of CIMT and carotid plaque in predicting prevalence and severity of coronary atherosclerosis and cardiovascular events in patients with asymptomatic type 2 DM. Relations were prospectively evaluated between CIMT and carotid plaques, and the presence and extent of obstructive CAD was assessed noninvasively by CTCA.

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Methods

The observational, prospective study enrolled 259 patients as part of the multicenter PROCEED trial (progression of coronary atherosclerosis in asymptomatic diabetics: evaluation of the role of computed tomography coronary angiography and novel biomarkers of vascular inflammation and endothelial function). Asymptomatic patients with type 2 diabetes were recruited from 3 National Health Service hospitals and a cardiovascular screening clinic in North-West London, United Kingdom. All subjects underwent carotid US and CTCA on the same day. Inclusion criteria were (1) no history of CAD, and (2) established type 2 diabetes for at least 1 year with or without microvascular complications of diabetes (retinopathy, peripheral neuropathy, and/or microalbuminuria). Microalbuminuria is defined as urinary albumin excretion of 30 to 300 mg/day. Exclusion criteria were (1) age <35 years, (2) pregnant women, (3) atrial fibrillation, (4) known allergy to iodine contrast, and (5) estimated glomerular filtration rate (eGFR) <45. Metformin was stopped on the day of contrast administration whose eGFR is <60 ml/min, and patients were advised to restart no sooner than 24 hours of contrast administration. All patients included in the study provided written informed consent before enrolment. This study is registered with ClinicalTrials.gov (identifier NCT02109835). Ethical approval was obtained from National Research Ethics Service, United Kingdom (REC reference 11/LO/16/96).

Carotid US was performed using a B-mode ultrasound system (11L, GE Vivid E9).[10] CIMT is defined as the distance between the leading edge of the lumen-intima interface and the leading edge of the media-adventitia interface. It 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 (anterior, lateral, and posterior). A composite mean intima-media thickness (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 for presence of plaque. Presence of carotid plaque was defined as a focal increase in thickness (>50%) of the surrounding CIMT.[11]

The CTCA was performed on a SOMATOM Definition Dual Source computed tomography scanner (Siemens Medical Systems, Forchheim, Germany). Coronary plaque lesions were categorized as <50% (nonsignificant), >50%, and >70% (significant) according to the degree of stenosis. Our scan protocol consisted of (1) topogram (scout chest radiograph), (2) test bolus scan to determine the circulation time using 20 ml contrast, and (3) contrast-enhanced coronary angiogram. Nitroglycerin 800 μg sublingually was administered immediately before the scan. Intravenous metoprolol (up to 20 mg) was given to patients presenting with heart rate >70 beats/min, except those contraindicated to β blockers.

All images were acquired in supine position craniocaudally in inspiration during a single breath-hold. Images were acquired with retrospective gating, electrocardiogram-controlled tube modulation with a gantry rotation time of 330 milliseconds, pitch of 0.2 to 0.5, detector collimation of $2 \times 32 \times 0.6$ mm (with double sampling in the Z axis, using flying focal spot technology). Scan parameters (tube voltage and tube current) were adjusted manually based on patients' body mass index. Contrast bolus (Iomeron 400, Bracco, Italy) was injected using a triple phase protocol followed by 30:70 mixture of 30 ml contrast and saline solution followed by a 70 ml saline flush, at a rate of 5.5 to 6.0 ml/s. Based on the scan time, volume of contrast bolus was calculated for each patient as follows: contrast volume (ml) = scan time (seconds) × flow rate + 10 ml (minimum volume 60 ml).

CTCA images were reconstructed with a slice thickness of 0.75 mm (and 0.5-mm increment) using B26 kernel in mid-diastole or in end-systole for patients with heart rate <70 or >70 beats/min, respectively. Multiple reconstruction images (including axial slices, multiplanar reconstructions, and maximum intensity projections) were used to assess the patency of coronary arteries. All images were analyzed by 2 experienced readers with 4 years' experience in cardiac computed tomography angiography who were blinded to the patients' clinical information and carotid US results.[12] Any discrepancies in interpretations were resolved through consensus.

Clinical follow-up was achieved for 250 patients with a median follow-up period of 22.8 months. Nine patients who completed all baseline investigations were lost to follow-up. Follow-up data from all patients (including adverse events) were obtained by telephone from family (general) practitioners and patients, and by reviewing hospital records. Those who adjudicated the events during follow-up were blinded for imaging data. Hard major adverse cardiovascular event (MACE) was defined as cardiac death, noncardiac death, stroke, and acute myocardial infarction. Total MACE was defined as any death, stroke, acute myocardial infarction, any revascularization procedure such as coronary artery bypass graft, and percutaneous coronary intervention.

The unpaired *t* test was used to compare groups for continuous variables found to be normally distributed. The Mann-Whitney test was preferred for continuous variables not following normal distribution. Categorical variables were compared between groups using the chi-square test. All patient outcomes were time-to-event measures and were thus summarized and analyzed using Kaplan-Meier methods. As the length of follow-up varied between patients, the Kaplan-Meier method was used to obtain estimates for the occurrence of outcomes at the point of longest follow-up (34 months). The log-rank test was used to compare outcomes between patients with and without carotid plaque. The next set of analyses examined factors associated with the time to total MACE using Cox regression in 2 stages—univariable and multivariable analyses. A backward selection procedure was used to retain only variables showing some evidence of an association with the outcome in the final model.

Logistic regression analysis was used to assess the relation between CIMT/carotid plaque (independent variables) and coronary plaque >50% stenosis (dependent variable) due to the binary nature of dependent variable outcomes. The models fitted were (1) unadjusted for any potentially confounding factors, (2) adjusted only for traditional risk factors, and (3) adjusted for traditional risk factors plus Framingham risk score.

Results

The analysis showed statistically significant differences between patients with and without carotid plaque for age, body

Table 1
Patient characteristics

Variable	All patients	Carotid plaque		P-value
	(n = 259)	No (n = 132)	Yes (n = 127)	
Age (in years)	62.0 ± 8.5	59.2 ± 8.1	64.8 ± 8.0	**<0.001**
Men	151 (59%)	75 (57%)	76 (60%)	0.67
BMI (kg/m^2)	28.4 [25.3, 32.4]	29.7 [26.5, 34.5]	26.8 [24.2, 30.5]	**<0.001**
White	79 (31%)	42 (33%)	37 (29%)	0.12
Asian	142 (56%)	65 (50%)	77 (61%)	
Black	34 (13%)	22 (17%)	12 (10%)	
Duration of diabetes mellitus (in years)	13 [8, 19]	13 [8, 18]	14 [8, 20]	0.34
Microvascular disease	123 (48%)	65 (50%)	58 (456%)	0.49
Retinopathy	99 (38%)	53 (41%)	46 (36%)	0.48
Microalbuminuria	21 (8%)	12 (9%)	9 (7%)	0.58
Hyperlipidemia*	203 (79%)	100 (76%)	103 (81%)	0.35
Hypertension†	192 (74%)	92 (70%)	100 (79%)	0.12
Smoker	20 (8%)	9 (7%)	11 (9%)	0.58
Statin use	188 (73%)	90 (69%)	98 (77%)	0.13
Hypertension treatment	216 (83%)	110 (83%)	106 (84%)	0.98
Family premature IHD	51 (21%)	21 (17%)	30 (25%)	0.13
Systolic BP (mmHg)	137.3 ± 15.8	133.4 ± 13.9	141.4 ± 16.7	**<0.001**
HbA1c	63 [52, 77]	64 [53, 80]	63 [50, 75]	0.22
eGFR	80.9 ± 18.4	83.3 ± 20.9	78.3 ± 15.1	**0.03**
Framingham risk	7 [3, 13]	5 [2, 10]	10 [5, 16]	**<0.001**
UKPDS risk	18.1 [10.1, 30.5]	13.4 [8.3, 24.9]	24.1 [14.8, 32.4]	**<0.001**
Q risk	25.6 [16.2, 33.4]	21.5 [13.0, 28.8]	30.8 [20.1, 38.8]	**<0.001**
Maximal IMT	0.87 ± 0.19	0.84 ± 0.16	0.90 ± 0.21	**0.007**
Mean IMT	0.76 ± 0.14	0.73 ± 0.12	0.78 ± 0.16	**0.003**
Coronary plaque >50%	95 (37%)	36 (27%)	59 (47%)	**0.001**
Any coronary plaque	205 (79%)	100 (76%)	105 (83%)	0.17

Values are expressed as n (%) or mean SD. Significant p values are given in bold.
BMI = body mass index; eGFR = estimated glomerular filtration rate; IMT = intima-media thickness; HbA1C = glycated hemoglobin.
* Serum total cholesterol ≥6 mmol/L (≥230 mg/dl) or treatment with lipid-lowering drugs.
† Systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or the use of antihypertensive medication.

mass index, systolic blood pressure, eGFR, all risk scores, maximal and mean IMT, and coronary plaque >50% (Table 1). Kaplan-Meier estimate for the percentage of patients who experienced an outcome at the time of longest follow-up (34 months) showed patients with carotid plaque had higher hard MACE (6.2% vs 0.9%, p = 0.04) and total MACE (12.3% vs 2.4%, p = 0.005) than those without carotid plaque. At the 34-month follow-up, the occurrence of any event (total MACE) was estimated to be 7.1% for the whole study population, of which 6 patients (3%) died, 11 (4%) underwent revascularization (4 coronary artery bypass graft + 7 percutaneous coronary intervention), and 1 patient had ischemic stroke. There was a statistically significant difference in the occurrence of hard MACE between the 2 subgroups, with higher occurrence in patients with carotid plaque (Figure 1). A statistically significant difference was found between the 2 subgroups, with the occurrence of any event being higher in patients with carotid plaque (Figure 2).

The next objective of this study was to examine factors associated with the time to a MACE (Table 2). The univariable analysis showed statistically significant associations between total MACE and age, gender, duration of diabetes, microalbuminuria, systolic blood pressure, waist-hip ratio, all 3 risk scores, and carotid plaque. The multivariable analysis suggests that age, gender, duration of diabetes, waist-hip ratio, and carotid plaque were associated with the time to an event.

Men were 7 times more likely to experience an event than women. The results for duration of diabetes suggest that a 5-year increase in duration was associated with almost a 50% increase in the risk of an event occurring at any time. Higher waist-hip ratios were also associated with an increased risk of an event occurring, with a 0.1-unit increase in waist-hip ratio doubling the associated risk.

Carotid plaque was found to be independently associated with the time to an event, after adjusting for the other significant factors. The risk of an event at any time was 5 times higher for patients with carotid plaque compared with those without carotid plaque. Consistent with the univariable analysis, the multivariable analysis suggests that maximal IMT, mean IMT, and IMT <0.8 and >0.8 mm were not associated with the risk of an event occurring (after adjusting for the other risk factors).

Higher values of maximal IMT were associated with an increased risk of coronary plaque >50%: a 0.1-unit maximal IMT increase was associated with a 20% increase in the likelihood of coronary plaque >50% being detected. All 4 analyses suggested that carotid plaque was significantly associated with coronary plaque >50% (Table 3). The odds of detecting coronary plaque >50% was 2.7 times greater for patients with carotid plaque compared with those with no carotid plaque in the unadjusted analyses. After adjusting for all other factors, the odds ratio decreased to 2.4. Table 4 shows the predictive

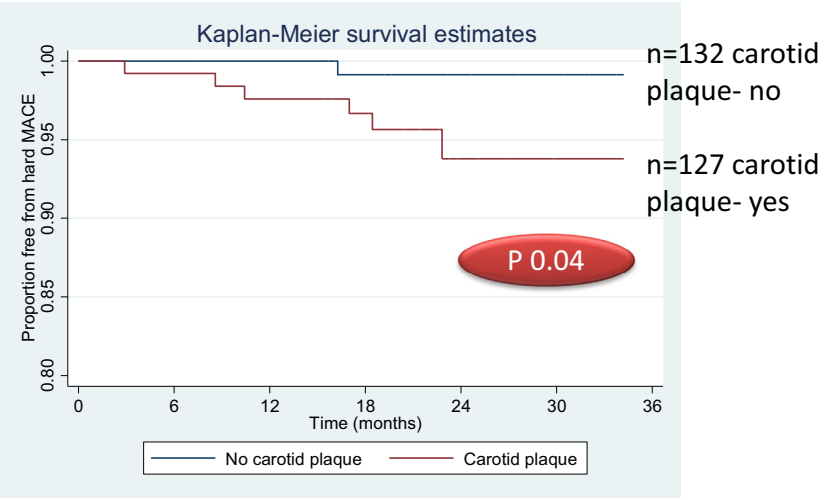

Figure 1. Kaplan-Meier analysis according to the presence of carotid plaque. The likelihood of hard MACE in relation to the presence of carotid plaque ($p = 0.04$).

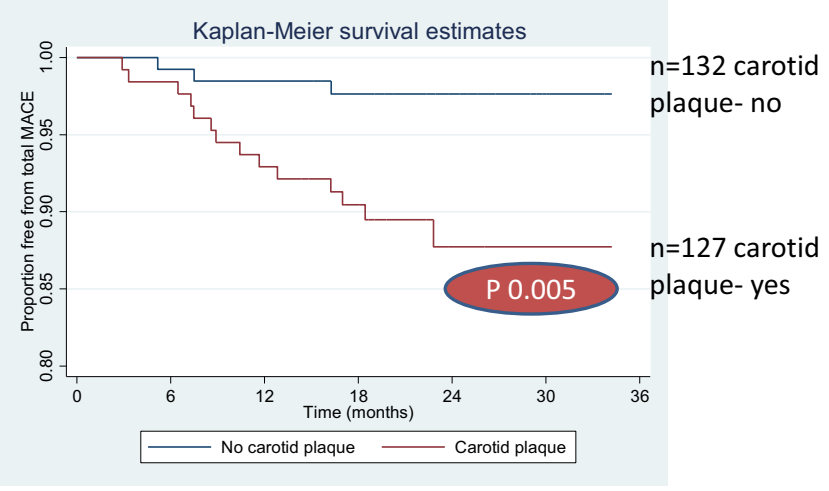

Figure 2. Kaplan-Meier analysis according to the presence of carotid plaque. The likelihood of total MACE in relation to the presence of carotid plaque ($p = 0.005$).

ability of CIMT and carotid plaque upon the 3 outcomes. The analysis suggests that for all outcomes, the poorest performance (i.e., that with the least predictive value, indicated by the lowest R^2 and area under curve values) was obtained by the Framingham risk score alone. For all outcomes, the best performance was obtained by combining traditional risk factors and carotid variables. This indicates the potential benefit of a new risk score combining CIMT/plaque and traditional risk factors compared with traditional risk factors alone.

Discussion

This study investigated the relation of CIMT, carotid plaque, and coronary plaque with future adverse events in asymptomatic patients with type 2 diabetes. It showed that carotid plaque was associated with total MACE even after adjustment for traditional risk factors. The study addresses a paucity of data investigating the prognostic value of carotid plaque in the asymptomatic diabetic population. The large number of Asians in this study group is suggestive of high prevalence of type 2 DM in this ethnic population. The prognostic benefit of sonographic characteristics of carotid plaque is currently controversial. Different carotid plaque morphologies (echolucent and echo-rich) have produced varying outcomes compared with each other.[13,14] Two studies have shown that different ultrasonographic characteristics of carotid atherosclerosis, such as IMT, stenosis, and plaque area, are genetically and biologically distinct.[15,16] However, we found the presence of carotid plaque itself has a prognostic value in asymptomatic diabetes, which is consistent with other studies.[17,18]

Findings of this study are consistent with previous studies that reported an association between the presence of carotid plaque and MACE.[17–20] Held et al studied 558 patients with stable angina who were followed-up for 3 years (median) after

Table 2
Risk factors in relation to total MACE[§]

Variable	Univariable		Multivariable	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (years) [‡]	2.61 (1.43, 4.77)	**0.002**	1.97 (1.01, 3.89)	**0.05**
Men	5.20 (1.88, 22.7)	**0.03**	7.03 (1.51, 32.8)	**0.01**
Duration of diabetes mellitus (years) [†]	1.38 (1.06, 1.79)	**0.02**	1.47 (1.13, 1.92)	**0.005**
Microalbuminuria	3.74 (1.21, 11.6)	**0.02**		
Waist-hip ratio [*]	2.03 (1.06, 3.89)	**0.03**	2.00 (0.93, 4.30)	**0.08**
Framingham risk [†]	1.75 (1.36, 2.24)	**<0.001**		
UKPDS risk [‡]	1.55 (1.23, 1.95)	**<0.001**		
Q risk [‡]	1.72 (1.28, 2.31)	**<0.001**		
Carotid plaque	5.08 (1.46, 17.7)	**0.01**	5.10 (1.37, 19.0)	**0.02**

[*] Hazard ratios given for a 0.1-unit increase in predictor variable.
[†] Hazard ratios given for a 5-unit increase in predictor variable.
[‡] Hazard ratios given for a 10-unit increase in predictor variable.
[§] Major adverse cardiovascular events.

Table 3
Relation between CIMT/carotid plaque and >50% coronary plaque: logistic regression analysis*

Variable	Adjustments	Odds Ratio (95% CI)	P-value
Maximal IMT [§]	Unadjusted	1.23 (1.06, 1.43)	**0.005**
	Traditional risk factors [†]	1.20 (1.02, 1.42)	**0.03**
	Traditional + Framingham [‡]	1.20 (1.01, 1.41)	**0.03**
Mean IMT [§]	Unadjusted	1.20 (0.99, 1.45)	0.06
	Traditional risk factors [†]	1.17 (0.94, 1.46)	0.16
	Traditional + Framingham [‡]	1.16 (0.93, 1.45)	0.20
Carotid plaque	Unadjusted	2.72 (1.59, 4.64)	**<0.001**
	Traditional risk factors [†]	2.77 (1.46, 5.25)	**0.002**
	Traditional + Framingham [‡]	2.57 (1.34, 4.92)	**0.004**

[*] Odds ratios given for a 0.1-unit increase in factor.
[†] Adjusted for age, gender, hyperlipidemia, hypertension, smoking, BMI, and family history premature ischemic heart disease.
[‡] Adjusted for traditional risk factors (as for previous model), plus Framingham score.
[§] IMT = intima media thickness.

they underwent carotid US. Carotid plaque was found to be a better predictor of cardiovascular events.[17] In a study by Petersen et al, 541 patients admitted to cardiology ward were followed-up for a median of 34 months after they underwent carotid US. The presence of carotid plaque and plaque morphology were found to be independent predictors of death.[19] Two studies have shown a significant relation between CIMT and cardiovascular events.[21,22] In our study, no independent relation was found between CIMT and cardiovascular events. This might be explained by the fact that our study cohort was treated with optimal medical management (75% of patients on statins and 83% of the patients on antihypertensives).

Carotid plaque was present in 105 (83%) patients with coronary atherosclerosis and 59 (46%) patients with >50% coronary stenosis. We observed high prevalence of carotid plaque (49%) in our study compared with other studies.[23,24] In a cross-sectional study by Coll et al, 2,354 patients with low-to-intermediate cardiovascular risk underwent carotid screening. The study found 25.1% of patients had carotid plaque.[23] A study by Postley et al included 715 individuals with low-to-intermediate Framingham risk and found the prevalence of carotid plaque to be 33% using carotid screening.[24]

Table 4
Relation between traditional risk factors, CIMT/carotid plaque and obstructive/non-obstructive coronary plaque: ROC[‡] analysis

Outcome	Adjustments	Pseudo R^2	AUC
Any coronary plaque	Traditional risk factors *	15.4%	0.790
	Framingham risk score	11.6%	0.751
	Traditional + mean IMT[†] + carotid plaque	21.1%	0.831
>50% coronary plaque	Traditional risk factors *	8.5%	0.698
	Framingham risk score	4.6%	0.670
	Traditional + max IMT + carotid plaque	13.3%	0.744
>70% coronary plaque	Traditional risk factors *	10.2%	0.708
	Framingham risk score	4.8%	0.681
	Traditional + max IMT + carotid plaque	13.7%	0.745

* Traditional risk factors used were age, gender, hyperlipidemia, hypertension, smoking, BMI, and family history of premature ischemic heart disease.
[†] Mean IMT (Intima media thickness) shows significant relation with any coronary plaque whereas maximal IMT shows significant relation with obstructive coronary disease (>50% and >70% stenosis).
[‡] ROC = receiver operating characteristic curve.

Silent CAD is not uncommon in diabetes due to autonomic neuropathy; in addition, persons with diabetes exhibit atypical symptoms.[25] It is worth noting that 38% of an asymptomatic young and middle aged group with <5% FRS had abnormal, high-risk carotid US, suggesting these patients were at an increased risk of a cardiovascular event.[26] Thus, it is of paramount importance to develop an integrated approach to identify patients at high risk at the earliest stage. In our study, maximal IMT and carotid plaque were predictive of obstructive CAD (>50% stenosis) even after adjustment for traditional risk factors. In our study, the relation between microvascular disease and carotid plaque was not significant. It is similar to the previous studies that have demonstrated the inconsistent relation between the two.[27,28]

The unique finding of this study was the presence of any carotid plaque strongly predicting obstructive coronary plaque. This supports and builds upon previous studies. A study by Inaba et al showed a similar strong and consistent correlation of coronary plaque with carotid plaque.[29] The Atherosclerosis Risk In Communities (ARIC) study established that CIMT and carotid plaque information can improve CAD risk prediction, showing the strongest association between CIMT and CAD for patients between 42 and 74 years of age.[1]

So far, there is no definite consensus whether the prediction of CAD by identifying carotid plaque and measuring CIMT is beneficial for an asymptomatic population. However, a few guidelines and recently published systematic reviews support the concept of subclinical atherosclerosis imaging to help improve risk stratification for CAD.[10,30,31] Finally, our study showed that CAD risk prediction (Table 4) can be improved by combining traditional risk factors with carotid variables (CIMT and carotid plaque). This is in concordance with the ARIC study by Nambi et al, which demonstrated improved CAD risk prediction using a model that combined traditional risk factors with CIMT and carotid plaque.[32]

This study was limited by small sample size (n = 259). Although the sample size was sufficient to assess the effect of CIMT and carotid plaque on coronary atherosclerosis, it was too small to confidently develop a risk model for use in the wider clinical context. The follow-up period of approximately 3 years is also relatively short compared with other primary prevention cohorts and trials. Another limitation of the study is that merely 18 incident events are available for the prediction models. In addition, 3/4 of the patients received statin treatment before recruitment, and vasoactive drugs were not withheld during the course of the study, which may have impacted the study outcomes and the predictive ability of carotid variables.

As cardiovascular disease remains the main cause of morbidity and mortality in diabetes, there is a need to develop an integrated approach for preclinical cardiovascular screening in this high-risk population. The prevalence of >50% coronary plaque in our study was 37% (95 patients), of which 47% (59 patients) had carotid plaque. Our study supports both the prognostic and the diagnostic value of carotid US in asymptomatic patients with type 2 diabetes. We show that detecting subclinical carotid atherosclerosis in asymptomatic diabetic population identifies individuals at risk of future adverse events. It has also been shown that carotid US can detect subclinical atherosclerosis in patients with low FRS. In our data, the median duration of diabetes is 13 years, and the prevalence of obstructive CAD (>50% stenosis) is 37%. Hence, carotid US may be considered for asymptomatic patients who have been diagnosed with type 2 DM for more than 10 years. However, further larger prospective studies are required to test the cost-effectiveness and efficiency, and to confirm our findings in asymptomatic patients with diabetes using carotid US.

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Disclosures

The authors have no conflicts of interest to disclose.

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