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Carotid plaque thickness and carotid plaque burden predict future cardiovascular events in asymptomatic adult Americans

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Introduction Prediction of cardiovascular events improves using imaging, i.e. coronary calcium score and ultrasound assessment of carotid plaque. This study analysed the predictive value of two ultrasound measures of carotid plaque size: carotid plaque thickness and carotid and intima–media thickness (IMT).

Methods and results A total of 6102 asymptomatic persons underwent assessment of conventional risk factors and imaging by carotid ultrasound. Carotid plaque burden (cPB) and maximum carotid plaque thickness (cPTmax) were measured from 'cross-sectional sweep' video acquisition of the carotid artery. IMT was measured from distal common carotid artery images. All participants were followed up for ~3 years, and major cardiovascular events (MACE) were collected and adjudicated. All data were available for 5808 participants, in whom 216 first MACE events were observed. Increasing both cPB and cPTmax were associated with increasing the risk of future MACE when compared with participants without carotid atherosclerosis. Fully adjusted for risk factors, hazard ratios for cPTmax were 1.96 [95% confidence interval (CI) 0.91–4.25, $P = 0.015$] for primary MACE and 3.13 (95% CI 1.80–5.51, $P < 0.001$) for secondary MACE, similar to that of cPB. IMT did not improve risk prediction significantly. Non-categorical net reclassification index (NRI) for cPTmax was 0.178 (95% CI 0.027–0.299, $P = 0.032$) for primary MACE and 0.173 (95% CI 0.109–0.243, $P < 0.001$) for secondary MACE, which is almost similar to cPB. IMT assessment did not result in significant NRI.

Conclusion The simpler cPTmax predicted cardiovascular events similarly to the more comprehensive cPB, whereas IMT did not. Awaiting true 3D ultrasound technology cPTmax may be a simple useful measure for prediction of future ASCVD.

Keywords carotid ultrasound • carotid plaque • IMT • prediction of cardiovascular events

Introduction

Despite advances in treatment for atherosclerotic cardiovascular disease (ASCVD), atherosclerosis and its complications remain the leading cause of morbidity and mortality, being the source of the greatest health care costs in the Western world. Although the underlying pathogenesis of atherosclerosis is well understood, predicting who will become affected and suffer clinical disease is not, despite much knowledge about risk factors. In fact, risk prediction derived from risk factors for ASCVD has been shown to perform rather poorly,[1] probably because individuals have different tolerance to lifestyle, cholesterol values and so on. Furthermore, health checks did not reduce mortality from ASCVD,[2] and individual risk prediction from risk factors for atherosclerosis followed by individual lifestyle counselling has not affected mortality and morbidity.[3]

An alternative approach for predicting symptomatic ASCVD is based on identifying subclinical atherosclerosis in presumably healthy people. The underlying hypothesis is that without atherosclerosis in the main arteries, the risk of ASCVD is minimal, and *vice versa*. Several methods for the assessment of asymptomatic atherosclerosis exist

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and most are based on the fact that atherosclerosis is a generalized disease of the arterial tree.[4–7] The most studied methods include coronary artery calcium score (CACS) and carotid ultrasound, the latter mostly used for measuring intima–media thickness (IMT) and lately for assessing carotid plaque. CACS has been documented to predict future coronary and other cardiovascular events for the individual person much better than risk factor-based scoring systems.[6–10] The drawbacks of this method include the use of radiation, the relative poor mobility of computed tomography (CT) scanners and that it identifies atherosclerosis at a relatively late stage.[11] IMT, in comparison with CACS, has been shown to be a rather weak predictor of future events for groups of people, whereas the value for the individual seems questionable.[7,12,13] On the other hand, using ultrasound for the assessment of carotid plaque seems a much stronger predictor than IMT and has recently been shown to have similar predictive value as CACS.[10] Moreover, ultrasound, in contrast to CT scanning, is harmless, mobile, and less expensive and may identify atherosclerosis at an early stage.

We recently reported that carotid plaque burden (cPB), derived from carotid ultrasound, was similarly predictive as CACS for the development of future cardiovascular events.[10] Although cPB is a comprehensive, offline assessment of all carotid plaque throughout the carotid artery, maximum carotid plaque thickness (cPTmax) is a simple measure that in principle can be performed during examination. This study reports the predictive value of cPTmax, carotid IMT, and cPB, all investigated in the High Risk Plaque BioImage Study.

Methods

The High Risk Plaque BioImage Study has previously been described in detail[14] and was a prospective study evaluating cross-sectional associations betwwen imaging and circulating biomarkers and their ability to predict near-term atherothrombotic events (3-year) in asymptomatic subjects (https://clinicaltrials.gov/ct2/show/NCT00738725?term=Bioimage+study&rank=1, NCT00738725).

Materials

Between January 2008 and June 2009, the BioImage Study enrolled 7687 asymptomatic men aged 55–80 years and women aged 60–80 years who were members of the Humana Health System and residents of the Chicago, IL, USA, or Fort Lauderdale, FL, USA, metropolitan areas. Of these, 6102 subjects entered the imaging arm of the study. Subject eligibility, including freedom from previous history of cardiovascular disease [myocardial infarction (MI), stroke, angina, heart failure, arterial revascularization], was ascertained by baseline review of administrative claims data, followed by telephone interview, and finally by in-person baseline examination and interview. Participants were additionally required to be free of active cancer treatment, any medical condition precluding long-term participation or inability to complete 3-year follow-up, and have no language barrier or inability to comply with study procedures. The BioImage Study was approved by the Western Institutional Review Board, Olympia, WA, USA. Before enrolment, all study participants provided written informed consent and Health Insurance Portability and Accountability Act authorization.

Baseline examinations

A non-fasting venous blood sample was processed for routine chemistry tests, including serum creatinine and lipid levels. Diabetes mellitus was defined as current use of oral hypoglycaemic agents, insulin, or self-report of the diagnosis. Hypertension was defined as systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, or current use of antihypertensive medication. Current smoking status was self-reported.

Acquisition of ultrasound data

Details regarding ultrasound examination in the BioImage Study were previously published.[4] In brief, Philips iU22 ultrasound systems (Philips Healthcare, Bothell, WA, USA) equipped with L12-5 and L9-3 transducers were used for all carotid studies. The scanning protocol included standard imaging of the carotid artery and its branches using generally accepted Doppler criteria for assessment of any degree of stenosis.[15] Measurement of IMT was performed offline in the core laboratory from a 10-s video clip of the distal common carotid artery (CCA) recorded from the lateral aspect of the neck in long axis, ensuring the CCA was parallel to the transducer surface (horizontal in the image). For assessment of plaque thickness and plaque burden, the carotid artery was scanned cross-sectionally, slowly moving the transducer manually in the cranial direction from the proximal CCA into the distal internal carotid artery, at an angle perpendicular to the neck. The resulting 10-s digital video clip of this 'manual 3D' cross-sectional sweep was examined offline in the core ultrasound laboratory for quantification of plaque.

Assessment of IMT, cPB, and cPTmax

Ultrasound scans were read by the core laboratory at the Department of Vascular Surgery, Rigshospitalet, University of Copenhagen, Denmark, after all ultrasound data had been acquired.

Measurement of IMT was performed with Philips QLAB IMT® plug-in, using the 10-s video clips mentioned above. The reader selected frames with good perpendicular alignment and image quality and adjusted IMT box position if necessary to ensure measurement of mean IMT over the distal 10 mm of the far wall of the CCA. For every participant, 5–10 mean IMT measurements were taken at the same phase of the cardiac cycle (diastole, electrocardiography gated) on each artery (right/left) for every participant. IMT measurements from both arteries were averaged to create an IMT score.

Carotid plaque was defined as a focal structure encroaching into the arterial lumen of at least 0.5 mm; or 50% of the surrounding IMT value; or demonstrating a thickness > 1.5 mm, as measured from the media–adventitia interface to the intima–lumen interface.[16,17] Assessment of plaque thickness and plaque burden was performed using Philips QLAB quantification software, which was enhanced with specially developed, semi-automated plaque analysis software, QLAB-VPQ® (Vascular Plaque Quantification) (*Figure 1*). The recorded 10-s cross-sectional sweeps were reviewed for the presence of plaque. Each image showing plaque was outlined as shown in *Figure 1*. Plaque areas from all images in the cross-sectional sweeps from both the right and left carotid arteries were summed as cPB, a quantitative metric of the total plaque area (mm^2) across the length of the visualized carotid artery.[4] From the outlined plaque images QLAB–VPQ automatically calculated carotid plaque thickness (cPT), being the radial distance from media/adventitia border to the centre of the vessel (*Figure 1*).

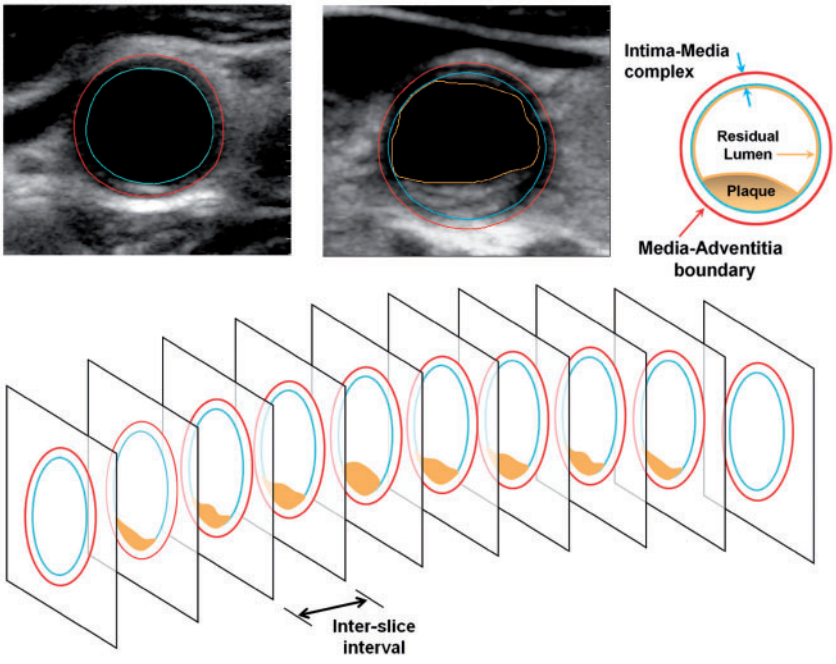

Figure 1 Segment of carotid artery with a plaque (orange), which is scanned with a linear array transducer as a series of image slices in transverse section (top). Each image is analysed with semi-automated software to quantify plaque area, plaque greyscale statistics, percent stenosis, and other metrics of interest. The lower left ultrasound image shows the common carotid artery when no plaque is present. The blue border represents the lumen/intima border; the red border represents the media–adventitia boundary. When plaque is present, the yellow line represents lumen/plaque border. Right ultrasound image shows the common carotid artery when plaque is present. The red and blue borders are the same as in previous image, but the orange border represents the boundary of the plaque. cPT is indicated by the light green line.

The outlined image with the greatest thickness of the plaque from either side (right and left carotid artery) was used as plaque thickness (cPTmax).

End points

The identification and adjudication of end points have previously been described.[10] An independent clinical events committee used source medical records to adjudicate non-fatal and fatal events. Myocardial infarction (MI) was defined according to the 2007 Universal Definition.[18] Unstable angina was defined according to the Braunwald classification.[19,20] Stroke was defined as a sudden focal neurological deficit of cerebrovascular aetiology persisting beyond 24 h and not due to another identifiable cause, such as a tumour or seizure, or as a clinically relevant new lesion detected on CT or magnetic resonance imaging.[21] Deaths were classified as cardiovascular or non-cardiovascular.

The primary end point included cardiovascular death, MI, or ischaemic stroke [major adverse cardiovascular events (MACE)]. The secondary MACE end point comprised all-cause death, MI, ischaemic stroke, unstable angina, or coronary revascularization.

Statistics

Baseline characteristics are presented as mean and standard deviation for continuous variables and number and percentage for categorical variables. Differences in baseline characteristics were compared across cPT groups using analysis of variance for continuous variables and the χ^2 test for categorical variables.

We categorized cPTmax and cPB as 'no measurable atherosclerosis'and by increasing tertiles for those with atherosclerosis. Thresholds for the first, second and third tertile of cPTmax were 0.7 mm, 1.84 mm, and 2.55 mm, respectively. Analogous cut-points for cPB were 4.3 mm^2, 169.4 mm^2 and 536.6 mm^2, respectively. We split IMT in quartiles: first quartile 0.43–0.65 mm, second quartile 0.66–0.73 mm, third quartile 0.74–0.84 mm, and fourth quartile 0.85–2.58 mm.

The rates of adverse events were estimated at 3 years using the Kaplan–Maier method and compared across groups using the log-rank test.

Associations between cPTmax, cPB, IMT, and adverse events were assessed using Cox proportional hazard regression models that included age, race, and gender in Model 1. Model 2 included in addition diabetes mellitus, current smoking, body mass index, systolic blood pressure, antihypertensive agent use, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and use of lipid-lowering drugs.

The incremental value of adding the log-transformed cPTmax, cPB, or IMT for risk prediction was evaluated using the metrics of the model: overall fit, calibration, and reclassification. The model fit changes were assessed using likelihood ratio test.[22]

Calibration was evaluated using a modified version of Hosmer–Lemeshow test.[23] Differences in C-index between models and 95% CI were calculated using the method of Newson.[24] To assess the net effect of adding a marker to the risk

Table 1 Baseline characteristics for persons with no carotid plaque (no atherosclerosis) and tertiles of carotid maximum plaque thickness (cPTmax)

	No atherosclerosis	Tertile 1	Tertile 2	Tertile 3	*P*-value
Age, years	67.4 ± 5.7	68.4 ± 6.0	69.2 ± 5.9	70.2 ± 5.8	<0.0001
Female	865 (66.5)	911 (60.3)	800 (53.4)	705 (47.0)	<0.0001
White race	827 (63.6)	1163 (77.0)	1143 (76.4)	1168 (77.9)	<0.0001
Diabetes mellitus	173 (13.3)	188 (12.5)	238 (15.9)	258 (17.2)	0.001
Current smoker	53 (9.6)	102 (13.0)	154 (17.3)	187 (19.5)	<0.0001
Hypertension	730 (56.1)	873 (57.8)	982 (65.6)	1029 (68.6)	<0.0001
BMI, kg/m^2	29.5 ± 5.8	28.5 ± 5.2	29.2 ± 5.6	29.0 ± 5.5	<0.0001
LDL-C, mg/dL	114.1 ± 32.6	115.6 ± 33.4	113.9 ± 33.3	113.0 ± 33.5	<0.0001
HDL-C, mg/dL	57.8 ± 15.3	56.9 ± 15.4	54.5 ± 15.2	53.8 ± 14.9	<0.0001
Total cholesterol, mg/dL	203.0 ± 38.2	204.7 ± 38.4	201.8 ± 38.6	200.6 ± 39.0	0.0294
Systolic BP, mmHg	136.6 ± 18.2	138.2 ± 18.2	140.4 ± 18.0	142.3 ± 19.2	<0.0001
Diastolic BP, mmHg	79.2 ± 9.3	78.0 ± 8.7	78.1 ± 9.0	77.6 ± 9.2	<0.0001
Lipid-lowering therapy	369 (28.4)	507 (33.6)	572 (38.2)	545 (36.3)	<0.0001
Serum creatinine, mg/dL	0.96 ± 0.18	0.96 ± 0.20	0.98 ± 0.22	1.00 ± 0.22	<0.0001
Framingham risk[a]					
<10%	745 (58.3)	773 (52.3)	629 (43.2)	582 (39.5)	<0.0001
10–20%	443 (34.7)	551 (37.3)	591 (40.6)	585 (40.2)	
≥20%	90 (7.04)	154 (10.4)	237 (16.3)	290 (19.9)	

Values are represented as mean ± SD of n (%).
[a]Framingham risk calculated from d'Agostino *et al.*[26]

prediction, we calculated the category-free net reclassification index (NRI).[25]

This study was designed to follow the participants for a minimum of 3 years or until the occurrence of 600 events.

All analyses were carried out using Stata version 14 (StataCorp, College Station, TX, USA) and R (version 3.2.1; R Foundation for Statistical Computing, Vienna, Austria) software.

Results

Of the 6102 individuals, who were included in the BioImage Study, 294 were excluded due to missing covariates and/or imaging data, yielding a final study population of 5808 adults. At the end of the study period, a total of 1139 (19.6%) study participants no longer were Humana members and had not experienced any adverse events during their membership. Median follow-up period among these individuals was 1.1 years. All analyses were repeated after excluding these participants, yielding similar results to the overall cohort. Over a median follow-up period of 2.7 years, there were a total of 216 first MACE events (4.2%) including 108 deaths (2.2%), of which 27 were cardiovascular (0.5%), 34 MIs (0.7%), 30 ischaemic strokes (0.6%), 18 hospitalizations for unstable angina (0.3%), and 79 coronary revascularization procedures (1.6%).

Table 1 presents baseline demographics and clinical characteristics for the entire cohort. The average age was ∼69 years, and 56% of participants were female.

Carotid plaque was found in 4507 (78%) individuals. The level of risk factors increased with increasing cPT.

Figure 2 shows the crude 3-year event rates for primary and secondary MACE by cPTmax and IMT groups. Trends of higher risk were observed with increasing cPTmax and IMT although slightly weaker for primary MACE. IMT quartiles seemed to separate poorer between low and high risk as did cPTmax (cPTmax log-rank $P < 0.001$, for primary MACE and $P < 0.001$, for secondary MACE when compared with IMT log-rank $P < 0.013$ and 0.009 for primary and secondary MACE) although both statistically significant.

Table 2 presents hazard ratios (HRs) for primary and secondary MACE associated with cPTmax, cPB, and IMT. Increasing HRs were observed with increasing values for all three, although only statistically significant for cPTmax and cPB after adjustment for all risk factors (Models 1 and 2). HRs for cPTmax predicted similarly to cPB with regard to future adverse events.

Tables 3 and *4* present the impact on model performance of adding cPTmax, cPB, and IMT to the baseline conventional risk factor (CRF) Model 1. All three parameters significantly improved model fit although IMT the least. cPTmax and cPB significantly improved category-free NRIs, both for primary and secondary MACE, when added to the baseline CRF model, whereas IMT did not. The model performance of adding the ultrasound parameters to only gender, age, and race yielded similar results.

Figure 3 shows HRs for cPTmax, IMT, and cPB. Both cPTmax and cPB had almost similar, strong prediction of primary and secondary MACE, but IMT did not. There was no difference in predictive value of cPB and cPTmax (primary end point *P*-value = 0.4279; secondary end point *P*-value = 0.7646). cPTsum, being the sum of the highest value from either side, was also analysed and found almost similarly predictive as cPTmax (data not shown).

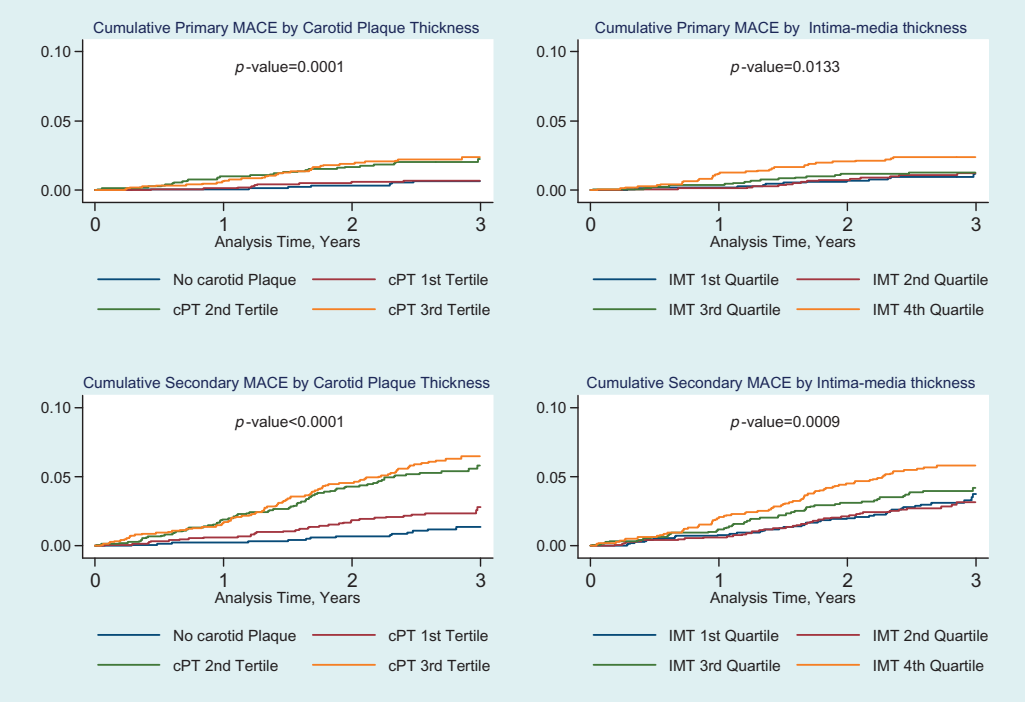

Figure 2 Crude rates calculated as the Kaplan–Meier estimates at 3 years for primary and secondary major adverse cardiac event(s) (MACE) by carotid plaque tickness (cPT) and intima–media Thickness (IMT).

Table 2 HRs (95% CI) for primary and secondary MACE end points associated with cPTmax, cPB, and carotid IMT

	No atherosclerosis	Tertile 1	Tertile 2	Tertile 3	*P*-value (trend)
Hazard ratios (95% CI) for primary MACE end point					
cPTmax					
Model 1	1.0 (ref)	0.88 (0.36–2.19)	2.41 (1.13–5.14)	2.52 (1.18–5.35)	0.001
Model 2	1.0 (ref)	0.85 (0.34–2.11)	2.09 (0.97–4.50)	1.96 (0.91–4.25)	0.015
cPB					
Model 1	1.0 (ref)	0.87 (0.36–2.10)	1.56 (0.72–3.36)	2.85 (1.39–5.82)	<0.001
Model 2	1.0 (ref)	0.78 (0.31–1.91)	1.45 (0.67–3.14)	2.36 (1.13–4.92)	0.030
IMT					
Model 1	1.0 (ref)	1.16 (0.57–2.34)	1.06 (0.52–2.18)	1.82 (0.95–3.50)	0.066
Model 2	1.0 (ref)	1.10 (0.54–2.23)	0.87 (0.42–1.18)	1.38 (0.71–2.70)	0.372
Hazard ratios (95% CI) for secondary MACE end point					
cPT max					
Model 1	1.0 (ref)	1.71 (0.94–3.10)	3.59 (2.09–6.19)	3.73 (2.16–6.41)	<0.001
Model 2	1.0 (ref)	1.66 (0.91–3.01)	3.18 (1.83–5.51)	3.13 (1.80–5.51)	0.001
cPB					
Model 1	1.0 (ref)	1.59 (0.92–2.74)	2.27 (1.36–3.79)	3.41 (2.08–5.58)	<0.001
Model 2	1.0 (ref)	1.53 (0.89–2.65)	2.14 (1.28–3.59)	2.87 (1.73–4.74)	<0.001
IMT					
Model 1	1.0 (ref)	0.85 (0.56–1.31)	1.03 (0.69–1.55)	1.36 (0.92–2.00)	0.052
Model 2	1.0 (ref)	0.84 (0.55–1.28)	0.90 (0.59–1.36)	1.09 (0.73–1.62)	0.502

Model 1 was adjusted for age, race, and gender. Model 2 was additionally adjusted for diabetes mellitus, current smoking, body mass index, systolic blood pressure, antihypertensive agent use, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and use of lipid-lowering drugs.
cPTmax, maximum carotid plaque thickness; CI, confidence interval; cPB, carotid plaque burden; HR, hazard ratio; IMT, intima–media thickness (quartile); MACE, major adverse cardiovascular events.

Table 3 Impact on model performance by adding cPTmax, cPB and carotid IMT

Model	Model fit[a]		Discrimination[b]	Calibration	
	χ^2	*P*-value	Change in C-index (95% CI)	χ^2	*P*-value
Impact on model performance for prediction of primary MACE end point					
Model (CRF)	41.5	Ref model	Ref model	4.3	0.37
Model (CRF) + cPT	50.7	<0.001	0.01 (-0.02 to 0.04)	6.3	0.18
Model (CRF) + cPB	50.1	0.003	0.01 (-0.02 to 0.04)	3.4	0.49
Model (CRF) + IMT	45.3	<0.001	-0.00 (-0.01 to 0.01)	3.8	0.44
Impact on model performance for prediction of secondary MACE end point					
Model (CRF)	92.3	Ref model	Ref model	7.8	0.09
Model (CRF) + cPT	128.9	<0.001	0.02 (0.001 to 0.04)	2.7	0.61
Model (CRF) + cPB	115.6	<0.001	0.03 (0.006 to 0.05)	4.6	0.33
Model (CRF) + IMT	98.4	<0.001	-0.00 (-0.004 to 0.003)	6.8	0.15

cPB, carotid plaque burden; cPT, carotid plaque thickness; CRF, conventional risk factor; IMT, intima–media thickness.
[a]Changes in model fit assessed using the likelihood ratio test.[23]
[b]Differences in c-index between models and 95% CI were calculated using the method of Newson.[24]

Table 4 Effect on categori-free net reclassification index (MRI) of adding cPTmac, cPB and carotid IMT

Model	Reclassification		
	NRI	(95% CI)	*P*-value
Impact on model performance for prediction of primary MACE end point			
Model 1 (CRF)	Ref model		
Model 1 + cPTmax	0.178	(0.027–0.299)	0.032
Model 1 + cPB	0.228	(0.002–0.320)	0.040
Model 1 + IMT	0.016	(-0.095–0.146)	0.798
Impact on model performance for prediction of secondary MACE end point			
Model 1 (CRF)	Ref model		
Model 1 + cPTmax	0.173	(0.109–0.243)	<0.0001
Model 1 + cPB	0.174	(0.102–0.245)	<0.0001
Model 1 + IMT	0.015	(-0.060–0.100)	0.559

NRI calculated using the category-free version.[25]
cPB, carotid plaque burden; CI, confidence interval; cPT, carotid plaque thickness; CRF, conventional risk factor; IMT, intima–media thickness; MACE, major adverse cardiovascular events; NRI, net reclassification index.

Discussion

The presence of plaque in the carotid artery has already been identified as an independent predictor for future cardiovascular events[9,27]; however, in this study, we quantified carotid plaque from cross-sectional images (short axis) and found it to be stepwise predictive of future ASCVD; the thicker the plaque the higher the risk. Considering progression of atherosclerosis/growth of plaques, the association between cPTmax and risk of atherosclerotic complications is not surprising. Lacking true 3D technology, we introduced assessment of cPB, summarizing plaque areas from serial cross-sectional 2D images[4] and showed that this approach could predict future adverse events similarly to CACS.[10] In this study, cPTmax performed more or less similar to cPB. Despite that cPB was a more comprehensive assessment tool, taking into account that plaques may have different shapes and that there may be more than one plaque, cPTmax being much simpler to assess, performed similarly. This can certainly relate to the nature of the 10-s, cross-sectional sweep without control of speed of movement (lack of true 3D), which potentially introduces inaccuracy of cPB. However, the 3D nature of the cross-sectional sweep, ensuring data capture from the entire cervical portion of the carotid artery, therefore allowing for identification of any plaque, may be of importance for our findings. Further, the cross-sectional image shows from which anatomical location the measurement should be made to measure the true radial distance from the media/adventitia border to the centre of the artery, where the plaque is thickest. Of course, given that the image is acquired at a perpendicular angle with respect to the long axis of the artery.

Rundek *et al.*[28] also measured cPT, however, acquired from images in long axis. They also showed cPT to be predictive of future cardiovascular events, however, in a different population as 21% already had established 'cardiac disease' at baseline. The theoretical

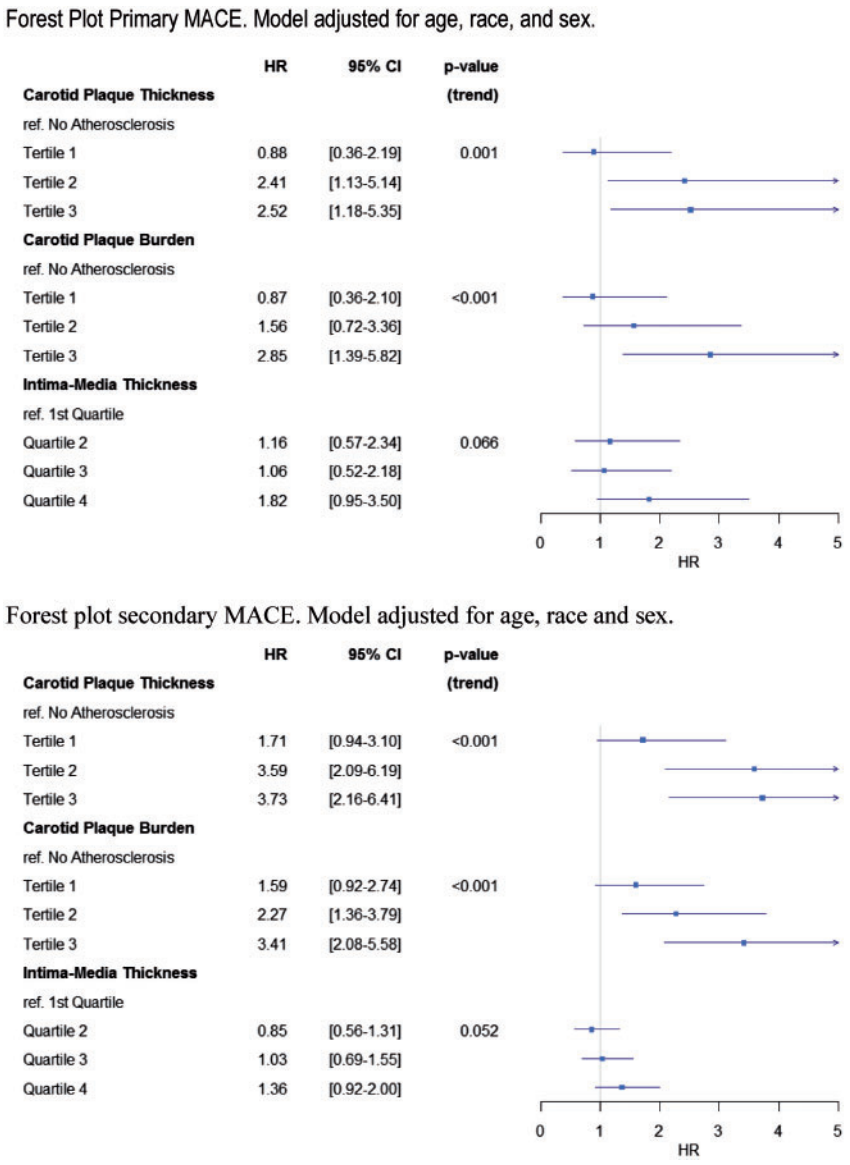

Figure 3 Hazard ratios for primary and secondary MACE, unadjusted and adjusted according to Model 1 for cPTmax, cPB, and IMT.

advantage of our technique is that only in cross-section can the true radial distance, plaque thickness, be measured. Due to focusing of the ultrasound beam to obtain sharp images, only a thin 'slice' of the artery/plaque is visualized, potentially not reflecting the true size of the plaque.

In principle, cPTmax can be assessed directly from frozen ultrasound images on the ultrasound machine without the need for offline analyses. Future true 3D applications might improve prediction not only for cPTmax, since it can then be estimated perpendicular to the centre line of the vessel, but also allow plaque volume measurements. Reproducibility should improve from 3D imaging, allowing for accurate repetitive scans over time.[29] In this manner, evaluation of anti-atherosclerotic treatment might improve being based on imaging observing changes in atherosclerosis amount rather than based on changes in blood tests.[30,31]

An alternative to cPTmax is cPTsum: the sum of the thickest plaque in both carotid arteries (right and left). The latter was also analysed and found to have almost similar predictive value (data not shown); however, since cPTmax is the simplest, we chose to analyse this primarily. In our study, we used semi-automated software outlining plaque in all images, automatically calculating plaque thickness as described above (*Figure 1*).

Other methods of quantifying carotid plaque size by ultrasound have shown similar results, e.g. measuring plaque area on 2D images acquired in long axis.[32,33] Whether this method is similar to, superior, or inferior to cPT cannot be judged as acquisition and analysis methods and populations are not directly comparable. However, data on plaque area are based on images in long axis with the limitations referred to the above, namely that only part of the plaque is visualized due to focusing of the ultrasound beam.

Although patients with the highest IMT values experienced more adverse events than those with low IMT, the predictive value was non-significant when adjusted for traditional risk factors. Especially, prediction of low risk was inferior to that of no plaque. That IMT did not predict risk very well is not surprising, considering the data available regarding IMT today.[7,10,12,34,35] Our study may be criticized for only acquiring IMT from one angle; however, apart from that, the methodology used was similar to the current recommendations. The important issue of IMT, and why it is not as predictive as presence and quantification of plaque, is the approach of only acquiring data from a given, small anatomical location, i.e. distal CCA, rather than interrogating the entire vessel for the presence of atherosclerosis. Other criticism of IMT has been raised, i.e. that thickening of the intima–media complex may be a result of hypertension rather than atherosclerosis. Most importantly, IMT does not predict risk beyond that of traditional risk factors in the individual person,[7,10,34] and therefore, serial IMT measurements are not recommended.[16,17,36]

Given the advantages of ultrasound being harmless, portable, and inexpensive, this technique may be an alternative to CT based, despite its potential disadvantages. On the other hand, ultrasound is operator dependent, thus training and certification remains essential. However, 3D technology will ease correct acquisition using simultaneous imaging of several planes. In addition, ultrasound can identify soft and small plaques and therefore potentially identify earlier stages of disease than CACS, widening the window for prevention further.

Another approach, potentially improving predictability, is to add observations from other anatomical locations, i.e. arteries of lower extremity where atherosclerosis may be more prevalent.[5,37]

Our study had limitations with regard to the method of participant follow-up and ultrasound technology. In case of the former, these have been described in detail[4,10]; however, in brief, the reliance on health insurance claims to identify adverse events may have resulted in a lower-than-expected rate of adverse events. However, comparing with other methods across the same population, this should have not affected our results. Longer period of follow-up would have strengthened the study. With respect to the ultrasound technology used in the BioImage Study, limitations of these have already been discussed in detail.[4,10] However, specifically for this study, acquisition of cross-sectional images were assumed to be at 90° with respect to the long axis of the carotid artery; however, if acquired at non-perpendicular angles, error could have been introduced with measurement of too high values for cPTmax (and cPB). Specifically at the location of the carotid bifurcation, where the internal carotid artery branches off, this is where plaque often develops and 'angle inaccuracy' might occur. Limitations with regard to IMT have been discussed above. cPTmax values were automatically derived from the semi-automated outlines of plaques performed using QLAB–VPQ. Although the operator analysing the 10-s ultrasound video's reviewed all outlines, especially in plaques reflecting ultrasound poorly (echo-weak/lucent plaques), or in case of calcification and/or severe stenosis, outlining was difficult and could be inaccurate.

In conclusion, we found the simple cPTmax being similarly predictive as cPB for the development of symptomatic ASCVD. The presented data add to the accumulating evidence that quantification of carotid plaque by ultrasound may contribute significantly to personalized ASCVD risk prediction.

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