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ORIGINAL RESEARCH

Carotid Plaque Score for Stroke and Cardiovascular Risk Prediction in a Middle-Aged Cohort From the General Population

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BACKGROUND: We aimed to explore the predictive value of the carotid plaque score, compared with the Systematic Coronary Risk Evaluation 2 (SCORE2) risk prediction algorithm, on incident ischemic stroke and major adverse cardiovascular events and establish a prognostic cutoff of the carotid plaque score.

METHODS AND RESULTS: In the prospective ACE 1950 (Akershus Cardiac Examination 1950 study), carotid plaque score was calculated with ultrasonography at inclusion in 2012 to 2015. The largest plaque diameter in each extracranial segment of the carotid artery on both sides was scored from 0 to 3 points. The sum of points in all segments provided the carotid plaque score. The cohort was followed up by linkage to national registries for incident ischemic stroke and major adverse cardiovascular events (nonfatal ischemic stroke, nonfatal myocardial infarction, and cardiovascular death) throughout 2020. Carotid plaque score was available in 3650 (98.5%) participants, with mean±SD age of 63.9±0.64 years at inclusion. Only 462 (12.7%) participants were free of plaque, and and 970 (26.6%) had a carotid plaque score of >3. Carotid plaque score predicted ischemic stroke (hazard ratio [HR], 1.25 [95% CI, 1.15–1.36]) and major adverse cardiovascular events (HR, 1.21 [95% CI, 1.14–1.27]) after adjustment for SCORE2 and provided strong incremental prognostic information to SCORE2. The best cutoff value of carotid plaque score for ischemic stroke was >3, with positive predictive value of 2.5% and negative predictive value of 99.3%.

CONCLUSIONS: The carotid plaque score is a strong predictor of ischemic stroke and major adverse cardiovascular events, and it provides incremental prognostic information to SCORE2 for risk prediction. A cutoff score of >3 seems to be suitable to discriminate high-risk subjects.

REGISTRATION INFORMATION: clinicaltrials.gov. Identifier: NCT01555411.

Key Words: atherosclerosis ■ cardiovascular disease ■ carotid plaque ■ prediction ■ stroke ■ ultrasonography

Stroke, as part of the cardiovascular diseases, is the second most common cause of death and the leading cause of disability in the Western world. Ischemic stroke accounts for ≈85% of all strokes, and 45% of ischemic strokes are directly attributable to vascular disease, according to the Trial of Org 10172 in Acute Stroke Treatment classification for stroke cause.[1] Atherosclerotic vascular disease for risk prediction can easily, noninvasively, and without exposure to radiation or intravenous contrast be assessed with

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CLINICAL PERSPECTIVE

What Is New?

- The carotid plaque score, a semiquantitative ultrasonographic measure of carotid atherosclerotic burden suited for clinical practice, is a strong predictor of future ischemic stroke and major adverse cardiovascular events.
- The carotid plaque score outperformed the Systematic Coronary Risk Evaluation 2 algorithm in risk prediction.

What Are the Clinical Implications?

- A carotid plaque cutoff score of >3 seems to be suitable to discriminate high-risk subjects, corresponding to 75% increased risk of ischemic stroke.

Nonstandard Abbreviations and Acronyms

ACE 1950	Akershus Cardiac Examination 1950 study
MACE	major adverse cardiovascular event
SCORE2	Systematic Coronary Risk Evaluation 2

ultrasonography, and the carotid arteries are suited for ultrasonographic examination as they are located relatively superficial and not covered by bone structure.

Atherosclerotic vascular disease ranges from a thickening of the innermost arterial layer, intima, to a more complex focal structure protruding into the arterial lumen, an atherosclerotic plaque. Presence of carotid plaque is age related, and in the mid-60s, almost 9 of 10 patients have visible plaques.[2] Atherosclerosis is mostly seen as a risk marker, as it is associated with traditional cardiovascular risk factors, such as hypertension, hypercholesterolemia, physical activity, and smoking.[2,3] In addition, carotid plaque burden, as a measure of the total amount of atherosclerosis, is independently associated with future incident stroke and cardiovascular events.[4–7]

However, the use of carotid ultrasonography in cardiovascular risk stratification is not routinely recommended, according to most recent guidelines.[8–10] There are several reasons for this, including lack of standardization of the ultrasonographic examination and lack of evidence that assessment of carotid atherosclerosis provides incremental prognostic information to established cardiovascular risk assessments tools, such as Systematic Coronary Risk Evaluation 2 (SCORE2), which calculates 10-year risk of a cardiovascular event based on the presence of traditional cardiovascular risk factors.[11] Accordingly, using data from a large population cohort with ultrasonographic assessment of carotid atherosclerosis, we aimed to assess the prognostic value of the carotid plaque score on ischemic stroke, major adverse cardiovascular events (MACEs), and all-cause mortality, compare the prognostic merit of the carotid plaque score with that of SCORE2, and determine the incremental prognostic value of the carotid plaque score to SCORE2. Furthermore, we aimed to assess an optimal prognostic cutoff of the carotid plaque score for incident ischemic stroke.

METHODS

The ACE 1950 (Akershus Cardiac Examination 1950 study) is a prospective cohort study of cardiovascular health of all men and women born in 1950 and residing in Akershus County, Norway. The baseline examination was performed at 2 hospitals in the county, Akershus University Hospital and Bærum Hospital, from 2012 to 2015. The cohort was aged 62 to 65 years at baseline, and 3706 of 5827 eligible residents entered the study (attendance rate, 64%). The study design has previously been published.[12] In short, at inclusion, a cardiovascular assessment was performed, including extensive ultrasonographic examination, fasting blood samples, interview, and a clinical examination. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline, and the data that support the findings of this study are available from the corresponding author on reasonable request.

Ethical Approval

The study was approved by the Regional Committees for Medical and Health Research Ethics in Norway (reference number 2011/1475). All participants signed a written informed consent before entering the study. The consent included later extraction of relevant end points from national health registries.

Carotid Plaque Score

Carotid ultrasonography was performed on both sides of the neck with the participant in supine position with a Vivid E9 machine (GE Healthcare) using a linear L9 array transducer for vascular imaging. A plaque was defined according to the latest version of the Mannheim Carotid Intima-Media Thickness and Plaque Consensus.[13] The carotid artery was divided into 4 segments bilaterally: common carotid artery, carotid bifurcation, internal carotid artery, and external carotid artery. We used cross-sectional sweeps to evaluate for the presence of plaque in each segment; and then once a plaque lesion was identified, the thickness of the largest plaque in each segment was measured (electronic calipers were placed beginning

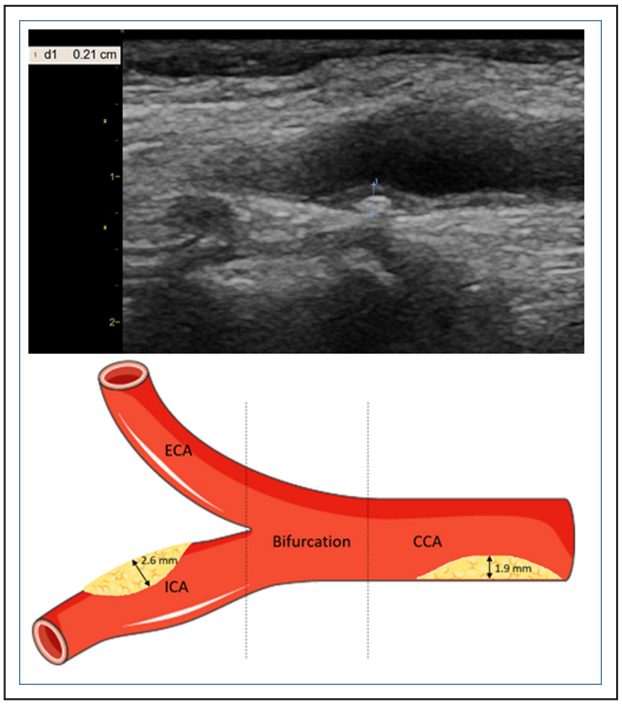

Figure 1. Calculation of carotid plaque score.
Top: B-mode still image of the left carotid bifurcation, longitudinal plane. A carotid plaque with the largest diameter of 2.1 mm is located at the far wall of the artery. According to the carotid plaque scoring system (plaque diameters ≥1.5, ≥2.5, and ≥3.5 mm are given 1, 2, and 3 points, respectively), the plaque is given 1 point. The sum of the largest plaque in each extracranial segment of the carotid artery, both sides (common carotid artery [CCA], carotid bifurcation, internal carotid artery [ICA], and external carotid artery [ECA]), constitutes the carotid plaque score, ranging from 0 to 24. A score of 0 denotes a subject free of plaques. Bottom: the 4 segments of the carotid artery (1 side) in longitudinal plane. A 1.9-mm plaque in CCA and a 2.6-mm plaque in ICA are seen, representing a plaque score of 3 on this side. The sum of the 4 segments on both sides provides the carotid plaque score.

along the origin of the plaque at the vessel wall, into the lumen along the most distended/projecting aspect of the plaque) and scored according to maximum diameter (≥1.5, ≥2.5, and ≥3.5 mm were given 1, 2, and 3 points, respectively) (Figure 1). An occluded segment was given 3 points. Finally, points for all segment on both sides were summarized to a total carotid plaque score ranging from 0 to 24.[2,14] Calculation of the carotid plaque score was performed online at the baseline examination, and the operators were blinded to the participant's cardiovascular morbidity/history. The examination was performed by 4 trained ultrasonographic operators, and interrater and intrarater analysis was performed twice during the inclusion period, with excellent results (Cronbach κ=0.999).

Cardiovascular Risk Factors and Risk

Hypertension was defined as the use of antihypertensive medication or resting systolic blood pressure (mean of second and third measures) >140 mm Hg in sitting position after 10 minutes of seated rest. Diabetes was defined as use of antidiabetic medication, hemoglobin A1c ≥6.5%, or fasting plasma glucose ≥7.0 mmol/L. Body mass index was calculated as weight in kilograms divided by height in meters squared, and obesity was defined as a body mass index ≥30 kg/m^2. Years of education, history of coronary heart disease and stroke, as well as smoking and atrial fibrillation were self-reported. The latter was validated through reviews of previous ECG and hospital records. The 10-year risk for cardiovascular disease was calculated for each participant using the SCORE2 risk prediction algorithm.[11] The low-risk model was used, as Norway is classified as a low-risk region, according to standardized cardiovascular disease mortality rates. According to SCORE2, cardiovascular risk can be divided into 3 categories: low (<5%), moderate (5%–<10%), and high (≥10%) 10-year risk for cardiovascular disease.

Outcome Variables

The cohort was followed up throughout 2020 for the main outcome of incident ischemic stroke (*International Classification of Diseases, Tenth Revision* [*ICD-10*], code I63.x), as well as 2 secondary outcomes: composite end point MACE (nonfatal ischemic stroke [code I63.x], nonfatal myocardial infarction [code I21.x], and cardiovascular death [all codes I and R96]) and all-cause mortality. The outcome variables were based on individual-level data from the mandatory Norwegian Patient Registry (NPR) and the Norwegian Cause of Death Registry.

Statistical Analysis

Continuous variables are given as mean±SD or as median and interquartile range, as appropriate, whereas categorical variables are presented as number and percentage. The Mann-Whitney *U* test was used for comparison of nonnormally distributed continuous variables, the Student *t*-test was used for comparison of normally distributed continuous variables, and the χ^2 test was used for comparison of categorical variables. Cox proportional hazards models were used to assess the prognostic value of carotid plaque score and SCORE2 on outcomes. The multivariable models were mutually adjusted for SCORE2 and carotid plaque score. We present hazard ratios (HRs) with 95% CIs. We compared the Cox proportional hazards for the carotid plaque score and SCORE2 in univariate models by use of the Akaike information criterion and the relative likelihoods of the 2 models. For the multivariable models, we compared coefficients by the χ^2 test. We used c statistic, net reclassification improvement, and integrated discrimination improvement to assess the incremental predictive performance of

the carotid plaque score to SCORE2. We compared model fit of the c statistic models by the likelihood ratio test.[15] Net reclassification improvement estimates how an enhanced model correctly reclassifies events and nonevents compared with a basic predictive model, and the integrated discrimination improvement estimates the improvement of the slopes of the discrimination curves for the enhanced model. We derived the Youden J statistic from the c statistic models to determine the best prognostic cutoff value for the carotid plaque score. To make the cohort more comparable to the target population of the SCORE2 risk algorithm, we performed sensitivity analysis by excluding patients with established diabetes, cerebrovascular disease, or coronary heart disease. We performed additional sensitivity analyses (1) according to sex, (2) after excluding patients with ≥50% carotid stenosis, and (3) after additional adjusting for atrial fibrillation, alcohol use, and use of antiplatelet therapy. Level of significance of $P<0.05$ was set for all analyses. All analyses were performed using IBM SPSS Statistics, version 28, and Stata, version 16.1.

RESULTS

Clinical Characteristics

Carotid plaque score was calculated in 3650 (98.5%) of the participants at the ACE 1950 baseline visit (Figure 2). The mean±SD age at inclusion was 63.9±0.64 years, and 1779 (48.7%) of participants were women. Hypertension was the most common cardiovascular

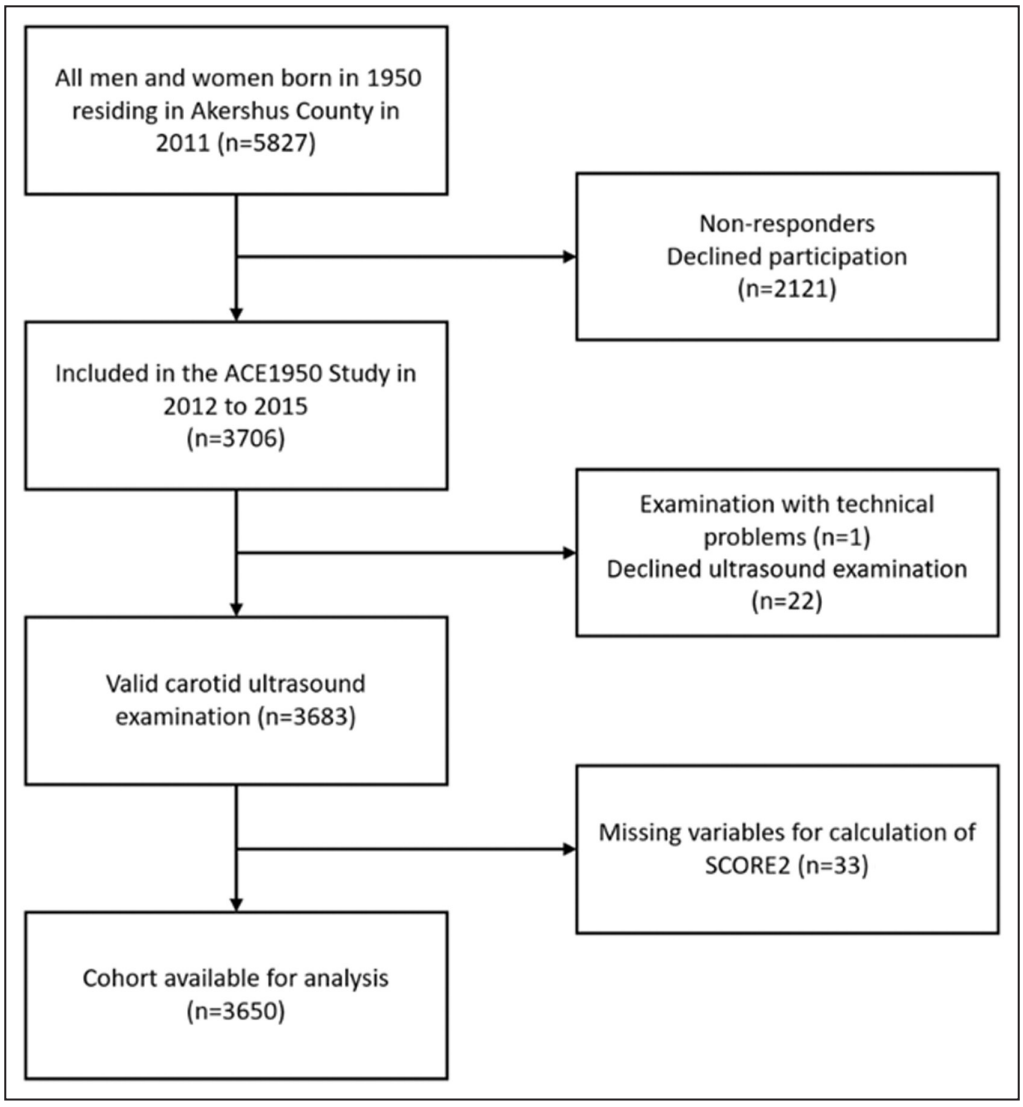

Figure 2. Flowchart of the study population.
ACE 1950 indicates Akershus Cardiac Examination 1950 study; and SCORE2, Systematic Coronary Risk Evaluation 2.

risk factor, present in 2265 (62.1%) subjects. Almost half of the participants (n=1728 [47.3%]) were former smokers, and 138 (3.8%) and 257 (7.0%) reported a history of cerebrovascular and coronary heart disease, respectively. In total, 3446 (94.4%) of participants were characterized as having low to moderate 10-year cardiovascular risk, according to SCORE2. Only 462 (12.7%) participants were free of carotid plaque, 2218 (60.8%) had a carotid plaque score ranging from 1 to 3, and 970 (26.6%) had a carotid plaque score of >3. Characteristics of the study population at study baseline are presented in Table 1, and the distribution of carotid plaque score is shown in Figure 3. Baseline characteristics according to sex are demonstrated in Table S1.

Predictive Value and Model Comparison

After a median follow-up time of 6.4 (interquartile range, 6.0–7.0) years, 42 (1.2%) study participants experienced an acute ischemic stroke, 145 (4.0%) experienced a MACE (40 strokes, 83 myocardial infarctions, and 22 cardiovascular deaths; Figure 4), and 114 (3.1%) died (Figure S1). Eighteen (42.9%) of all the strokes appeared among patients with plaque score from 0 to 3. In comparison, 36 (85.7%) of all strokes appeared in the

Table 1. Characteristics of the Study Population

Variable	Total (n=3650)	Carotid plaque score 0–3 (n=2680)	Carotid plaque score >3 (n=970)	*P* value for comparison
Female sex, n (%)	1779 (48.7)	1457 (54.4)	322 (33.2)	<0.001
Age, mean (SD), y	63.9 (0.64)	63.9 (0.64)	63.9 (0.65)	0.64
Higher education, n (%)*	1679 (46.0)	1287 (48.1)	392 (40.6)	<0.001
Cardiovascular risk				
Hypertension, n (%)	2265 (62.1)	1538 (57.4)	727 (74.9)	<0.001
Diabetes, n (%)†	312 (8.5)	199 (7.4)	113 (11.6)	<0.001
Total cholesterol, mmol/L, mean (SD)	5.4 (1.1)	5.5 (1.0)	5.3 (1.2)	<0.001
Obesity, n (%)	823 (22.5)	582 (21.7)	241 (24.8)	0.05
Atrial fibrillation, n (%)	160 (4.4)	105 (3.9)	55 (5.7)	0.03
Smoking, n (%)				<0.001
Current	529 (14.5)	279 (10.4)	250 (25.8)	
Former	1728 (47.3)	1269 (47.4)	459 (47.3)	
Alcohol units/14 d, mean (SD)	7.9 (10.0)	7.6 (8.2)	8.9 (13.7)	<0.001
Comorbidity, n (%)				
Coronary heart disease	257 (7.0)	125 (4.7)	132 (13.6)	<0.001
Cerebrovascular disease	138 (3.8)	77 (2.9)	61 (6.3)	<0.001
SCORE2				
Mean (SD)	6.1 (2.2)	5.8 (2.0)	7.0 (2.3)	<0.001
Median (IQR)	5.8 (4.5–7.4)	5.5 (4.8–6.2)	6.7 (5.3–8.4)	<0.001
Low risk, n (%)‡	1257 (34.5)	1072 (40.1)	185 (19.1)	<0.001
Moderate risk, n (%)‡	2189 (60.0)	1503 (56.3)	686 (70.7)	<0.001
High risk, n (%)‡	194 (5.3)	95 (3.6)	99 (10.2)	<0.001
Carotid plaque, n (%)				
Carotid stenosis ≥50%	84 (2.3)	6 (0.2)	78 (8.0)	<0.001
Presence of hypoechogenic plaque	559 (15.3)	298 (11.1)	261 (26.9)	<0.001
Ischemic stroke	42 (1.2)	18 (0.7)	24 (2.5)	<0.001
Female sex	15 (0.8)	8 (0.5)	7 (2.2)	0.01
MACEs	145 (4.0)	71 (2.6)	74 (7.6)	<0.001
All-cause mortality	114 (3.1)	64 (2.4)	50 (5.2)	<0.001

IQR indicates interquartile range; MACE, major adverse cardiovascular event; and SCORE2, Systematic Coronary Risk Evaluation 2.
*There are 10 missing values. Higher education is defined as >12 years of formal education.
†There is 1 missing value.
‡Low risk indicates <5%; moderate risk, 5% to <10%; and high risk, ≥10%.

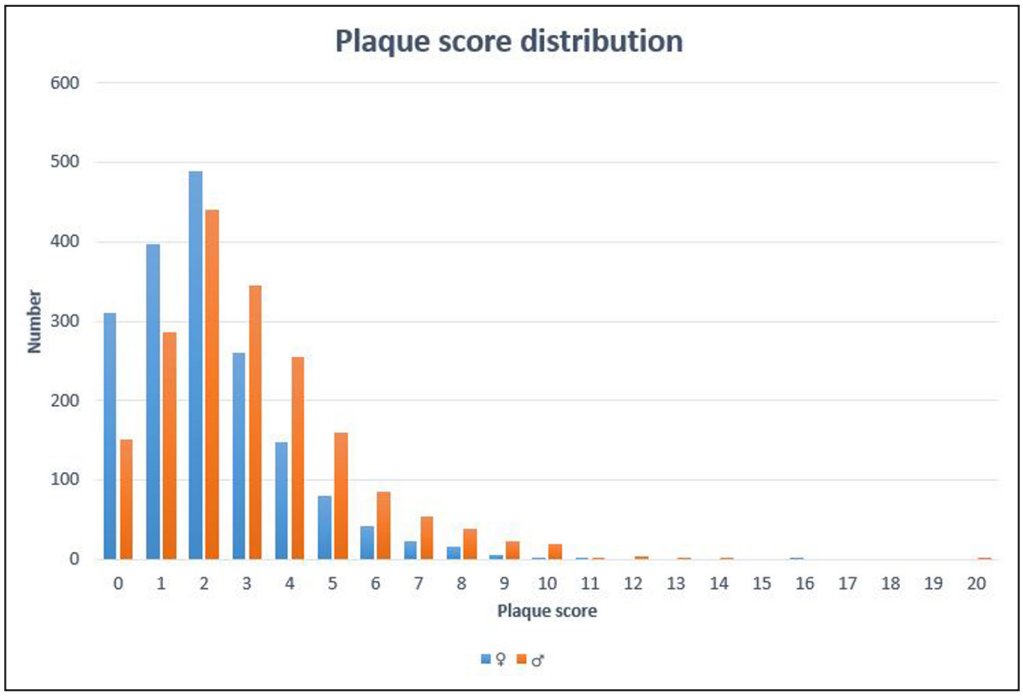

Figure 3. Carotid plaque score distribution.
The *x* axis shows the number of participants. The *y* axis shows the plaque score. ♀ Indicates female; and ♂, male.

low- to moderate-risk group, according to SCORE2. Both carotid plaque score and SCORE2 were associated with incident stroke, MACEs, and all-cause mortality in univariate analysis. After adjusting for SCORE2, carotid plaque score remained associated with all outcomes, whereas SCORE2 no longer was associated with all-cause mortality. The carotid plaque score was consistently more strongly associated with incident ischemic stroke compared with SCORE2 (*P* value for comparison of HRs=0.001; Table 2). In the sensitivity analysis, excluding patients with established diabetes, cerebrovascular disease, or coronary heart disease at inclusion, or excluding participants with carotid stenosis (≥50%), the results were comparable to those for the entire cohort (Tables S2 and S3). The result were comparable in analyses stratified according to sex, but with stronger associations of the carotid plaque score in predicting MACEs for women (Table S4). Multiple adjustment for competing cardiovascular risk factors did not change the results (Table S5). Other high-risk characteristics of the carotid plaques were not associated with outcomes (Table S6).

Prognostic Accuracy and Reclassification Merit of Carotid Plaque Score

The c statistic were 0.70 (95% CI, 0.61–0.78) for the carotid plaque score and 0.66 (95% CI, 0.58–0.75) for SCORE2 in predicting incident ischemic stroke. Adding carotid plaque score to SCORE2 improved the c statistic of the risk model (0.72 [95% CI, 0.64–0.80]; *P* value for comparison <0.001). Both the continuous net reclassification improvement and integrated discrimination improvement for incident ischemic stroke were

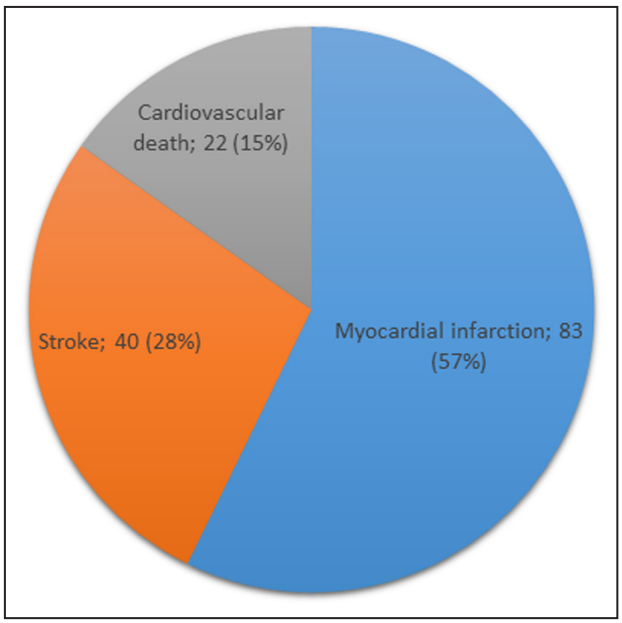

Figure 4. Proportion of ischemic stroke, myocardial infarction, and cardiovascular death in major adverse cardiovascular events.

Table 2. Associations of Carotid Plaque Score and SCORE2 With Outcomes

Variable	Hazard ratio (95% CI)		*P* value for comparison
Univariate	Carotid plaque score	SCORE2	
Ischemic stroke	1.30 (1.20–1.41)	1.25 (1.12–1.40)	0.001
MACEs	1.26 (1.20–1.32)	1.23 (1.16–1.31)	<0.001
All-cause mortality	1.16 (1.09–1.24)	1.11 (1.03–1.20)	0.014
Multivariable*	Carotid plaque score	SCORE2	
Ischemic stroke	1.25 (1.15–1.36)	1.16 (1.03–1.31)	0.40
MACEs	1.21 (1.14–1.27)	1.16 (1.08–1.24)	0.40
All-cause mortality	1.14 (1.06–1.22)	1.07 (0.98–1.16)	0.32

MACE indicates major adverse cardiovascular event; and SCORE2, Systematic Coronary Risk Evaluation.
*Mutually adjusted for carotid plaque score and SCORE2.

improved by the addition of the carotid plaque score to SCORE2. The results were comparable for the outcomes of MACEs and all-cause mortality (Table 3).

Establishing a Prognostic Cutoff Value for Plaque Score

Using the Youden J statistic for the main outcome of incident ischemic stroke, we found that a carotid plaque score of >3 provided the optimal cut point, with sensitivity of 57.1%, specificity of 73.8%, positive predictive value of 2.5% and negative predictive value of 99.3%. In the survival analysis, this cut point for carotid plaque score was a strong predictor of incident ischemic stroke (adjusted HR, 2.98 [95% CI, 1.58–5.63]). The addition of the cut point of carotid plaque score >3 to the SCORE2 model improved the c statistic of the model (0.71 [95% CI, 0.64–0.79]; *P* value for comparison <0.001). In our cohort, 15 of the 29 (51.7%) subjects experiencing stroke in the moderate-risk category, according to SCORE2, were reclassified to the high-risk group using the plaque cutoff score. Both the continuous net reclassification improvement (0.618 [95% CI, 0.298–0.921]) and the integrated discrimination improvement (0.004 [95% CI, 0.000–0.011]) were significantly improved by the addition of the cut point of carotid plaque score >3 to the SCORE2 model.

DISCUSSION

In a middle-aged cohort from the general population, we found that carotid plaque score, a rapid and robust ultrasonographic measure of carotid atherosclerotic burden, is a strong predictor of future strokes and MACEs. The carotid plaque score outperformed SCORE2 head to head in the prognostic models and provided incremental prognostic information to the SCORE2 risk model.

Measures of carotid atherosclerosis may have an unfulfilled potential in risk stratification, as various measurements of carotid atherosclerosis have been linked to overall atherosclerosis as well as cardiovascular disease.[7,14,16] Most of the previous studies on the relationship between carotid atherosclerosis and cardiovascular outcomes have shown that presence of carotid plaques

Table 3. Incremental Value of Carotid Plaque Score to SCORE2 in Risk Prediction

Variable	C statistic (95% CI)	Continuous NRI (95% CI)	IDI (95% CI)
Ischemic stroke			
Carotid plaque score	0.70 (0.61–0.78)	N/A	N/A
SCORE2	0.66 (0.58–0.75)	Reference	Reference
SCORE2+carotid plaque score	0.72 (0.64–0.80)*	0.452 (0.130–0.749)	0.012 (0.001–0.044)
MACEs			
Carotid plaque score	0.70 (0.66–0.74)	N/A	N/A
SCORE2	0.65 (0.60–0.69)	Reference	Reference
SCORE2+carotid plaque score	0.72 (0.68–0.76)*	0.447 (0.274–0.586)	0.014 (0.005–0.031)
All-cause mortality			
Carotid plaque score	0.61 (0.56–0.67)	N/A	N/A
SCORE2	0.59 (0.54–0.64)	Reference	Reference
SCORE2+carotid plaque score	0.63 (0.58–0.68)*	0.301 (0.101–0.508)	0.003 (0.000–0.009)

IDI indicates integrated discrimination improvement; MACE, major adverse cardiovascular event; N/A, not applicable; NRI, net reclassification improvement; and SCORE2, Systematic Coronary Risk Evaluation 2.
*$P<0.001$ compared with SCORE2 model.

represents a more advanced form of atherosclerosis, and it is a better predictor for future stroke and cardiovascular events compared with carotid intima-media thickness.[6,17–21] Furthermore, there is a strong association between measure of carotid atherosclerotic burden, including total plaque area and volume, and future cardiovascular events.[7,22] These modalities are less suitable for daily clinical practice, as they are operator dependent and time-consuming.[23] Our results confirm the strong association between carotid atherosclerotic burden and cardiovascular events, but in comparison to total plaque area and volume, carotid plaque score is easier to perform, less time-consuming, and, accordingly, well suited for a busy clinical setting. Our method to measure carotid plaque burden, which is a semiquantitative approach, combines the affected segments and maximal plaque thickness in each segment. This combination reduces the risk of underestimation of the extent of atherosclerosis. Furthermore, plaque height measure, as used in this study, is highly reproducible,[23] and the use of similar semiquantitative plaque scores has shown acceptable reproducibility.[5] The technique does have its limitations, especially with regard to plaque localization and morphologic features (including echogenicity), which are not weighted or included in the score. Nevertheless, the carotid plaque score is similar to and in accordance with the American Society of Echocardiography recommendation on how to assess carotid atherosclerotic plaques.[23]

To make the carotid plaque score a clinically useful tool, we aimed to establish a prognostic cutoff value that could further improve the clinical applicability. Our results suggest that a cutoff score >3 is appropriate to discriminate high-risk individuals with a high negative predictive value. This further suggests that the occurrence of small amounts of carotid plaques at predisposed areas (ie, carotid bifurcation and proximal internal carotid artery) is a common finding in middle-aged individuals and associates with limited risk of future events.

Assessment of carotid atherosclerosis is not part of the recommended routine examination, according to the current guidelines on cardiovascular disease prevention. This is attributable to lack of evidence that indexes of carotid atherosclerosis provide incremental prognostic value to cardiovascular risk estimation algorithms.[9] In the current investigation, we demonstrate that the carotid plaque score provides strong incremental prognostic information to SCORE2, the most recent European risk prediction algorithm for incident cardiovascular disease. A few previous studies have shown an additional effect of carotid ultrasonography to risk scores, including the REFINE (Risk Evaluation for Infarct Estimates) Reykjavik study and a study with pooled data from the ARIC (Atherosclerosis Risk in Communities) study, MESA (Multi-Ethnic Study of Atherosclerosis), and DHS (Dallas Heart Study).[11,24,25] Our results indicate that carotid plaque score is not only a risk marker, but indeed a risk factor for cardiovascular disease, as the carotid plaque score performed better than SCORE2 in risk prediction and remained independently associated with outcomes even after multivariable adjustment. This is further corroborated by the fact that the carotid plaque score provided strong incremental prognostic value when added to SCORE2. In addition, because the carotid plaque score was more strongly associated with future ischemic stroke than the composite end point, MACEs, it is likely to assume that carotid plaques serve as a thromboembolic source and a particularly strong proxy for cerebral thromboembolism, which is in line with the conclusions from the Rotterdam study.[5]

The current study has its strengths and limitations. We performed an extensive ultrasonographic examination of both carotid arteries with a high degree of agreement between operators. The cohort was more than moderately sized, increasing the internal validity of our results. We used multiple statistical indexes to evaluate the associations with outcomes, and our results uniformly favored the carotid plaque score in risk prediction. The follow-up time was shorter and number of clinical events was lower than for comparable clinical studies. The ultrasonographic examinations were performed by a few trained operators, which may have overinflated the operator agreement. Our cohort is homogeneous and well phenotyped and treated for cardiovascular risk factors, which may affect the generalizability of the results. In addition, the discriminatory effect of age on the outcomes was not assessed, as we studied a birth cohort examined at approximately the same age. Clinical outcomes were derived from national registries, and diagnostic misclassification may have been an issue. Furthermore, national registries are lacking information on stroke cause. On the other hand, the ACE 1950 is a population-based cohort study of recent date with an acceptable attendance rate, state-of-the-art examinations, and robust outcome variables collected from nationwide health registries with almost complete coverage, ultimately strengthening the results.

Overall, the carotid plaque score, as used in this study, appears suitable and reasonable for cardiovascular risk estimation, either as a lone risk assessment tool or in addition to cardiovascular risk prediction algorithms, and may guide decision-making for cardiovascular preventive therapies. Future studies with extended follow-up are needed to validate our results and explore whether the method will be useful in secondary prevention.

CONCLUSIONS

Carotid plaque score is a strong predictor of incident stroke and MACEs and outperforms SCORE2 for risk

prediction in a middle-aged cohort recruited from the general population. A cutoff score of >3 appears suitable to discriminate high-risk subjects.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S6
Figure S1

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