Circulation: Cardiovascular Imaging

ORIGINAL ARTICLE

Carotid Plaque Composition and Prediction of Incident Atherosclerotic Cardiovascular Disease

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BACKGROUND: Whether information on carotid plaque composition contributes to prediction of incident atherosclerotic cardiovascular disease (ASCVD) remains to be investigated. We determined the sex-specific added value of carotid plaque components for predicting incident ASCVD events, beyond traditional cardiovascular risk factors.

METHODS: Between 2007 and 2012, participants from the population-based Rotterdam Study with asymptomatic carotid wall thickening >2.5 mm on ultrasonography were invited for carotid magnetic resonance imaging. Among 1349 participants (mean age: 72 years [SD±9.3], 49.5% women) without cardiovascular disease, we assessed plaque thickness, luminal stenosis (>30%), presence of intraplaque hemorrhage, lipid-rich necrotic core, and calcification. Follow-up for ASCVD was complete until January 1, 2015. Using Cox proportional hazards models, we fitted sex-specific prediction models including traditional cardiovascular risk factors (base model). We extended the base model by single and simultaneous additions of plaque characteristics and calculated improvement of model performance by the *C* statistics.

RESULTS: During a median follow-up of 4.8 years, 60 men and 48 women developed ASCVD. In women, presence of intraplaque hemorrhage was associated with incident ASCVD (adjusted hazard ratio, 3.37 [95% CI, 1.81–6.25]). The *C* statistic (95% CI) improved from 0.73 (0.66–0.79) to 0.76 (0.70–0.83) after single addition of intraplaque hemorrhage to the base model. Simultaneous addition of plaque components, plaque thickness, and stenosis did not change the results. In men, only carotid stenosis was statistically significantly associated with incident ASCVD (adjusted hazard ratio, 1.75 [95% CI, 1.00–3.08]); yet, the association diminished after the addition of other plaque characteristics, and no improvements were observed in *C* statistics.

CONCLUSIONS: Presence of intraplaque hemorrhage contributes to the prediction of incident ASCVD in women, beyond traditional cardiovascular risk factors, other plaque components, plaque size, and stenosis.

Key Words: cardiovascular diseases ■ carotid artery diseases ■ epidemiology ■ magnetic resonance imaging

Atherosclerotic cardiovascular disease (ASCVD), including coronary heart disease and stroke as major clinical events, is the leading cause of morbidity and mortality worldwide.[1] Accurate identification of high-risk individuals remains the cornerstone of the current approach to primary prevention of ASCVD.[2] Considering that the performance of current cardiovascular risk prediction algorithms based on traditional cardiovascular risk factors remains suboptimal,[3] and in view of the uncertainty regarding the potential benefits of preventive drug therapy for specific groups of individuals, additional assessment of subclinical atherosclerosis is reasonable.[2]

The clinical value of ultrasound assessments of carotid atherosclerosis, including the degree of carotid stenosis, is still a topic of debate.[4,5] The 2021 update of the US Preventive Services Task Force reaffirmed that because of the lack of clinically meaningful benefits, routine ultrasound-based screening for asymptomatic carotid stenosis is not recommended.[6] The limited value of degree of carotid stenosis could be because of the fact that it is not

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CLINICAL PERSPECTIVE

In 1349 participants with asymptomatic carotid wall thickening from the Rotterdam Study, we assessed the sex-specific added value of plaque components in prediction of incident atherosclerotic cardiovascular disease. We found that, in women, in particular, intraplaque hemorrhage was a predictor of atherosclerotic cardiovascular disease, beyond traditional cardiovascular risk factors, other plaque components, and plaque size. Our findings indicate that carotid intraplaque hemorrhage has the potential to be used as marker of systemic plaque vulnerability in clinical practice, particularly among women, and thus carries promise for cardiovascular disease prevention.

Nonstandard Abbreviations and Acronyms

ASCVD	atherosclerotic cardiovascular disease
HR	hazard ratio
MRI	magnetic resonance imaging

per se indicative of plaque vulnerability. Indeed, plaque rupture does not necessarily correlate with plaque size and the severity of stenosis.[7] A growing body of evidence suggests that the composition of plaque plays an important role in plaque vulnerability, beyond luminal stenosis and plaque size,[8–10] and might thus carry a potential for prevention of cardiovascular disease.[11]

Intraplaque hemorrhage and lipid-rich necrotic core—detected on magnetic resonance imaging (MRI)—have been associated with prior cardiovascular events[12,13] and contribute considerably to the risk of (recurrent) coronary heart disease and stroke events.[14–17] However, the added value of plaque components, beyond traditional risk factors, for prediction of first-ever ASCVD events remains unknown. Moreover, while differences between men and women in the pathophysiology and clinical presentation of cardiovascular disease have been recognized,[18] the sex-specific value of plaque components for prediction of incident ASCVD has not yet been addressed.

Within the prospective population-based Rotterdam Study, among subjects with asymptomatic carotid wall thickening, plaque characteristics were determined using MRI. We assessed the added value of information on carotid plaque characteristics—as marker of systemic plaque vulnerability, beyond traditional cardiovascular risk factors, for prediction of incident ASCVD, separately for women and men.

METHODS

Requests to access the data and materials may be sent to the management team of the Rotterdam Study (secretariat.epi@erasmusmc.nl), which has a protocol for approving data requests. Because of restrictions based on privacy regulations and informed consent of the participants, data cannot be made freely available in a public repository.

Study Population

This study is embedded within the Rotterdam Study, a prospective, population-based cohort among adults aged ≥40 years.[19] Each participant undergoes extensive follow-up examinations at a dedicated research center every 3 to 4 years, which also include carotid ultrasonography to assess carotid intima-media thickness.[20] Between 2007 and 2012, participants with an intima-media thickness larger than 2.5 mm in one or both carotid arteries on ultrasonography were invited to undergo an MRI examination of the carotid arteries to further investigate carotid atherosclerosis. In total, 2666 participants were invited for MRI. Of those, 684 did not undergo the MRI examination because of claustrophobia (n=57), physical limitations (n=191), MRI contraindications (n=115), refusal to participate (n=272), no show or lost follow-up (n=49), leaving 1982 participants. Another 242 were excluded from the analysis because of poor image quality (n=95), scan interruption due to claustrophobia (n=106) or absence of plaque in both carotid arteries (n=41), leaving 1740 participants with a complete carotid MRI examination. We further excluded those with prevalent stroke, coronary heart disease, or incomplete follow-up information (n=391), resulting in 1349 persons for the current analyses.

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

Assessment of Carotid Atherosclerotic Plaque

To assess carotid atherosclerotic plaque, an MRI of the carotid arteries was performed using a 1.5-T MR scanner (GE Healthcare, Milwaukee, WI) with a bilateral phased-array surface coil (Machnet, Eelde, The Netherlands).[21] High-resolution images were obtained using a standardized protocol, as described previously.[21] Briefly, both carotid bifurcations were identified using 2D time of flight MR-angiography. The following high-resolution MRI sequences were obtained: a proton density weighted fast spin echo black-blood (PDw-FSE-BB) sequence; a PDw-FSE-BB with an increased in-plane resolution; a PDw-echo planar imaging (EPI) sequence; a T2w-EPI sequence; a 3D-T1w-gradient echo (GRE) sequence; and, a 3D phase-contrast MR-angiography.

We assessed plaque composition by visually evaluating the presence of lipid-rich necrotic core, intraplaque hemorrhage, and calcification using a standardized protocol. Scans were reviewed by trained observers who were blinded to all characteristics of the participant. Intraplaque hemorrhage was defined as the presence of a hyperintense region in the atherosclerotic plaque on 3D-T1w-GRE.[21–23] Calcification was defined

as presence of a hypointense region in the plaque on all sequences.[21,24,25] After assessment of intraplaque hemorrhage, and calcification we assessed the presence of lipid-rich necrotic core. Lipid-rich necrotic core was defined as an hypointense region within the atherosclerotic plaque, which was not classified as calcification, on PDw-FSE or PDw-EPI and T2w-EPI images, or as a region that showed a signal intensity drop when comparing the T2w-EPI images with the PDw-EPI images. A plaque component was present if the component was identified in one or both carotid arteries.

We also assessed the size of the carotid plaque and the degree of stenosis. The maximum plaque thickness and degree of luminal stenosis using the NASCET criteria[26] were obtained from the PDw-FSE images. For the analyses, stenosis was defined as > 30% luminal narrowing.

Assessment of ASCVD

The outcome measure, incident ASCVD, composed of fatal and nonfatal myocardial infarction, other coronary heart disease mortality, and stroke. Information on the events was obtained through digital linkage with general practitioner files and discharge reports from medical specialists. Subsequently, research physicians adjudicated all events as described previously.[27,28] Follow-up for ASCVD was completed until January 1, 2015. Participants were censored at date of first ASCVD event, death due to other causes, loss to follow-up, or January 1, 2015, whichever came first.

Assessment of Cardiovascular Risk Factors

Data collection on cardiovascular risk factors included a standardized home interview, clinical examination, and blood sampling. Blood samples were obtained to determine cholesterol and glucose levels. Blood pressure was measured with a random-zero sphygmomanometer, and the average of 2 readings was used. By means of interview, we obtained information on smoking habits, and medication use. Diabetes was defined as fasting plasma glucose ≥7.0 mmoL/L and/or the use of blood glucose-lowering medication. Information on history of cardiovascular disease, defined as myocardial infarction, stroke, and coronary revascularization procedures was obtained at baseline and during follow-up visits as described previously.[27,28]

Statistical Analysis

Using Cox proportional hazards regression with first ASCVD event as outcome, we fitted a prediction model to our data, which was based on the cardiovascular risk factors included in the Pooled Cohort Equations,[29] that is, age, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, current smoking, and diabetes. We took into account blood pressure lowering medication by adding a constant of 15 mm Hg to the systolic blood pressure measure among participants using blood pressure lowering medication.[30] In addition, we took into account lipid-lowering medication by dividing total cholesterol by 0.8 among participants using lipid-lowering medication.[31] Models were fitted for men and women separately. Considering the nonlinearity of age, we included a restricted cubic spline with 4 knots for age. We call this model the base model. Using the beta coefficients of this base model, we calculated 5-year ASCVD risks for each individual. We then categorized participants into risk categories following the 2019 American College of Cardiology/American Heart Association guideline.[32] Since the risk thresholds of the 2019 American College of Cardiology/American Heart Association guideline reflect the10-year ASCVD risks, we annualized the thresholds and multiplied by 5 to define estimated 5-year ASCVD risk groups as has been done previously.[33,34] The risk categories were defined as follows: low- risk: <2.5%; borderline risk: 2.5% to <3.75%; intermediate risk: 3.75% to <10%; and high-risk: 10% or higher.

Next, we expanded the base model by single additions of the MRI-defined plaque characteristics including presence of lipid-rich necrotic core, intraplaque hemorrhage, calcification, plaque thickness in mm, and presence of stenosis of >30%. We provided the hazard ratios (HRs) and 95% CIs for each plaque characteristic. We repeated the analyses while additionally adding maximum plaque thickness to each model. In addition, we constructed a model in which all plaque characteristics were simultaneously added to the base model to assess whether the predictive value of any plaque characteristic was independent of other plaque characteristics. Also, we computed a model including the base model and simultaneous addition of all plaque characteristics after excluding participants receiving lipid-lowering medication.

To assess the incremental predictive performances of the plaque characteristics, we estimated the bootstrap-corrected *C* statistic with 95% CIs (n=200 repetitions). For the predictors with the greatest discriminative ability (*C* statistic), we plotted the 5-year ASCVD risk distribution derived from the base model and the extended model—using kernel density estimation—to visualize any shift in risk distribution following expanding the base model with information on carotid plaque characteristics. For these predictors, we also calculated the category-free net reclassification improvements for events and nonevents.[35]

All analyses were stratified by sex beforehand based on literature and the demand for sex-specific prediction algorithms.[36] Notably, we also formally tested interaction by computing a base model in the total population and adding multiplicative interaction terms of sex and plaque characteristics (one-by-one) into the model. Multiplicative interaction terms were considered statistically significant at a *P* of <0.05. Finally, within the total study population, we performed additional analyses to investigate the contributions of information on carotid plaque components to the prediction of separate disease entities. To this end, we estimated the HRs (95% CIs) and the bootstrap corrected (200 repetitions) *C* statistics (95% CIs) after additions of plaque characteristics to the base model while stratifying for coronary heart disease and stroke in the total population. Missing data of covariables were handled using multiple imputation by chained equations (n=5 imputations) along with age, sex, plaque characteristics, cardiovascular risk factors, and ASCVD events. Analyses were performed using Stata version 15 (StataCorp).

RESULTS

Baseline characteristics of the study population are provided in Table 1. The mean age at the time of MRI scan was 72.3 (SD, 9.3) years and 49.5% were women. Lipid-rich necrotic core and intraplaque hemorrhage were

Table 1. Baseline Characteristics of the Study Population

Characteristics	Women	Men	*P* Value*
Number	668	681	
Age, y	73.1 (9.4)	71.4 (9.2)	<0.001
Body mass index, kg/m^2	27.1 (4.2)	27.2 (3.5)	0.62
Systolic blood pressure, mm Hg	144.7 (21.8)	145.7 (19.4)	0.36
Diastolic blood pressure, mm Hg	78.8 (11.1)	82.5 (10.7)	<0.001
Total cholesterol, mmol/L	6.2 (3.8)	5.5 (1.1)	<0.001
High-density lipoprotein cholesterol, mmol/L	1.8 (3.9)	1.4 (3.5)	0.12
Current smokers, N (%)	141 (21.1%)	159 (23.3%)	0.32
Diabetes, N (%)	97 (14.5%)	134 (19.7%)	0.012
Hypertension, N (%)	464 (69.5%)	487 (71.5%)	0.41
Blood pressure–lowering medication, N (%)	245 (36.7%)	241 (35.4%)	0.62
Lipid-lowering medication, N (%)	182 (27.2%)	204 (30.0%)	0.27
Lipid-rich necrotic core, N(%)	255 (38.2%)	341 (50.1%)	<0.001
Intraplaque hemorrhage, N(%)	182 (27.2%)	252 (37.0%)	<0.001
Calcification, N(%)	535 (80.1%)	552 (81.1%)	0.65
Stenosis >30%, N(%)	113 (16.9%)	130 (19.1%)	0.30
Maximum intima-media thickness, mm	3.4 (0.8)	3.6 (1.0)	<0.001

Presented is the mean (SD) or absolute number (percentage), at the time of magnetic resonance imaging scan. Values are based on imputed data.

*P Value for differences in characteristics between women and men estimated using *t* test for continuous variables and χ^2 test for categorical variables.

more prevalent in men (lipid-rich necrotic core: 50.1%, and intraplaque hemorrhage: 37.0%) than in women (lipid-rich necrotic core: 38.2%, and intraplaque hemorrhage: 27.2%). The maximum plaque thickness was 3.6 mm on average (SD, 1.0) in men and 3.4 mm (SD, 0.8) in women. Stenosis of >30% was present in 17% of women and 19% of men. During a median follow-up of 4.8 years, 60 men and 48 women had incident ASCVD (incidence rate: 19.9 per 1000 person years among men, 15.7 per 1000 person years among women).

Based on traditional cardiovascular risk factors alone, among women, 24.7% were at low risk, 13.3% borderline, 40.0% intermediate, and 22.0% high-risk of ASCVD. Among men, 2.5% were at low risk, 4.6% borderline, 48.3% intermediate, and 44.6% high-risk (Figure 1).

Plaque Characteristics in Association With Incident ASCVD

In women, we found that intraplaque hemorrhage yielded a strong HR for incident ASCVD (adjusted HR for the presence of intraplaque hemorrhage: 3.37 [95% CI, 1.81–6.25]; Table 2). As shown in Table S1, intraplaque hemorrhage remained strongly associated with incident ASCVD after additionally expanding the model with carotid plaque thickness (HR, 3.79 [95% CI, 1.98–7.26]) and after simultaneous addition of all plaque

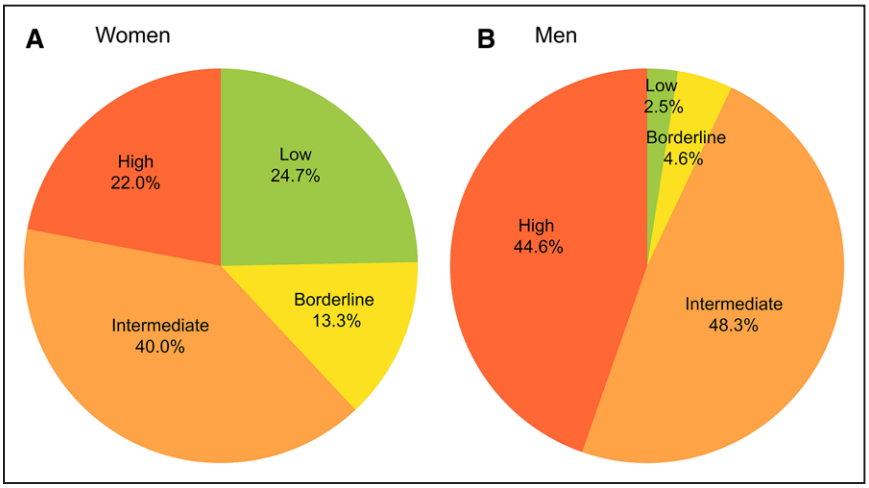

Figure 1. Distribution of the study population across 5-year atherosclerotic cardiovascular disease risk categories.
A, Risk distribution among women; (**B**) Risk distribution among men. Low-risk: <2.5%; borderline risk: 2.5% to <3.75%; intermediate risk: 3.75% to <10%; and high risk: 10% or higher.

Table 2. Association of Carotid Plaque Characteristics With Incident Atherosclerotic Cardiovascular Disease

			Risk of atherosclerotic cardiovascular disease
	n/N	Plaque characteristics	Hazard ratio (95% CI)
		Lipid-rich necrotic core	1.23 (0.68–2.21)
Women	48/668	Intraplaque hemorrhage	3.37 (1.81–6.25)
		Calcification	2.06 (0.72–5.89)
		Plaque thickness	1.05 (0.77–1.45)
		Stenosis >30%	1.58 (0.82–3.05)
		Lipid-rich necrotic core	0.84 (0.50–1.41)
Men	60/681	Intraplaque hemorrhage	1.67 (0.98–2.79)
		Calcification	0.79 (0.41–1.52)
		Plaque thickness	1.17 (0.95–1.45)
		Stenosis >30%	1.75 (1.00–3.08)

Associations are adjusted for age (restricted cubic spline), total cholesterol corrected for lipid-lowering medication use, high-density lipoprotein cholesterol, systolic blood pressure corrected for blood pressure lowering medication use, current smoking, and diabetes. n indicates number of participants with incident atherosclerotic cardiovascular disease; and N, total number for participants.

Table 3. Optimism-Corrected *C* Statistic for the Base Model and the Extended Models With Plaque Characteristics

	Women	Men
	Optimism-corrected *C* statistic (95% CI)	
Base model*	0.73 (0.66–0.79)	0.66 (0.59–0.72)
Base model+lipid-rich necrotic core	0.73 (0.66–0.79)	0.65 (0.60–0.71)
Base model+intraplaque hemorrhage	0.76 (0.70–0.83)	0.66 (0.60–0.72)
Base model+calcification	0.73 (0.67–0.80)	0.66 (0.60–0.72)
Base model+plaque thickness	0.73 (0.66–0.79)	0.65 (0.59–0.71)
Base model+stenosis >30%	0.73 (0.66–0.80)	0.65 (0.59–0.71)
Base model+lipid-rich necrotic core, intraplaque hemorrhage, calcification, plaque thickness, stenosis >30%	0.77 (0.71–0.83)	0.66 (0.60–0.72)

*Base model includes age (restricted cubic spline), total cholesterol corrected for lipid-lowering medication use, high-density lipoprotein cholesterol, systolic blood pressure corrected for blood pressure lowering medication use, current smoking, and diabetes.

characteristics (HR, 3.55 [95% CI, 1.80–6.99]). Among men, only >30% stenosis was statistically significantly associated with incident ASCVD (adjusted HR for the presence of >30% stenosis: 1.75 [95% CI, 1.00–3.08]; Table 2). This HR became nonsignificant after additionally adding plaque thickness (HR, 1.60 [95% CI, 0.86–2.98; Table S1). Interactions of plaque characteristics with sex were tested on the multiplicative scale. Only the interaction term of intraplaque hemorrhage with sex reached statistical significance (P=0.045). Restricting the analyses to participants not receiving lipid-lowering medication did not materially change the results (Table S2).

Discriminative Ability of Plaque Characteristics for ASCVD Risk Prediction

Table 3 shows the C statistics of the base model and the extended models. In women, single addition of intraplaque hemorrhage most substantially improved the discriminative ability of the model (*C* statistic improved from 0.73 to 0.76). Adding all plaque characteristics to the base model in women led to an improvement in *C* statistic from 0.73 to 0.77. In men, the discriminative ability of the base model did not improve after single additions of any plaque characteristic (Table 3).

Since intraplaque hemorrhage among women was the only predictor with a considerable discriminative ability based on the *C* statistic, we plotted the risk distributions according to the base− and base+ intraplaque hemorrhage model (Figure 2). Particularly among women without events, we observed a shift toward the left (lower risks) after expanding the base model with intraplaque hemorrhage. The category-free net reclassification improvement was 0.25 among events and 0.42 among nonevents. HRs for coronary heart disease and stroke as well as the *C* statistics after expansion of the base model with plaque components in the total population stratified by coronary heart disease and stroke, are shown in Table S3 and S4. Overall, the performances of the models were better for prediction of coronary heart disease than for stroke. Addition of intraplaque hemorrhage to the model led to an improvement in discriminative ability for prediction of both coronary heart disease and stroke.

DISCUSSION

In this population-based sample of asymptomatic individuals with carotid wall thickening, presence of carotid intraplaque hemorrhage was a robust predictor of incident ASCVD in women, beyond traditional cardiovascular risk factors, other plaque components, and stenosis. Our findings indicate that carotid intraplaque hemorrhage has the potential to be used as marker of systemic plaque vulnerability in clinical practice, particularly among women.

Over the recent years, there has been debate on the use of plaque size and luminal stenosis to predict the risk of cardiovascular events. Current guidelines for primary prevention of overall ASCVD do not recommend carotid imaging modalities, including intima-media thickness and stenosis, for enhancing ASCVD risk predictions.[2] Accumulating evidence highlights the shortcomings of using stenosis as sole imaging marker because, even with negligible luminal narrowing, carotid plaques are often present.[7] Our study extends on this by showing the added value of plaque components, in particular intraplaque hemorrhage among women, beyond carotid stenosis and traditional cardiovascular risk factors for the prediction of cardiovascular events. In men, intraplaque hemorrhage had no additional value compared with carotid stenosis for prediction of incident ASCVD.

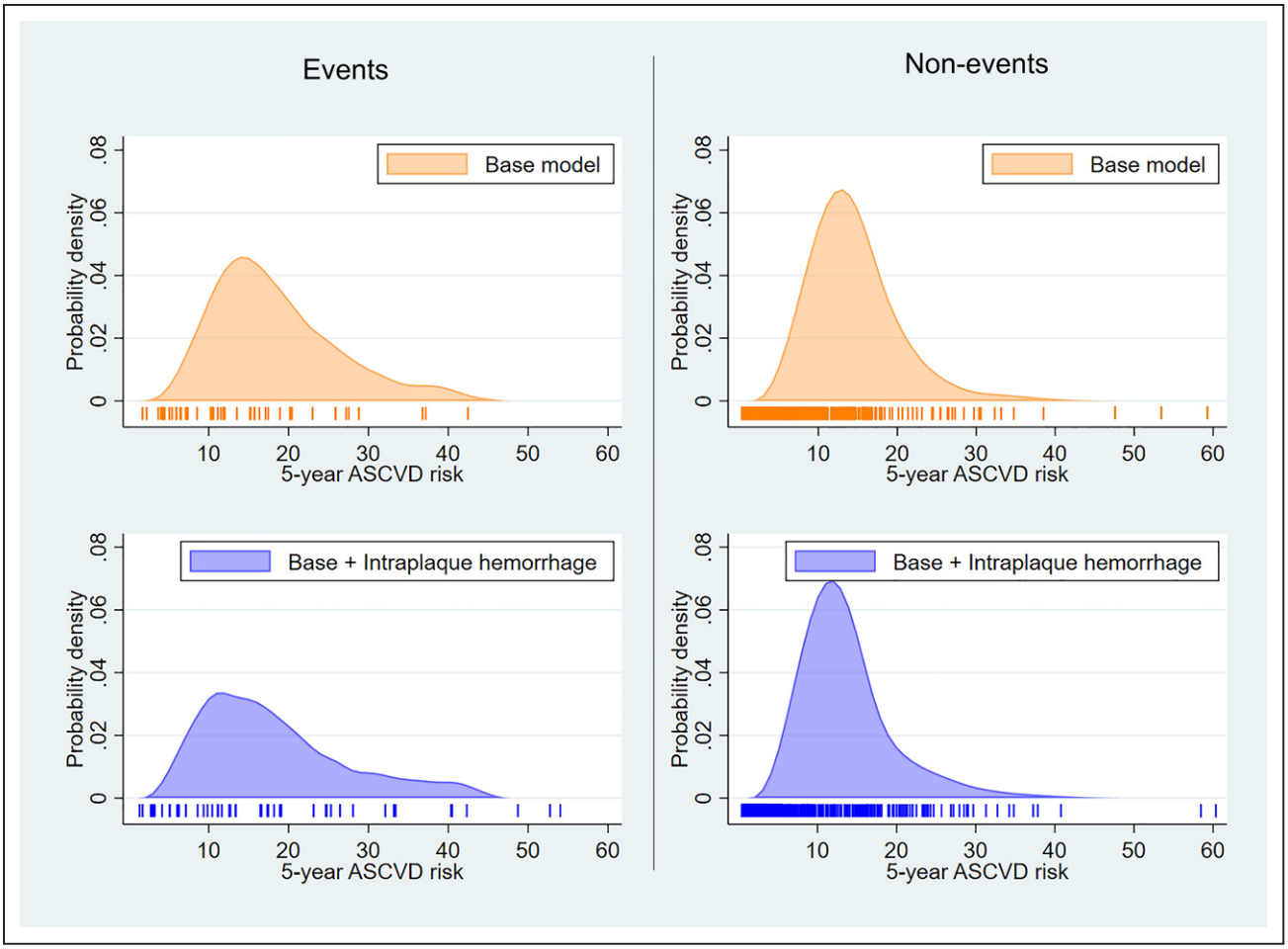

Figure 2. Risk distribution according to the base model and the extended model with intraplaque hemorrhage among women. The left represents the risk distributions for women who developed an atherosclerotic cardiovascular disease (ASCVD) event during follow-up; the right represents the risk distributions for women who did not develop an ASCVD event. The plots at the top show the risk distributions according to the base model. The plots at the bottom show the risk distributions according to the base+intraplaque hemorrhage model. Vertical stripes below each plot represent estimated 5-y ASCVD risks per individual.

It has been suggested that intraplaque hemorrhage is a consequence of intimal neovascularization by microvessels as a response on positive arterial remodeling, which could induce leakage of red blood cells, resulting into unstable plaque.[37] Intraplaque hemorrhage has been associated with cardiovascular events,[13,38–40] although its sex-specific value for the prediction of incident ASCVD has not been assessed. In contrast with our findings, previous research showed an association of intraplaque hemorrhage with cardiovascular events in men but not in women.[13,38] However, the limited number of previous studies on this topic were not prospective[13] or were performed among symptomatic patients.[38] The incidence rate of cardiovascular disease increases strongly with aging, particularly in women.[41] As such, the cross-sectional design of prior studies and differences in study populations, for example, with a lower age range than our population, may explain the previously reported nonsignificant associations of plaque components with cardiovascular disease in women. We observed that the prevalence of intraplaque hemorrhage and lipid-rich necrotic core was higher in men than in women. We may hypothesize that more men than women with an unfavorable cardiovascular risk profile already developed ASCVD and died before study entry. This highlights the importance of developing personalized risk prediction strategies.

In men, stenosis was associated with incident ASCVD, although the association attenuated after additional adjustments for plaque components. Although in women the association of stenosis with incident ASCVD did not reach statistical significance, the effect estimate was of similar magnitude in men and women. It has been shown that among persons with acute coronary syndrome, obstructive coronary artery disease is more prevalent in men than in women.[42] Our results suggest that the male-predominance of coronary artery obstruction cannot be extrapolated to the carotid arteries.

We did not find predictive value of lipid-rich necrotic core for ASCVD. It remains debatable whether lipid-rich necrotic core predicts plaque vulnerability and rupture. In line with our findings, previous histological research—among

patients who underwent endarterectomy—showed that intraplaque hemorrhage but not lipid-rich necrotic core was related to cardiovascular events.[40] It could be possible that lipid-rich necrotic core is a lower-risk feature than intraplaque hemorrhage. Yet, others show that lipid-rich necrotic core is associated with incident cerebrovascular events[43] and predicts plaque rupture.[44] However, these studies used volumetric measurements of lipid-rich necrotic core, which could explain the discrepancy with our results.

Likewise, the presence rather than volumetric assessment of plaque components may also explain why we did not find a statistically significant association of calcification with ASCVD, as micro-calcifications are likely to be associated with plaque rupture while macro-calcifications may result in stabilization of plaque.[45] However, although not statistically significant, calcification in women conferred an increased risk of ASCVD. Whether micro-calcifications could play a particular role in women needs to be further evaluated.

Interestingly within our sample of higher-risk individuals who were selected based on ultrasound-assessed carotid wall thickening, above one-third of women were classified as low- or borderline 5-year ASCVD risk, solely based on traditional cardiovascular risk factors. The majority of men (>90%) were classified as intermediate-or high 5-year ASCVD risk. This further adds to the debate regarding the efficiency of cardiovascular risk estimation tools based on traditional risk factors in women.[46] This also suggests that presence of carotid wall thickening provides a better reflection of an unfavorable cardiovascular risk profile in men than it does in women. Presence of intraplaque hemorrhage provided a category-free NRI of 0.25 and 0.42 among women with and without events, respectively, which implies that intraplaque hemorrhage has potential to appropriately reclassify ASCVD risk in women. However, the clinical utility remains to be assessed given that the continuous NRI does not take into account the magnitude of a correct movement and is thus susceptible to small changes in estimated risks. As our study population was enrolled based on asymptomatic carotid wall thickening, it already reflects a high risk group. Hence, assessing NRI based on guideline suggested risk thresholds for primary prevention might not be optimally clinically relevant. Nevertheless, our findings point toward the potential of MRI assessment of carotid plaque components, in particular, carotid intraplaque hemorrhage, as a tool to optimize personalized clinical decision-making. In this regard, information on carotid intraplaque hemorrhage may complement currently available risk stratification tools. Our findings also suggest assigning more weight to the presence of intraplaque hemorrhage in women when calculating individual risks. Further research is needed to assess the ability of plaque components for ASCVD reclassification, in light of clinically relevant risk categories.

Strengths of our study include the large sample that underwent MRI and detailed cardiovascular risk factor assessment and the accurately adjudicated cardiovascular events during the follow-up period. There are also some limitations to address. First, we only assessed the presence of plaque components whereas volumetric measurements of these components would provide more insight into the extent of the atherosclerotic burden. Second, we lacked statistical power to stratify by both sex and disease entity. Sex-specific differences in stroke and coronary heart disease rates may be partly explained by delayed onset of carotid intraplaque hemorrhage in women.[47] Further studies should determine the sex-specific value of plaque components, including intraplaque hemorrhage, for prediction of coronary heart disease and stroke as separate entities.

CONCLUSIONS

In our sample of individuals with asymptomatic carotid wall thickening, carotid intraplaque hemorrhage as proxy for the systemic burden of atherosclerosis, was a strong predictor of incident ASCVD in women, independent of other plaque components, plaque size, and stenosis. Particularly in women, it is important to look beyond traditional cardiovascular risk factors and carotid lumen while developing strategies for cardiovascular disease prevention.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S4

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