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Atherosclerotic Carotid Plaque Composition and Incident Stroke and Coronary Events

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ABSTRACT

BACKGROUND Increasing evidence suggests that atherosclerotic plaque composition rather than plaque size is linked to ischemic cardiovascular events, yet largescale population-based data in asymptomatic individuals remain scarce.

OBJECTIVES This study sought to investigate carotid plaque composition in relation to incident stroke and coronary heart disease (CHD) in a population-based setting.

METHODS Between 2007 and 2012, 1,349 persons (mean age 72 years, 49.5% women) from the population-based Rotterdam Study who were free from a history of stroke or CHD, in whom carotid ultrasonography showed subclinical atherosclerosis, and who underwent high-resolution magnetic resonance imaging of the carotid arteries to assess plaque characteristics. These included the presence of specific plaque components (intraplaque hemorrhage [IPH], lipid-rich necrotic core, and calcification), and measures of plaque size (maximum plaque thickness and presence of stenosis of more than 30%). Individuals were continuously followed for the occurrence of stroke or CHD until January 1, 2015. The authors used Cox regression models to assess the association of the plaque characteristics with the incidence of stroke and CHD, with adjustments for age, sex, and cardiovascular risk factors.

RESULTS During a median of 5.1 years' follow-up for stroke and 4.8 years for CHD, 51 individuals had a stroke and 83 developed CHD. Independent of maximum plaque thickness and cardiovascular risk factors, the presence of IPH was associated with incident stroke and CHD (fully adjusted hazard ratio: 2.42 [95% confidence interval: 1.30 to 4.50], and 1.95 [95% confidence interval: 1.20 to 3.14]). Presence of a lipid-rich necrotic core and calcification were not associated with stroke or CHD.

CONCLUSIONS The presence of IPH in the carotid atherosclerotic plaque is an independent risk factor for stroke and CHD. These findings indicate the promise of IPH as a marker of plaque vulnerability in healthy persons with subclinical atherosclerosis. (J Am Coll Cardiol 2021;77:1426–35) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Ischemic cardiovascular disease, comprising coronary heart disease (CHD) and stroke, remains the top cause of morbidity and mortality worldwide (1). Within the etiological framework of these diseases, atherosclerosis is firmly established as the culprit for causing the clinical events (1). The size of the atherosclerotic plaque and the accompanying luminal narrowing have long been the center of research on the role of atherosclerosis in ischemic cardiovascular disease (2). Yet, improvements in the

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capability of in vivo imaging of atherosclerosis, especially using magnetic resonance imaging (MRI), provided important novel insights suggesting that the vulnerability of an atherosclerotic plaque is more dependent on its composition than on its size or the extent of luminal narrowing (3–5). In this light, studying atherosclerosis in the carotid artery bifurcation has proven instrumental because of several reasons. First, the carotid artery bifurcation is easily accessible for imaging. Second, atherosclerosis in the carotid artery bifurcation plays a paramount role in the development of ischemic stroke (6,7). Third, the composition of atherosclerosis in the carotid bifurcation shows a high correlation with plaque composition in the coronary arteries (8–10), for which detailed imaging is complicated by the small size of the arteries and cardiac motion (11).

Against this background, intraplaque hemorrhage (IPH) and a lipid-rich necrotic core (LRNC) have been shown to increase plaque vulnerability (4,12,13). IPH and LRNC are more prevalent in patients with a history of ischemic cardiovascular disease (14) and associated with an increased risk of recurrent stroke and CHD (8,15,16). However, our understanding of the role of plaque components in first-ever clinical manifestations of cardiovascular disease in asymptomatic persons with subclinical atherosclerosis remains limited, as was explicitly highlighted by a recent meta-analysis (17). Such data may contribute to establishing the position of the imaging assessment of plaque composition in cardiovascular disease pathophysiology and may guide the development of strategies for its primary prevention.

In a prospective population-based setting, among subjects with asymptomatic carotid wall thickening determined by ultrasonography, we determined the association of carotid plaque characteristics, assessed by MRI, with incident stroke and CHD events.

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METHODS

SETTING. The study was embedded within the Rotterdam Study, a prospective, population-based study among subjects ≥45 years of age, aimed at investigating determinants of various chronic diseases (18). At regular intervals (3 to 5 years), all participants are invited to undergo follow-up examinations at the research center, which also include carotid ultrasonography to assess carotid intima-media thickness (IMT; measured as the maximum distance between the near and far walls) (19). Between the years 2007 and 2012, 2,666 participants with an IMT larger than 2.5 mm in 1 or both carotid arteries on ultrasonography were invited to undergo an MRI examination of the carotid arteries to further investigate carotid atherosclerosis. The median time between the carotid ultrasound and the MRI was 2.7 months (range 1.4 to 3.5 months).

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus Medical Center (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 and into the World Health Organization International Clinical Trials Registry Platform 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.

ABBREVIATIONS AND ACRONYMS

3D = 3-dimensional
CHD = coronary heart disease
CI = confidence interval
EPI = echo planar imaging
FSE = fast spin echo
HR = hazard ratio
IMT = intima media thickness
IPH = intraplaque hemorrhage
LRNC = lipid-rich necrotic core
MI = myocardial infarction
MRI = magnetic resonance imaging
PDw = proton density-weighted
T1w = T1-weighted
T2w = T2-weighted

ASSESSMENT OF CAROTID ATHEROSCLEROTIC PLAQUE. MRI of the carotid arteries was performed on a 1.5-T MR scanner (GE Healthcare, Milwaukee, Wisconsin) with a bilateral phased-array surface coil (Machnet, Eelde, the Netherlands) (20). Subjects were stabilized in a custom-designed head pouch to reduce motion artefacts. High-resolution images were obtained using a previously described standardized protocol (20). In brief, both carotid bifurcations were identified by means of 2-dimensional time of flight MR angiography after which the following high-resolution MRI sequences were obtained: a proton density-weighted (PDw) fast spin echo (FSE) black-blood (PDw-FSE-BB) sequence; a PDw-FSE-BB with an increased in-plane resolution; a PDw-echo planar imaging (EPI) sequence; a T2-weighted (T2w)-EPI sequence; a 3-dimensional (3D) T1-weighted (T1w)-gradient echo (GRE) sequence; and 3D phase-contrast MR angiography.

First, we visually assessed plaque composition by evaluating the presence of IPH, LRNC, and calcification using a standardized evaluation protocol. IPH was defined as the presence of a hyperintense region in the atherosclerotic plaque on 3D-T1w-GRE (20–22). LRNC presence was defined as an hypointense region, not classified as IPH or calcification, in the plaque on PDw-FSE or PDw-EPI and T2w-EPI images, or a region of relative signal intensity drop in the T2w-EPI images compared with the PDw-EPI images (12,20,23–25). Calcification was defined as the presence of a hypointense region in the plaque on all sequences (12,20,24). Subjects were recorded as positive for the presence of a plaque component if the component was identified in 1 or both carotid arteries.

Second, we assessed carotid plaque size by obtaining maximum plaque thickness and degree of luminal stenosis using the NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria (2) on the PDw-FSE images. For the analyses, we used the largest plaque thickness and stenosis per individual.

All scans were reviewed for plaque characteristics by trained observers who were blinded to all participant characteristics, overseen by an experienced neuroradiologist. In cases of doubt or disagreement, the judgment of the neuroradiologist was considered definite. Detailed information on intrasubject and interobserver reliability (Cohen's κ values ranging from 0.85 to 0.95) have been reported previously (20).

ASSESSMENT OF STROKE. The definition of stroke was based on the World Health Organization criteria (26). History of stroke was assessed at baseline and verified by reviewing medical records. After enrollment, participants were continuously monitored for incident stroke through linkage of the study databases with medical records from general practitioners. Also, nursing home physicians' records and records from the general practitioners of participants that moved out of the district were checked on a regular basis. All potential strokes were reviewed by research physicians and verified by an experienced stroke neurologist (26). All participants were followed for incident stroke until January 1, 2015.

ASSESSMENT OF CHD. The definitions and procedures of the adjudication of CHD have been described in detail previously (27). Incident CHD was defined as fatal or nonfatal myocardial infarction (MI), CHD mortality (mortality from definite MI, definite fatal CHD, and possible fatal CHD), or surgical or percutaneous coronary revascularization procedure (as a proxy for unstable or incapacitating angina) (27). For CHD mortality, in brief, definite fatal MI was defined as no known nonatherosclerotic cause and definite MI within 28 days of death. Definite fatal CHD was defined as no known nonatherosclerotic cause, and at least 1 of the following: cardiac pain within 72 h of death, or a history of ischemic heart disease in the absence of significant valvular heart disease or nonischemic cardiomyopathy. Possible fatal CHD was defined as no known nonatherosclerotic cause and mode of death consistent with CHD in the absence of significant valvular heart disease or nonischemic cardiomyopathy (27). All participants were followed for incident CHD until January 1, 2015.

OTHER MEASUREMENTS IN THE ROTTERDAM STUDY. We collected detailed information on cardiovascular risk factors and medication use by interview, physical examination, and blood sampling (18).

TABLE 1 Baseline Characteristics of Study Participants (N = 1,349)

Female	668 (49.5)
Age, yrs	72.3 ± 9.3
Body mass index, kg/m^2	27.2 ± 3.7
Systolic blood pressure, mm Hg	145 ± 21
Diastolic blood pressure, mm Hg	81 ± 11
Use of blood pressure-lowering medication	475 (35.2)
Diabetes mellitus	231 (17.1)
Serum total cholesterol, mmol/l	5.8 ± 1.0
Serum HDL cholesterol, mmol/l	1.4 ± 0.4
Use of lipid-lowering medication	224 (26)
Use of lipid antithrombotic medication	225 (17.0)
Current smokers	291 (21.6)

Values are n (%) or mean ± SD. Data represent original data without imputed values. Missing values were present for body mass index (4.0%), blood pressure (3.5%), total cholesterol (4.7%), HDL cholesterol (4.7%), lipid-lowering medication (4.4%) blood pressure–lowering medication (2.4%), and smoking (2.9%).
HDL = high-density lipoprotein.

Body mass index was calculated based on weight in kilograms divided by height in meters squared. We measured systolic and diastolic blood pressure twice using a random-zero sphygmomanometer on the right arm and used the average of the measurement in the analyses. From blood samples, we measured serum total cholesterol and high-density lipoprotein cholesterol using an automatic enzymatic procedure (Hitachi analyzer, Roche Diagnostics, Risch-Rotkreuz, Switzerland). Glucose was determined enzymatically by the hexokinase method. Diabetes mellitus was defined as fasting serum glucose levels ≥7.0 mmol/l (or nonfasting serum glucose levels ≥11.1 mmol/l if fasting samples were unavailable) or use of antidiabetic therapy. Using questionnaires, we assessed information on the use of blood pressure-lowering medication, antithrombotic medication and lipid-lowering medication. Smoking status was categorized into never, former, and current smoking.

POPULATION FOR ANALYSIS. From the 2,666 participants that were invited to undergo a carotid MRI examination, 684 participants did not undergo scanning (claustrophobia [n = 57], physical limitations [n = 191], MRI contraindications [n = 115], refusal to participate [n = 272], and no show or lost to follow-up [n = 49]), leaving 1,982 participants. From these, another 242 were excluded due to poor image quality (n = 95), scan interruption due to claustrophobia (n = 106), or absence of plaque in both carotid arteries (n = 41), leaving 1,740 participants with a complete carotid MRI examination. From these, we excluded those with prevalent stroke, CHD, or incomplete follow-up information (n = 391), resulting in 1,349 persons for the current analyses. The end date for

follow-up was defined as the date of stroke or CHD, date of death, date of last follow-up visit, or January 1, 2015, whichever came first.

STATISTICAL ANALYSIS. We explored the differences in population characteristics of the individuals that were eligible for carotid MRI, but not in the current study, with the current study participants, by means of Student's *t*-tests for continuous variables and chi-square tests for dichotomous variables.

We recorded the prevalence of plaque characteristics (plaque composition and plaque size) and investigated coexistence of plaque components by creating new variables that coded for the specific combinations of plaque components (IPH with LRNC, IPH with calcification, LRNC with calcification, and a combination of all 3 components).

We investigated the associations of carotid plaque characteristics with incident stroke and incident CHD using the following strategy. First, we examined the association of the presence of the separate plaque components (IPH, LRNC, calcification) with incident stroke and CHD using 3 Cox-regression models. The first model was an unadjusted model. The second model (model 2) was adjusted for age, sex, and maximum plaque thickness (in order to correct for plaque size). The third model (model 3) was additionally adjusted for body mass index, systolic and diastolic blood pressure, use of blood pressure–lowering medication, diabetes mellitus, total cholesterol, high-density lipoprotein cholesterol, use of lipid-lowering medication, and smoking status. Second, we focused on the association of plaque size (maximum plaque thickness and presence of stenosis of more than 30%) with stroke and CHD using the similar models, yet without maximum plaque thickness as a covariable. Next, we created a fourth Cox regression model (model 4) in which age, sex, IPH, LRNC, calcification, maximum plaque thickness, and stenosis >30% were entered simultaneously to investigate the mutual coherence of the characteristics with regard to incident stroke and CHD. We also calculated the C-statistic (28) to determine the added discriminative value of plaque characteristics that were statistically significantly associated with incident stroke and CHD, above the risk factors included in model 3.

Fourth, we compared the cumulative incidence of stroke and CHD between persons with and without each of the plaque components using the Kaplan-Meier method and log-rank test. Finally, using the abovementioned variables, we investigated associations of coexistent plaque components with incident stroke and CHD using the same models as highlighted under the first step. We also performed 2 sensitivity analyses. First, on the basis of previous evidence on the importance of IPH in stroke incidence, we further focused on the presence of unilateral and bilateral IPH, and investigated incident stroke and CHD accordingly. Second, we repeated all analyses for stroke, restricted to ischemic strokes only.

Missing values in the covariables (up to 4.7%) were handled by a multiple imputation algorithm (n = 5). All analyses were performed with IBM SPSS Statistics version 25.0 software (IBM Corp, Armonk, New York), and SAS version 9.4 software (SAS Institute, Cary, North Carolina).

TABLE 2 Carotid Plaque Characteristics in 1,349 Study Participants

Plaque size	
Maximum plaque thickness, mm	3.5 ± 0.9
Stenosis >30%*	243 (18.0)
Presence of components	
Intraplaque hemorrhage	434 (32.2)
Lipid-rich necrotic core	596 (44.2)
Calcification	1087 (80.6)
Presence of coexistent components	
Intraplaque hemorrhage + lipid-rich necrotic core	253 (18.8)
Intraplaque hemorrhage + calcification	405 (30.0)
Lipid-rich necrotic core + calcification	489 (36.2)
Intraplaque hemorrhage + lipid-rich necrotic core + calcification	233 (17.3)

Values are mean ± SD or n (%). *Measured according to the NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria.

RESULTS

The mean age of the study population was 72.3 years, and 49.5% of population were women (Table 1). Participants of the current study were on average younger and had a more favorable cardiovascular risk factor profile than participants who were eligible for carotid MRI, but not included in the current sample (Supplemental Table 1). The mean of the maximum plaque thickness was 3.5 mm, and a carotid artery stenosis of more than 30% was present in 18% of the participants. A stenosis degree of more than 50% was found in 5.7% of the participants, and an asymptomatic vessel occlusion in 1.3%. The most prevalent plaque component was calcification (80.6%), followed by LRNC (44.2%) and IPH (32.2%) (Table 2). In terms of coexistence of plaque components, a combination of LRNC with calcification was most frequently observed (36.2%). The coexistence of all 3 components was the least common combination (17.3%).

CAROTID PLAQUE CHARACTERISTICS AND INCIDENT STROKE AND CHD. During 6,429 person-years of follow-up for stroke (median 5.1 years) and 6,125 person-years for CHD (median 4.8

TABLE 3 Carotid Plaque Characteristics and the Risk of Stroke and CHD

	Stroke (n/N = 51/1,349)				Coronary Heart Disease (n/N = 83/1,349)			
	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
Presence of plaque components*								
Intraplaque hemorrhage	2.95 (1.63–5.32)	2.41 (1.31– 4.44)	2.42 (1.30–4.50)	2.46 (1.29–4.69)	2.48 (1.56–3.93)	2.18 (1.35– 3.51)	1.95 (1.20–3.14)	2.11 (1.27–3.48)
Lipid-rich necrotic core	0.94 (0.53–1.67)	0.94 (0.53–1.67)	0.92 (0.51–1.66)	0.82 (0.46–1.47)	1.11 (0.71–1.74)	1.04 (0.66–1.62)	1.08 (0.68–1.70)	0.92 (0.59–1.44)
Calcification	1.31 (0.61–2.81)	0.97 (0.44–2.11)	0.87 (0.39–1.94)	0.78 (0.35–1.76)	1.10 (0.63–1.94)	0.97 (0.55–1.74)	0.85 (0.47–1.56)	0.84 (0.46–1.52)
Plaque size								
Maximum plaque thickness, per mm increase	1.25 (0.98–1.59)	1.23 (0.97–1.57)	1.20 (0.94–1.53)	1.04 (0.77–1.41)	1.24 (1.02–1.50)	1.18 (0.97–1.43)	1.15 (0.94–1.39)	0.95 (0.75–1.21)
Presence of stenosis >30%	1.96 (1.08–3.59)	1.85 (1.01–3.38)	1.77 (0.95–3.27)	1.40 (0.70–2.77)	2.30 (1.45–3.63)	2.19 (1.38–3.47)	1.92 (1.21–3.06)	1.88 (1.11–3.17)

Values are hazard ratio (95% confidence interval). n/N indicates the number of cases/number of persons at risk. Model 1: Unadjusted. Model 2: Adjusted for age and sex. Model 3: Adjusted for age, sex, body mass index, systolic and diastolic blood pressure, use of blood pressure–lowering medication, diabetes mellitus, total cholesterol, high-density lipoprotein cholesterol, use of lipid-lowering medication, and smoking status. Model 4: All plaque characteristics entered together, adjusted for age and sex. *For analyses on the plaque components, maximum plaque thickness was included in models 1 and 2 to correct for plaque size.

years), 51 participants suffered from a stroke (incidence rate 7.9 per 1,000 person-years), and 83 developed CHD (incidence rate 13.6 per 1,000 person-years). Supplemental Table 2 shows the incidence rates of stroke and CHD according to the presence or absence of the plaque components. The follow-up for stroke and CHD was virtually complete (95.2% and 94.9%, respectively).

Table 3 describes the associations of the plaque characteristics with incident stroke and CHD. We found that the presence of IPH was associated with incident stroke (hazard ratio [HR]: 2.42; 95% confidence interval [CI]: 1.30 to 4.50) and CHD (HR: 1.95; 95% CI: 1.20 to 3.14), independent of cardiovascular risk factors (**Table 3**). We found no associations of LRNC or calcification with the incidence of stroke or CHD. With regard to measures of plaque size, we found that a stenosis of more than 30% was associated with incident CHD (HR: 1.92; 95% CI: 1.21 to 3.06), independent of cardiovascular risk factors (**Table 3**). We found no statistically significant associations between maximum plaque thickness and stroke or CHD incidence. After entering all plaque characteristics simultaneously into 1 model, we found that IPH remained statistically significantly associated with incident stroke (HR: 2.46; 95% CI: 1.29 to 4.69) and CHD (HR: 2.11; 95% CI: 1.27 to 3.48). As IPH was the single plaque component that was associated with both stroke and CHD, we investigated the additive discriminative value of IPH above the variables included in model 3. Adding IPH improved the discrimination for stroke and for CHD (C-statistic from 0.67 [95% CI: 0.60 to 0.75] to 0.70 [95% CI: 0.62 to 0.78] for stroke, and from 0.72 [95% CI: 0.67 to 0.78] to 0.74 [95% CI: 0.68 to 0.79 for CHD]).

Kaplan-Meier analyses for the cumulative incidence of stroke and CHD according to plaque components showed that the cumulative incidence for both were significantly higher for persons with IPH (**Figure 1, Central Illustration**). No significant differences were found for the presence or absence of LRNC or calcification.

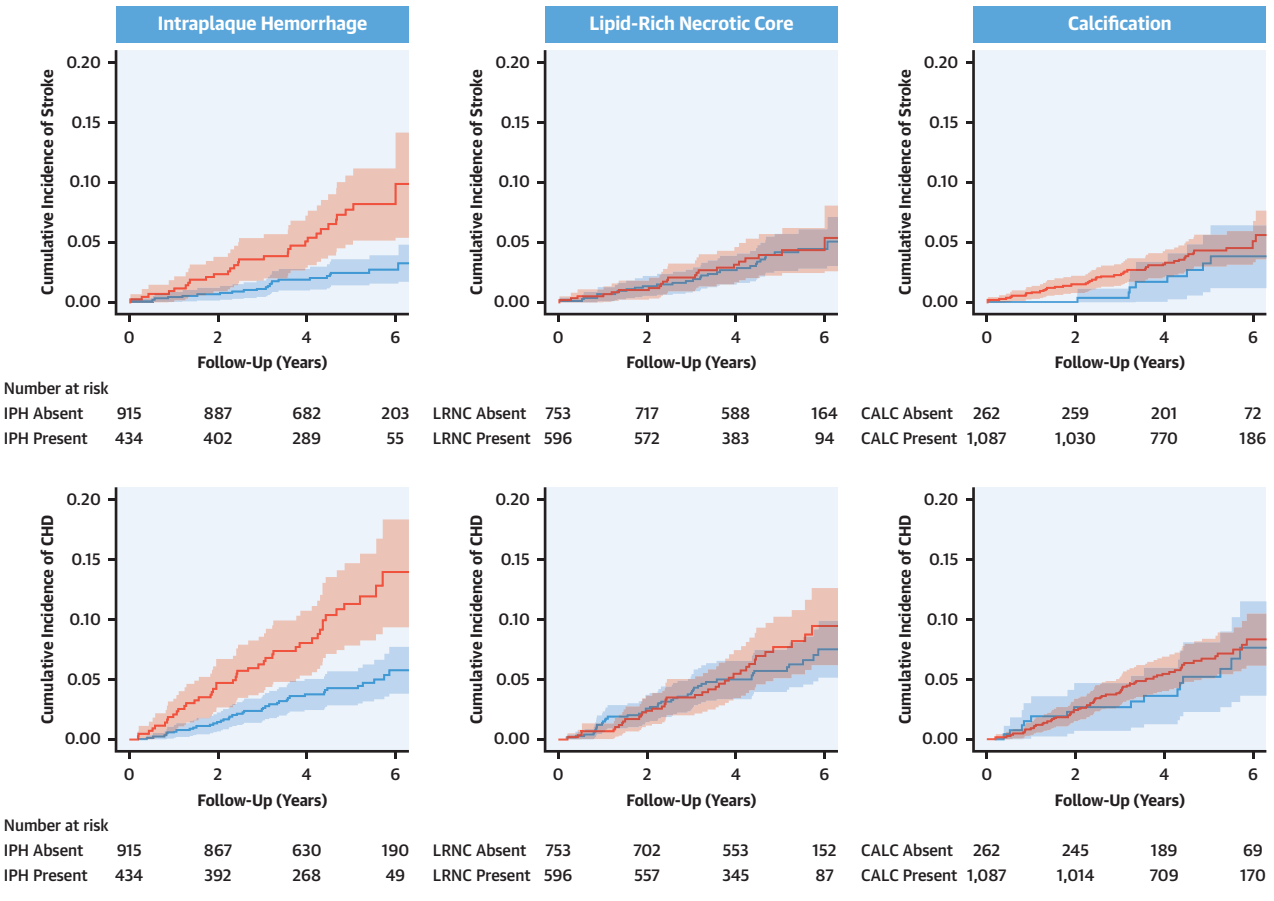
In terms of the coexistence of carotid plaque characteristics and the incidence of stroke and CHD, we found that the combination of IPH and calcification was consistently associated with incident stroke (HR: 2.18; 95% CI: 1.18 to 4.05) and CHD (HR: 1.65; 95% CI: 1.02 to 2.68), whereas the combination of IPH and LRNC was associated with incident CHD only (HR: 1.68; 95% CI: 1.01 to 2.77) (Supplemental Table 3).

Our sensitivity analysis focusing on the association of IPH with stroke and CHD, according to the presence of unilateral and bilateral IPH, revealed that individuals with bilateral IPH are more likely to suffer a stroke or CHD than those without IPH or unilateral IPH (HR: 4.37 [95% CI: 1.86 to 10.24] for stroke, and 2.20 [95% CI: 1.08 to 4.51 for CHD]) (Supplemental Table 4). After restricting the analyses on stroke to ischemic strokes only (n = 39), the results did not change (Supplemental Table 5).

DISCUSSION

In this large population-based sample of individuals with asymptomatic carotid artery atherosclerosis, we found that IPH is associated with new-onset stroke and CHD, independent of cardiovascular risk factors or other plaque characteristics. Compared with individuals without IPH, individuals with IPH were 2

FIGURE 1 Kaplan-Meier Curves for the Cumulative Incidence of Stroke and CHD



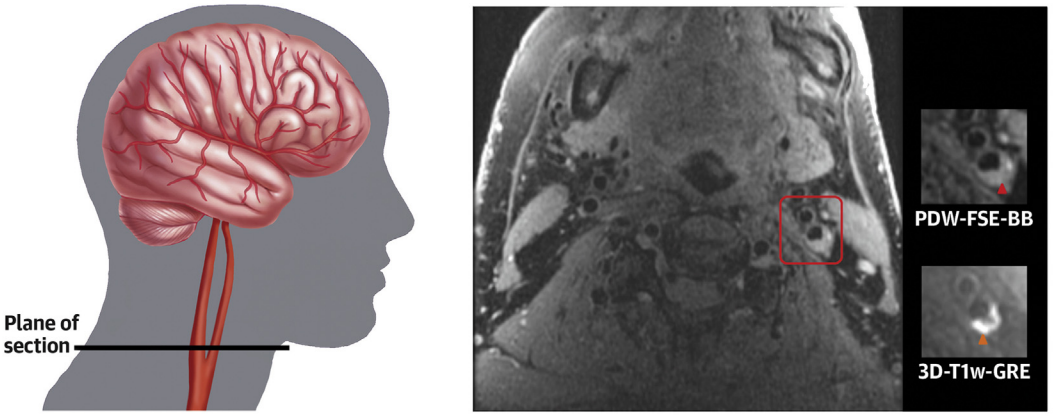
Kaplan-Meier curves for the cumulative incidence of stroke and coronary heart disease according to plaque components. Kaplan-Meier plots for the cumulative incidence of stroke and CHD according to the absence (**blue lines**, with 95% confidence interval) or presence (**red lines**, with 95% confidence interval) of the 3 different plaque components. The difference in cumulative incidence of stroke and CHD between the absence and presence of IPH was statistically significant as determined by the log-rank test ($p < 0.001$). CALC = calcification; CHD = coronary heart disease; IPH = intraplaque hemorrhage; LRNC = lipid-rich necrotic core.

times more likely to develop either stroke or CHD within 5 years, which was higher than what we found for any of the other plaque characteristics. Our findings indicate the promise of IPH as a marker of plaque vulnerability even in persons with asymptomatic atherosclerotic disease.

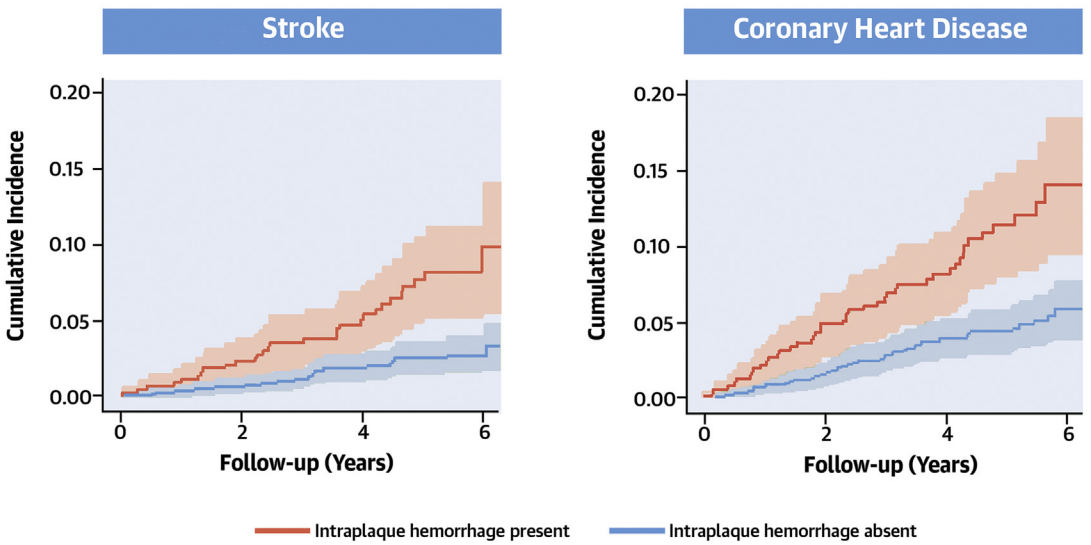
IPH is thought to be a consequence of leakage of erythrocytes from dysfunctional microvessels in the atherosclerotic plaque (29,30). This process of leakage of erythrocytes attracts macrophages into the plaque, which creates a highly reactive environment that again triggers the formation of novel immature intraplaque microvessels that further destabilize the plaque (30). We found a strong association of IPH with incident stroke. Interestingly, the stroke and CHD events seemed to be evenly distributed across the follow-up period, which requires further investigation. Over the years, several studies have established the importance of IPH as a risk factor for stroke in patients with symptomatic carotid artery stenosis, and as a risk factor for stroke recurrence (13,15–17,31). Our results extend these findings by showing evidence that even in asymptomatic individuals with nonstenotic or low-grade stenotic carotid artery atherosclerosis, IPH is the most important risk factor for developing a first-ever stroke. Interestingly, we also found an association between IPH and incident CHD. This is likely explained by earlier findings that highlighted that the presence of vulnerable properties of plaques (including the presence of intraplaque hemorrhage) within an individual is indicative of vulnerable plaques across the whole arterial system within that individual (32). Specifically for the carotid and coronary arteries, it has been

CENTRAL ILLUSTRATION **Carotid Intraplaque Hemorrhage Increases the Risk of Stroke and Coronary Heart Disease**

Intraplaque Hemorrhage on Carotid MRI



Intraplaque Hemorrhage and Incident Stroke and Coronary Events



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The presence of intraplaque hemorrhage in carotid atherosclerotic plaque as detected by MRI is associated with a higher incidence of stroke and CHD (**red lines** in the survival curves). The large MRI slice shows a cross section of the neck with the carotid arteries at both sides (a proton density–weighted fast spin echo black-blood [PDw-FSE-BB] sequence). The **red square** indicates the carotid artery bifurcation with the presence of plaque in the left internal carotid artery. The **magnified images** show atherosclerotic disease (thickening of the arterial wall, **red triangle**) with the presence of intraplaque hemorrhage **(orange triangle)**. The dedicated 3D-T1w-GRE sequence **(lower image)** clearly shows intraplaque hemorrhage as hyperintense **(white)** region in the plaque **(orange triangle)**.
3D = 3-dimensional; CHD = coronary heart disease; GRE = gradient echo; T1w = T1-weighted.

demonstrated that vulnerable plaque phenotypes commonly co-occur (8,9).

We found no associations of LRNC or calcification with the risk of stroke or CHD. Especially for LRNC, its exact role in plaque vulnerability remains questionable. Histopathological work on carotid specimen from patients undergoing carotid endarterectomy (33) showed an association of the presence of IPH, but not of the presence of LRNC, with plaque vulnerability. Others highlighted that specifically the size of the LRNC rather than the presence is linked with plaque vulnerability (6,34), which may explain the discrepancy with our results because we only assessed the presence of LRNC. With regard to calcification, our finding of no prominent associations with the risk of stroke or CHD corroborates the notion that macrocalcifications may result in more stable atherosclerotic plaques (35,36). Interestingly, when investigating the coexistence of different plaque components, we found that the combination of IPH with calcification contributed most prominently to the risk of stroke and CHD. This finding underlines the hypothesis of a complex interaction between IPH and calcifications in the atherosclerotic plaque (37,38). Increasing evidence suggests that smaller, superficial calcifications are associated with more IPH and thus linked to increased plaque vulnerability (39). Unfortunately, we were not able to differentiate between different types of calcification in our study, but the link between calcification morphology and plaque vulnerability is an important topic that requires further research.

Over the last years, there has been growing criticism on the use of markers of plaque size, especially IMT, plaque thickness, and degree of stenosis, to estimate one's risk of a cardiovascular event. Our results further fuel this debate by highlighting that plaque thickness did not associate with incident stroke or CHD and that a stenosis of more than 30% was only associated with incident CHD. An important consideration about these markers of plaque size, in particular of stenosis, is that it only captures plaques that induce luminal narrowing. However, many arteries with plaques only show outward remodeling and will never reach a degree of luminal narrowing that will be regarded as clinically significant (40). Yet, these plaques may very well display vulnerable characteristics such as IPH and be at risk of rupture. In that light, it is important to re-emphasize the value of IPH as an independent risk factor for stroke and CHD, even in persons with nonstenotic subclinical carotid artery disease. Future studies on MRI-based assessments of IPH may specifically add considerable clinical value if these would be focusing on investigating the role of different plaque characteristics as assessed on different modalities, including MRI, computed tomography, and ultrasound, to obtain optimal predictive value at high cost-effectiveness.

STUDY STRENGTHS AND LIMITATIONS. Strengths of our study are the large population-based sample, the accurate follow-up procedures for incident stroke and CHD, and the relatively long follow-up time. Moreover, we used a dedicated MRI sequence for intraplaque hemorrhage detection that had a high interobserver agreement, sensitivity, and specificity (41,42). There are also some limitations that need to be discussed. First, a lipid core is more optimally detected with a contrast-enhanced MRI sequence. Given our population-based approach, we were not able to administer a contrast agent. Yet, the non-contrast-enhanced sequences we used were shown to have good accuracy in validation studies (12,24). Second, we only assessed the presence or absence of plaque components, whereas volumetric assessments of the 3 components may provide more detailed information. Nonetheless, the relatively simple assessment of whether IPH is present already provides crucial information on the risk of cardiovascular events. Third, the current sample consists of people with established atherosclerosis (IMT of at least 2.5 mm in 1 or both carotid arteries as determined by ultrasonography), which precludes generalizability to persons with a lesser extent of carotid atherosclerotic disease. However, selecting participants who were free of cardiovascular disease and with a rather small increase in IMT (2.5 mm) provided us with the unique opportunity to obtain a large sample of people with subclinical atherosclerosis in different stages of the disease.

CONCLUSIONS

The presence of IPH in the carotid atherosclerotic plaque is an independent risk factor for stroke and CHD. Our findings indicate the promise of IPH as marker of plaque vulnerability in healthy persons with subclinical atherosclerosis.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: MRI-detected intraplaque hemorrhage in patients with carotid atherosclerosis is a strong, independent risk factor for stroke and coronary events, even in those with non-stenotic subclinical carotid disease.

TRANSLATIONAL OUTLOOK: Further studies should focus on applications of carotid MRI to select patients likely to benefit most from interventions for stroke prevention.

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KEY WORDS carotid atherosclerosis, coronary heart disease, epidemiology, imaging, MRI, stroke

APPENDIX For supplemental tables, please see the online version of this paper.