Carotid Atherosclerotic Plaque Characteristics on Magnetic Resonance Imaging Relate With History of Stroke and Coronary Heart Disease

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Background and Purpose—Because atherosclerosis is a systemic disease, presence and composition on 1 location may relate to ischemic events in distant locations. We examined whether carotid atherosclerotic wall thickness, stenosis, and plaque composition are related to history of ischemic stroke and coronary heart disease (CHD).

Methods—From the population-based Rotterdam Study, 1731 asymptomatic participants (mean age, 72.4±9.1 years; 55% males) underwent magnetic resonance imaging of both carotid arteries. We assessed carotid wall thickness, stenosis and plaque composition, that is presence of intraplaque hemorrhage, lipid, and calcification. History of ischemic stroke and CHD was assessed until date of magnetic resonance imaging. The study was approved by the institutional review board, and all participants gave informed consent. Logistic regression analyses adjusted for age and traditional cardiovascular risk factors were used to study sex-specific associations between plaque characteristics and clinical events.

Results—We found that both carotid stenosis and intraplaque hemorrhage were associated with ischemic stroke in men but not in women (men: odds ratio [OR] for stenosis [per 10% increase]: 1.17 [95% CI, 1.06–1.30] and for intraplaque hemorrhage 2.39 [95% CI, 1.32–4.35]). In both men and women, carotid stenosis was associated with CHD (men: OR per 10% increase 1.12 [95% CI, 1.04–1.21] and women: OR, 1.17 [95% CI, 1.03–1.34]) and carotid wall thickness was associated with CHD (men: OR, 1.20 [95% CI, 1.03–1.39] and women: OR, 1.21 [95% CI, 0.88–1.65]). None of the plaque components was associated with CHD.

Conclusions—Whereas carotid plaque thickness and stenosis are associated with the history of ischemic stroke and CHD, carotid intraplaque hemorrhage is associated with ischemic stroke, but not with CHD, providing novel insights into the pathogenesis of cardiovascular events. (Stroke. 2016;47:1542-1547. DOI: 10.1161/STROKEAHA.116.012923.)

Key Words: atherosclerosis ■ cardiovascular disease ■ carotid stenosis ■ magnetic resonance imaging ■ stroke

Atherosclerosis is the primary cause of cardiovascular disease, with coronary heart disease (CHD) and ischemic stroke as its most important clinical manifestations. Atherosclerosis is clinically silent for years with gradual thickening of the vessel wall and changes in plaque composition. Previous data suggest that plaque vulnerability depends on its composition, rather than on its thickness or the severity of stenosis.1 One of the vessel beds most extensively studied in atherosclerosis is the carotid artery because it can be easily visualized using different imaging techniques. Whereas ultrasound was for long the main modality for assessing carotid wall thickness, technical advances in other imaging modalities, especially magnetic resonance imaging (MRI), now allow a better characterization of plaque composition. Plaque components that can reliably be characterized on MRI are lipid deposits with or without a necrotic core, calcification, and intraplaque hemorrhage (IPH). Among these, IPH has gained much attention because it has been recognized as an important determinant of plaque instability and subsequent risk of stroke.2,3

An important feature of atherosclerosis is that it is a systemic vascular disease and that the presence of atherosclerotic disease at one specific location may predict ischemic events in distant locations.4-8 In this context, intima media thickness (IMT) in the carotid arteries has previously been used to assess the risk of CHD.9-11 Also, specific properties of carotid
plagues, such as irregularity of the plaque surface, were found to be associated with atherosclerotic plaque irregularity in other vessel beds. Subsequently, it was postulated that systemic risk factors might lead to a systemic predisposition to irregularity and rupture of atherosclerotic plaques. Such a predisposition to plaque instability attributable to systemic risk factors would suggest that plaque composition and instability in the carotid arteries could be related not only to stroke but also to other events, such as CHD. Therefore, in this study, we investigated the association of extent of carotid atherosclerosis and carotid plaque composition with a history of ischemic stroke and CHD in a population-based cohort study.

Methods

Study Population

The subjects of this study are participants of the Rotterdam Study, a prospective population-based cohort study initiated in 1990 among persons 55 years and older in the municipality of Rotterdam, the Netherlands. The original cohort of the Rotterdam Study was expanded in 2000, and again in 2006 to include participants who were 45 years and older. All study participants routinely undergo carotid ultrasonography to assess carotid IMT (measured as maximum distance between the near and far wall). Of 10073 participants with carotid ultrasound, 3795 participants (38%) had wall thickness ≥2.5 mm in at least one carotid, which was the inclusion criterion for participating in the current carotid MRI study. From the 3795 with wall thickening we invited 2666 participants to undergo an MRI of the carotid arteries. The remaining 1129 participants had passed away, moved out of the study area, were physically disabled (n=701), or had known MRI contraindications (n=428). From the 2666 persons, 684 did not undergo MRI scanning, because of claustrophobia (n=57), physical restrictions (n=191), contraindications (n=115), refusal to participate (n=272), no show or lost to follow-up (n=49). The remaining 1982 participants (74% of those initially invited) underwent MRI scanning of both carotid arteries. Scans were excluded if image quality was bad (n=95), if no plaque ≥2 mm were observed bilaterally (n=41) or if scanning was interrupted due to claustrophobia (n=106). Of the remaining 1739 participants with carotid MRI scans, we excluded participants with incomplete information on prevalence of CHD (n=8) or stroke (n=48). The Rotterdam Study has been approved by the medical ethics committee according to the Population Study Act Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of the Netherlands. A written informed consent was obtained from all participants.

Carotid MRI Scanning and Analysis of Plaque Characteristics

Imaging was performed with a 1.5-Tesla scanner (GE Healthcare, Milwaukee, WI) with a bilateral phased-array surface coil (Machnet, Eelde, The Netherlands). A standard scanning protocol was used with a total scanning time of 30 minutes. The carotid MRI protocol, reading, and reproducibility are described elsewhere. We evaluated both carotid arteries over a range of 15 mm caudally to 30 mm cranially of the bifurcation. We assessed plaque characteristics in all plaques with a maximum thickness of 2.0 mm on MRI. On the proton density weighted fast spin echo images, maximum carotid wall thickness was measured, and degree of luminal stenosis was calculated using the North American Symptomatic Carotid Endarterectomy Trial criteria. Plaques were reviewed for the presence of 3 different plaque components: IPH, lipid core, and calcification. In short, we defined IPH as the presence of a hyperintense focus within the plaque on the 3-dimensional T1-weighted gradient echo sequence. Calcification was defined as a hypointense region in the plaque on all sequences. Finally, the presence of lipid core was defined as a hypointense region in the plaque on proton density weighted fast spin echo or proton density weighted echo planar image and T2-weighted echo planar image, or a region of relative signal intensity drop in the T2-weighted echo planar images compared with the proton density weighted echo planar image. Multiple components were permissible in one plaque.

History of Stroke or CHD

A history of ischemic stroke or CHD was based on either a history of event self-reported at study entry, verified by clinical data from the medical records, or the occurrence of an event during study follow-up but before the time of carotid MRI scanning. The follow-up system involved linkage of the study to files from general practitioners in the study area and subsequent collection of information from letters of medical specialists, brain imaging, and discharge reports in case of hospitalization. For the diagnosis of stroke and cardiac events, 2 research physicians independently coded all reported events according to the International Classification of Diseases, 10th Revision. In case of disagreement, a decision was made by a neurologist or cardiologist. Stroke was defined as a history of ischemic or unspecified stroke but not hemorrhagic stroke (International Classification of Diseases, 10th Revision codes I61, I63, and I64). To define CHD, we used a combined outcome of nonfatal myocardial infarction and myocardial revascularization (ie, percutaneous coronary intervention and coronary artery bypass grafting, International Classification of Diseases, 10th Revision codes I21, I24, and I25). Information on incidence of stroke and CHD was completed until January 1, 2012.

Assessment of Covariates

Information on cardiovascular risk factors was obtained from the visit to the research center, which took place before the MRI scanning. Smoking status was classified as ever or never. Serum total cholesterol and high-density lipoprotein-cholesterol values were measured using standard laboratory techniques. On the basis of weight and height, the body mass index was calculated. Diabetes mellitus was defined as a fasting blood glucose ≥7.0 mmol/L, nonfasting glucose >11.0 mmol/L, or use of antidiabetic medication. Blood pressure was measured using a random-zero sphygmomanometer at the study center visit. Hypertension was defined as a blood pressure >140/90 mm Hg or the use of antihypertensive medication. Medication dispensing data were obtained from the fully computerized pharmacies in the Ommoord suburb. Information on all filled prescriptions of antihypertensive drugs on date of carotid MRI scans was available.

Statistical Analysis

We compared the baseline characteristics between men and women using age-adjusted linear regression for continuous variables and logistic regression for dichotomous variables. We also examined the mean wall thickness and degree of stenosis in persons with and without IPH, lipid core, and calcification (Table I in the online-only Data Supplement). To investigate the relation of the different plaque characteristics (IPH, lipid, calcification, stenosis [per 10%], and carotid wall thickness) with the history of ischemic stroke and CHD, we used binomial logistic regression. Next, we analyzed these relations in the whole sample and for men and women separately. In the first model, analyses were adjusted for age, sex (in the overall model only), and carotid wall thickness (only for the analyses with IPH, lipid, and calcification as determinant). In the second models, we additionally adjusted the associations for cardiovascular risk factors (smoking, total cholesterol, high-density lipoprotein-cholesterol, body mass index, diabetes mellitus, and hypertension).

We also evaluated effect modification by sex. Finally, we performed additional analyses in which all plaque characteristics were further adjusted for the other plaque components (Tables I and II in the online-only Data Supplement). All analyses were carried out using SPSS Statistical Package version 20.0 (Chicago, IL). Missing values in the covariates were imputed using the Expectation Maximization method.
Results

Table 1 reports the characteristics for the 1731 participants. The population consisted of 936 men (55%; mean age, 72.3±9.0 years) and 795 women (46%; mean age, 73.6±9.3 years). Men had lower total cholesterol values, lower high-density lipoprotein-cholesterol, higher prevalence of smoking, diabetes mellitus, and diastolic blood pressure. The mean carotid wall thickness was 3.6 mm (±1.1) and mean degree of stenosis was 13.1% (±18). IPH was prevalent in 35%, lipid in 41%, and calcification in 82%. Information on carotid plaque characteristics and history of CHD was available for 1731 participants and for history of stroke in 1683 participants. Before the carotid MRI scanning, a total of 105 individuals (61 men [6.5%] versus 44 women [5.5%]) experienced an ischemic stroke and 199 individuals (164 men [15.6%] versus 53 women [6.7%]) experienced a CHD event.

Table 2 presents overall and sex-specific associations between plaque characteristics and history of ischemic stroke, adjusted for age, carotid wall thickness (model 1), and for cardiovascular risk factors (model 2). In the multivariable model (model 2), only carotid stenosis was significantly associated with stroke (odds ratio [OR] per 10% increase in stenosis 1.14 [95% CI, 1.05–1.24]). However, after we stratified for sex, we found a strong association for IPH and carotid stenosis with stroke in men but not in women (OR for IPH: men: 2.39, [95% CI, 1.32–4.35], women: 0.69 [95% CI, 0.33–1.46]). OR for stenosis per 10% increase 1.17, [95% CI, 1.06–1.30], women: 1.10 [95% CI, 0.95–1.28]). When we tested for effect modification by sex, we only found the interaction term with IPH to be significant (P=0.03). Lipid, calcification, and carotid wall thickness were not associated with stroke in the fully adjusted model.

Table 3 shows overall and sex-specific associations between plaque characteristics and history of CHD, adjusted for age, carotid wall thickness (model 1), and for cardiovascular risk factors (model 2). In the overall analysis, only carotid stenosis was significantly associated with CHD after adjustment for cardiovascular risk factors (OR per 10% increase 1.14 [95% CI, 1.06–1.22]). Stratifying for sex did not materially change this association in both men and women. Also, carotid wall thickness was significantly associated with CHD in men (OR, 1.20 [95% CI, 1.03–1.39]) but not in women (OR, 1.21 [95% CI, 0.88–1.65]). For carotid stenosis and wall thickness, no effect modification by sex was observed (data not shown). None of the various plaque components was associated with the history of CHD, also after stratification for sex. All analyses for the association between plaque characteristics and stroke and CHD were repeated with additional adjustment for the remaining plaque components, but this did not alter the results (Tables II and III in the online-only Data Supplement).

Discussion

In this population-based study, we found carotid atherosclerotic plaque characteristics to be differentially related to history of ischemic stroke and CHD. Whereas the extent of atherosclerosis, expressed as plaque thickness or stenosis, was associated both with the history of ischemic stroke and CHD, plaque composition, and specifically IPH, seemed to be associated with the history of stroke only. These associations were primarily present in men and less prominent in women.

The relation between carotid IMT as measured with B-mode ultrasound and cardiovascular disease has been well established and IMT serves as a marker of generalized atherosclerosis.9–11 To this extent, IMT has been increasingly used for risk stratification models and contributes greatly to the prediction of CHD.10,22 To our knowledge, no studies have mainly focused on the relation between carotid plaque composition as detected with MRI and CHD. Most imaging studies used ultrasound measurements, because these measurements are relatively simple and noninvasive, but the resolution is of limited value for characterization of plaque composition.3 By using MRI, we found that carotid wall thickness and stenosis are more associated with a history of CHD than any of the specific carotid plaque components.

We found a prominent association of stenosis and IPH with history of stroke, which is in line with several clinical studies that investigated carotid plaque composition and neurological ischemic events.2,3,24–26 In a meta-analysis among 394 asymptomatic subjects, it was found that especially IPH was related to a substantially increased risk of stroke (hazard ratio, 3.5).2 However, because atherosclerosis is a chronic inflammatory condition with various local and systemic manifestations,17 researchers have raised the hypothesis that plaque instability may also be a systemic condition, influenced by systemic risk factors.28,29 For this reason, the term vulnerable patient was introduced, indicating that changes found in 1 vessel bed may be predictive of risk of events in another vessel bed.6,12 Whereas several reports previously suggested...
a relation between carotid IPH and CHD, we did not find any significant association between any of the carotid plaque components and history of CHD. Although we used previous clinical history with no clear information on how long exactly the CHD event had occurred before the carotid artery was imaged, carotid plaque composition seemed to be less important for CHD than for ischemic stroke. A possible explanation for the discrepancy with previous literature is that some of these studies used carotid tissue specimens derived after carotid endarterectomy or autopsy, in which it is difficult to distinguish between IPH and intraluminal thrombi after the tissue preparation. Other explanations may be related with the fact that others used a composite end point of cerebral and cardiovascular disease, or did not stratify for sex. This may have resulted in a dilution of the association between IPH and stroke and an overestimation of the association with CHD. Furthermore, a precise mechanism describing how atherosclerosis rather than the vulnerability of the plaque.

With respect to clinical events, we found that carotid atherosclerotic plaque characteristics differed between men and women. These differences could, in part, be explained by the smaller number of CHD events in women, leading to a lack in statistical power, as the estimates for the association between plaque thickness and stenosis and CHD were similar in women as in men. Alternatively, the larger OR of the association between IPH and history of stroke that we observed in men as opposed to women is in line with the male predominance of IPH as observed in several other studies. In a recent study of symptomatic patients who underwent carotid endarterectomy, IPH seemed to be associated with an increased risk of stroke and cardiovascular events in men, but not in women. A possible explanation may relate to more efficient repair, as stable, more fibrous less inflammatory, plaques were found in women, especially asymptomatic women, compared with men in histology studies. It was also suggested that although women may have similar amount of atherosclerosis, they may differ in clinical presentation of CHD or stroke because of estrogen- or genetic-related reasons.

Several strengths and limitations of our study need to be addressed. The advantages of this study are the population-based design and the large sample size. Furthermore, we focused on history of stroke and CHD separately instead of restricting the study to 1 end organ or using composite end

### Table 2. Atherosclerotic Plaque Characteristics and History of Ischemic Stroke

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Men</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Women</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>IPH</td>
<td>1.61 (1.04–2.50)</td>
<td>0.03</td>
<td>1.47 (0.94–2.30)</td>
<td>0.09</td>
<td>2.54 (1.41–4.57)</td>
<td>0.002</td>
<td>2.39 (1.32–4.35)</td>
<td>0.04</td>
<td>0.82 (0.39–1.71)</td>
</tr>
<tr>
<td>Lipid</td>
<td>0.85 (0.57–1.29)</td>
<td>0.4</td>
<td>0.91 (0.60–1.39)</td>
<td>0.7</td>
<td>0.82 (0.48–1.39)</td>
<td>0.4</td>
<td>0.83 (0.48–1.44)</td>
<td>0.5</td>
<td>0.93 (0.49–1.79)</td>
</tr>
<tr>
<td>Calcification</td>
<td>1.45 (0.77–2.72)</td>
<td>0.2</td>
<td>1.32 (0.70–2.50)</td>
<td>0.4</td>
<td>1.40 (0.61–3.19)</td>
<td>0.4</td>
<td>1.29 (0.56–3.00)</td>
<td>0.5</td>
<td>1.53 (0.58–4.06)</td>
</tr>
<tr>
<td>Stenosis*</td>
<td>1.17 (1.08–1.26)</td>
<td>&lt;0.001</td>
<td>1.14 (1.05–1.24)</td>
<td>0.002</td>
<td>1.18 (1.08–1.30)</td>
<td>0.001</td>
<td>1.17 (1.06–1.30)</td>
<td>0.02</td>
<td>1.13 (0.98–1.30)</td>
</tr>
<tr>
<td>Wall thickness</td>
<td>1.22 (1.04–1.43)</td>
<td>0.02</td>
<td>1.17 (0.99–1.38)</td>
<td>0.07</td>
<td>1.24 (1.03–1.48)</td>
<td>0.02</td>
<td>1.18 (0.98–1.43)</td>
<td>0.09</td>
<td>1.17 (0.84–1.65)</td>
</tr>
</tbody>
</table>

Model 1: adjusted for sex (only in overall model), age, and carotid wall thickness (except for carotid wall thickness and stenosis that were only adjusted for sex and age). Model 2: as model 1, and additionally for smoking, total cholesterol, high-density lipoprotein-cholesterol, body mass index, diabetes mellitus, and hypertension. CI indicates confidence interval; IPH, intraplaque hemorrhage; and OR, odds ratio.

*Per 10% increase.

### Table 3. Atherosclerotic Plaque Characteristics and History of Coronary Heart Disease

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Men</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Women</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>IPH</td>
<td>1.06 (0.75–1.48)</td>
<td>0.8</td>
<td>1.02 (0.72–1.45)</td>
<td>0.9</td>
<td>0.86 (0.57–1.29)</td>
<td>0.5</td>
<td>0.82 (0.54–1.25)</td>
<td>0.4</td>
<td>1.74 (0.93–3.25)</td>
</tr>
<tr>
<td>Lipid</td>
<td>0.85 (0.62–1.17)</td>
<td>0.3</td>
<td>0.92 (0.67–1.28)</td>
<td>0.6</td>
<td>0.91 (0.63–1.31)</td>
<td>0.6</td>
<td>0.98 (0.66–1.44)</td>
<td>0.9</td>
<td>0.72 (0.39–1.34)</td>
</tr>
<tr>
<td>Calcification</td>
<td>1.22 (0.75–1.97)</td>
<td>0.4</td>
<td>1.15 (0.70–1.89)</td>
<td>0.6</td>
<td>0.97 (0.56–1.66)</td>
<td>0.9</td>
<td>0.90 (0.51–1.58)</td>
<td>0.7</td>
<td>2.73 (0.82–9.05)</td>
</tr>
<tr>
<td>Stenosis*</td>
<td>1.15 (1.08–1.23)</td>
<td>&lt;0.001</td>
<td>1.14 (1.06–1.22)</td>
<td>&lt;0.001</td>
<td>1.14 (1.06–1.23)</td>
<td>&lt;0.001</td>
<td>1.12 (1.04–1.21)</td>
<td>0.004</td>
<td>1.18 (1.04–1.34)</td>
</tr>
<tr>
<td>Wall thickness</td>
<td>1.25 (1.10–1.42)</td>
<td>&lt;0.001</td>
<td>1.20 (1.05–1.37)</td>
<td>0.07</td>
<td>1.26 (1.10–1.45)</td>
<td>0.001</td>
<td>1.20 (1.03–1.39)</td>
<td>0.01</td>
<td>1.21 (0.89–1.65)</td>
</tr>
</tbody>
</table>

Model 1: adjusted for sex (only in overall model), age, and carotid wall thickness (except for carotid wall thickness and stenosis that were only adjusted for sex and age). Model 2: as model 1, and additionally for smoking, total cholesterol, high-density lipoprotein-cholesterol, body mass index, diabetes mellitus, and hypertension. CI indicates confidence interval; IPH, intraplaque hemorrhage; and OR, odds ratio.

*Per 10% increase.
points. We used prevalent cardiovascular events in which symptoms of ischemia were clinically confirmed or treated. Although linkage with data from general practitioners ensured validation of the majority of the diagnoses, events that occurred before entering the Rotterdam Study were based on self-report and may, therefore, be less reliable. An important issue to consider with respect to our findings is that we specifically investigated the relation of plaque characteristics with prevalent stroke and CHD. As a consequence, we cannot infer any temporality between the determinants and the outcomes. Moreover, fatal events, in which advanced atherosclerosis is expected, were not considered in this study. This may have led to an underestimation of the association between vulnerable plaque characteristics and clinical events. In addition, lifestyle changes or medication use initiated after primary stroke or CHD may have affected atherosclerotic plaque development. This could have stabilized the atherosclerotic plaque and reduced the differences in plaque characteristics between individuals with and without a history of clinical event. However, we cannot exclude that the plaque has evolved after experiencing stroke or CHD. These considerations highlight the need for prospective studies that investigate the relation between carotid plaque characteristics and incident stroke and CHD, and determine the incremental value of carotid MRI parameters beyond the traditional cardiovascular risk factor included in, for example, the Framingham risk score.

In summary, we found that carotid plaque thickness and stenosis are associated with a history of ischemic stroke and CHD, whereas carotid IPH is only associated with a history of ischemic stroke and CHD. These considerations highlight the need for prospective studies that investigate the relation between carotid plaque characteristics and incident stroke and CHD, and determine the incremental value of carotid MRI parameters beyond the traditional cardiovascular risk factor included in, for example, the Framingham risk score.

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Disclosures
None.

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22. Lorenz MW, Markus HS, Bots ML, Roswall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a
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An erratum has been published regarding this article. Please see the attached page for:
/content/47/7/e201.full.pdf

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2016/05/10/STROKEAHA.116.012923.DC1
http://stroke.ahajournals.org/content/suppl/2017/07/10/STROKEAHA.116.012923.DC2

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In the article by Selwaness et al (Selwaness M, Bos D, van den Bouwhuijsen Q, Portegies MLP, Ikram MA, Hofman A, Franco OH, van der Lught A, Wentzel JJ, Vernooij MW. Carotid atherosclerotic plaque characteristics on magnetic resonance imaging relate with history of stroke and coronary heart disease. *Stroke*. 2016;47:1542–1547. DOI: 10.1161/STROKEAHA.116.012923.), which published online on May 10, 2016, and appeared in the June 2016 issue of the journal, a correction was needed.

On page 1545, Table 2, column Women Model 1 $P$ value, row Wall thickness, “0.04,” has been changed to read “0.4.”

This correction has been made to the online version of the article, which is available at [http://stroke.ahajournals.org/content/47/6/1542](http://stroke.ahajournals.org/content/47/6/1542).
Supplemental table I. Mean wall thickness and degree of stenosis in persons with and without IPH, lipid core and calcification.

<table>
<thead>
<tr>
<th></th>
<th>Wall thickness</th>
<th>Degree of stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>IPH present</td>
<td>4.1 (1.2)</td>
<td>28.0 (24.7)</td>
</tr>
<tr>
<td>IPH absent</td>
<td>3.2 (0.8)</td>
<td>13.6 (15.0)</td>
</tr>
<tr>
<td>Lipid core present</td>
<td>3.8 (1.1)</td>
<td>22.8 (21.9)</td>
</tr>
<tr>
<td>Lipid core absent</td>
<td>3.4 (0.9)</td>
<td>15.2 (18.0)</td>
</tr>
<tr>
<td>Calcification present</td>
<td>3.6 (1.0)</td>
<td>19.8 (20.7)</td>
</tr>
<tr>
<td>Calcification absent</td>
<td>3.2 (0.9)</td>
<td>12.7 (16.2)</td>
</tr>
</tbody>
</table>

SD: standard deviation, IPH: intraplaque hemorrhage
### Supplemental Table II. Atherosclerotic Plaque Characteristics and History of Ischemic Stroke, Adjusted for Other Plaque Components

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th></th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
<td>Model 1</td>
<td>Model 2</td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td>P (95%CI)</td>
<td>OR</td>
<td>P (95%CI)</td>
<td>OR</td>
<td>P (95%CI)</td>
</tr>
</tbody>
</table>
| IPH            | 1.61    | 0.04 (1.03;2.51)| 1.45    | 0.1 (0.92;2.27)| 2.60     | 0.002 (1.43;4.73)| 2.45    | 0.004 (1.33;4.49)| 0.78     | 0.5 (0.37;1.64) | 0.66     | 0.3 (0.31;1.40)
| Lipid          | 0.83    | 0.4 (0.55;1.25)| 0.87    | 0.5 (0.57;1.33)| 0.74     | 0.3 (0.43;1.27)| 0.76    | 0.4 (0.44;1.34)| 0.96     | 0.9 (0.50;1.84)| 1.10     | 0.8 (0.56;2.17)
| Calcification  | 1.22    | 0.4 (0.71;2.52)| 1.23    | 0.5 (0.64;2.34)| 1.20     | 0.7 (0.52;2.70)| 1.09    | 0.8 (0.46;2.57)| 1.59     | 0.4 (0.60;4.24)| 1.49     | 0.4 (0.55;4.05)
| Stenosis*      | 1.14    | 0.003 (1.05;1.24)| 1.12    | 0.01 (1.03;1.22)| 1.13     | 0.03 (1.02;1.25)| 1.13    | 0.03 (1.02;1.25)| 1.15     | 0.08 (1.00;1.35)| 1.13     | 0.1 (0.96;1.34)
| Wall thickness | 1.25    | 0.1 (0.97;1.38)| 1.10    | 0.3 (0.92;1.31)| 1.11     | 0.3 (0.90;1.36)| 1.07    | 0.5 (0.87;1.33)| 1.20     | 0.3 (0.83;1.74)| 1.18     | 0.4 (0.81;1.72)

**IPH:** intraplaque hemorrhage, **OR:** odds ratio, **CI:** confidence interval

**Model 1:** adjusted for sex (only in overall model), age and carotid wall thickness (except for carotid wall thickness and stenosis which were only adjusted for sex and age).

**Model 2:** as model 1, and additionally for smoking, total cholesterol, HDL-cholesterol, BMI, diabetes mellitus and hypertension.

* per 10% increase
Supplemental table III. Atherosclerotic plaque characteristics and history of CHD, adjusted for other plaque components

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th></th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
<td>OR (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>IPH</td>
<td>1.13 (0.80;1.59)</td>
<td>1.04 (0.73;1.48)</td>
<td>0.87 (0.57;1.31)</td>
<td>0.5</td>
<td>0.82 (0.54;1.26)</td>
<td>0.4</td>
</tr>
<tr>
<td>Lipid</td>
<td>0.95 (0.70;1.30)</td>
<td>0.99 (0.71;1.37)</td>
<td>0.92 (0.64;1.34)</td>
<td>0.8</td>
<td>0.99 (0.67;1.47)</td>
<td>0.9</td>
</tr>
<tr>
<td>Calcification</td>
<td>1.19 (0.73;1.93)</td>
<td>1.15 (0.70;1.89)</td>
<td>0.99 (0.58;1.71)</td>
<td>0.6</td>
<td>0.93 (0.53;1.64)</td>
<td>0.6</td>
</tr>
<tr>
<td>Stenosis*</td>
<td>1.16 (1.08;1.25)</td>
<td>1.14 (1.06;1.23)</td>
<td>1.16 (1.07;1.26)</td>
<td>&lt;0.001</td>
<td>1.14 (1.05;1.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wall thickness</td>
<td>1.31 (1.14;1.50)</td>
<td>1.23 (1.07;1.42)</td>
<td>1.29 (1.11;1.51)</td>
<td>&lt;0.001</td>
<td>1.24 (1.05;1.45)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

IPH: intraplaque hemorrhage, OR: odds ratio, CI: confidence interval

Model 1: adjusted for sex (only in overall model), age and carotid wall thickness (except for carotid wall thickness and stenosis which were only adjusted for sex and age).

Model 2: as model 1, and additionally for smoking, total cholesterol, HDL-cholesterol, BMI, diabetes mellitus and hypertension.

* per 10% increase
Carotid Atherosclerotic Plaque Characteristics on Magnetic Resonance Imaging Relate With History of Stroke and Coronary Heart Disease

Mariana Selwaness, MD, PhD; Daniel Bos, MD, PhD; Quirijn van den Bouwhuijsen, MD; Marileen L.P. Portegies, MD; M. Arfan Ikram, MD, PhD; Albert Hofman, MD, PhD; Oscar H. Franco, MD, PhD; Aad van der Lugt, MD, PhD; Jolanda J. Wentzel, PhD; Meike W. Vernooij, MD, PhD

Background and Objectives: Atherosclerosis is a systemic disease, which can be accompanied by ischemic events in various vascular territories. This study investigated whether carotid atherosclerotic plaque characteristics related to history of stroke and coronary heart disease (CHD) in the general population.

Methods: In the Rotterdam Study, 1731 asymptomatic participants (mean age 72.4 ± 9.1 years, 55% male) were recruited. Carotid wall thickness, plaque burden, and plaque composition on magnetic resonance imaging (MRI) were assessed. The study was approved by the institutional review board, and all participants gave informed consent.

Results: Among men, carotid plaque burden and intraplaque hemorrhage were associated with stroke history, while plaque thickness and intraplaque hemorrhage were associated with CHD. Among women, no significant associations were found.

Conclusions: Carotid atherosclerotic plaque characteristics are associated with stroke and CHD in men, but not in women.

Keywords: Atherosclerosis; Cardiovascular disease; Carotid artery; Magnetic resonance imaging; Stroke
的双侧颈动脉斑块均小于 2 mm (n=41) 以及因为幽闭恐惧症而中断 (n=106) 等情况而被除外研究。在剩余的 1739 例接受 MRI 平扫的受试者中, 还排除了既往关于 CHD 病史 (n=8) 或卒中史 (n=48) 病史信息不完整的受试者。Rotterdam 研究经药物伦理委员会认可并通过了荷兰卫生福利体育部颁布的 Rotterdam 人口研究计划，所有受试者全部签署了书面知情同意书。

颈动脉 MRI 平扫与斑块特点分析

MRI 设备: 使用 1.5T 场强的磁共振扫描仪 (GE Healthcare, Milwaukee, WI) 获取图像，这种 MRI 设备有双侧相控阵表面线圈 (Machnet, Eelde, The Netherlands)，标准平扫要求总共的扫描时间要在 30 min 左右。颈动脉 MRI 平扫操作方法、阅片和可重复性已在其他论文加以阐述 16。本研究评估了颈动脉分叉处向下 15 mm 和向上 30 mm 范围的双侧颈动脉, 利用 MRI 分析了所有斑块中最大厚度≥ 2.0 mm 的斑块特点。在质子密度加权快速自旋回波图像中, 根据北美症状性颈动脉内膜切除手术试验标准 17, 测量颈动脉壁的最大厚度, 计算出动脉狭窄率。斑块主要分为 3 种不同成分: IPH、脂质核、钙化。IPH 表现为 T1 加权序列出现高信号。钙化表现为在所有序列斑块内出现低信号。脂质核表现为质子密度加权快速自旋回波或质子密度加权平扫和 T2 加权颈动脉内膜厚度成像出现低信号, 或者表现为与质子密度加权颈动脉内膜厚度成像相比, T2 加权颈动脉内膜厚度成像的区域的相对信号降低。单个斑块中可能包含多种成分 16。

既往卒中史或 CHD 病史

既往缺血性卒中史或 CHD 病史是根据患者入组前自述、经过病历档案核实, 或是基于 MRI 扫描之前的随访期间出现的临床事件。随访系统的临床材料包括了受试者提供的病例材料、医学专家的信件、脑部影像学检查和住院治疗的出院小结。对于卒中和心脏事件的诊断, 2 名参与研究的内科医生独立根据国际疾病分类 (ICD10) 对所有被报告的临床事件进行了编码 18。对于有争议的病例, 最终的诊断决定由神经科专科医生或心血管专科医生做出。卒中定义为缺血性卒中或非出血性卒中 (ICD10, I61, I63, I64) 19。CHD 定义为非致死性心肌梗死和心肌血管重建术 (例如, 经皮冠状动脉介入治疗和冠状动脉搭桥术, ICD10, I21, I24, I25) 20。卒中和 CHD 发生率的统计于 2012 年 1 月 1 日前完成。

协变量分析

心血管危险因素资料在 MRI 扫描之前的研究中心访视时进行采集: 根据吸烟状况分为有或无; 血清总胆固醇和高密度脂蛋白胆固醇的数值通过标准的实验室技术进行测量; 计算得出体重指数; 糖尿病定义为空腹血糖 >7.0 mmol/L, 非空腹血糖 >11.0 mmol/L, 或使用抗糖尿病药物治疗。在研究全过程中受试者应用磁共振成像仪进行血压测量, 高血压被定义为血压 >140/90 mmHg 或使用降压药物。药物使用数据从 Ommoord 社区药店计算机系统获取。所有患者应用抗高血压处方药物信息在完成颈动脉 MRI 当日获取 21。

统计分析

采用经过年龄校正的线性回归分析处理连续变量和 Logistic 回归分析处理二元变量比较男性和女性 2 组间的基线特征。对有 / 无 IPH、脂质核及钙化的患者平均动脉壁厚度和动脉狭窄程度进行分析 (表 1, 在线数据补充)。为了研究不同斑块成分特点 [IPH、脂质、钙化 (每 10%)、颈动脉壁的厚度] 与既往缺血性卒中史及 CHD 病史的关系, 本研究采用了二元 Logistic 回归分析分别对整个样本、男性组和女性组进行统计学分析。在模型 1 中对整个样本组中校正了年龄、性别和颈动脉壁厚度的影响。在模型 2 中研究者又额外校正了心血管病相关危险因素 (吸烟、总胆固醇、高密度脂蛋白胆固醇、体重指数、糖尿病和高血压) 的相关影响。本研究还评估了性别对结果的影响。本研究校正了其他斑块成分对全部斑块特征影响并进一步进行相关性分析 (见在线数据补充表 1 和表 2)。本研究使用统计软件 SPSS 20.0 (Chicago, IL) 进行所有的统计学分析。在协变量中, 丢失的数据通过期望最大化方法进行估算 21。

结果

表 1 数据显示了 1731 例受试者的基本特点。受试人群的构成: 男性 936 例(55%, 平均年龄为 72.3±9.0 岁), 女性 795 例(46%, 平均年龄为 73.6±9.3 岁)。与女性受试者相比, 男性受试者的总胆固醇与高密度脂蛋白胆固醇较低, 吸烟率、糖尿病患病率和舒张高压的发病率较高。平均颈动脉壁厚度为 3.6 mm(±1.1), 平均动脉狭窄程度为 13.1%(±18), IHP 发生率为 35%, 脂质核 41%, 钙化 82%。1731 例受试者有颈动脉斑块特征和 CHD 病史, 1683 例受试者有卒中病史。在 MRI 平扫之前, 共有 105 例 [61 例男性(6.5%):44 例女性(5.5%)] 曾罹患缺血性卒中, 199 例 [164 例男性(15.6%):53 例女性(6.7%)] 发生 CHD 事件。表 2 数据显示整体和性别相关的斑块特点与缺血性卒中病史之间的相关性, 模型 1 校正了年龄、颈动脉壁厚度, 模型 2 校正了心血管危险因素。在多变量的模型 2 中, 只有颈动脉狭窄与卒中率显著相关 [OR 值在狭窄率每增加 10% 为 1.14 (95%CI, 1.05–1.24)]。在对性别进行分层分析后, 发现 IPH 和颈动脉狭窄与男性卒中密切相关, 而在女性中没有如此的相关性 [IPH OR 值, 男性为 2.39 (95%CI, 1.32–4.36); 女性为 0.69 (95%CI, 0.33–1.46); 血管狭窄每增加 10% 的 OR 值: 男性: 1.17 (95%CI, 1.06–1.30); 女性: 1.10 (95%CI, 0.95–1.28)]。当校正性别因素后, 本研究发现仅有 IPH 有重要的意义 (P=0.03)。

脂质核、钙化及颈动脉壁厚度与卒中在充分校正模型中与卒中无明显相关。
表 3 显示了整体和性别相关的斑块特点与既往 CHD 病史之间的相关性，但校正了年龄、颈动脉壁厚度（模型 1）、心血管危险因素（模型 2）。在校正心血管危险因素后的总体分析中显示仅有颈动脉狭窄与 CHD 病史密切相关 [OR 值在颈动脉狭窄率每增加 10% 为 1.14 (95% CI, 1.06~1.22)]。对性别分层分析并没有在本质上改变不同性别中斑块特点与 CHD 病史之间的相关性。同时, 颈动脉壁厚度与男性罹患 CHD 密切相关 [OR 值, 1.20 (95% CI, 1.03~1.39)] 而与女性却无相关性 [OR 值, 1.21 (95% CI, 0.88~1.65)]。对于颈动脉狭窄和血管壁厚度, 无性别相关性(数据未显示), 任何一种斑块成分与 CHD 病史无明显相关, 经过性别分层校正后亦无关联。对于斑块特点与卒中史的相关分析, 即使在调整了其他斑块成分的影响进行重复分析后结果仍一致（见在线数据补充表 2 和表 3）。

讨论

本项基于人群的研究发现, 颈动脉粥样硬化斑块特征与缺血性卒中史和 CHD 病史之间的相关性, 并校正了年龄、颈动脉壁厚度 (模型 1)、心血管危险因素（模型 2）。在正心血管危险因素后的总体分析中显示仅有颈动脉狭窄与 CHD 病史密切相关 [OR 值在颈动脉狭窄率每增加 10% 为 1.14 (95% CI, 1.06~1.22)]，对性别分层分析并没有在本质上改变不同性别中斑块特点与 CHD 病史之间的相关性。同时，颈动脉壁厚度与男性罹患 CHD 密切相关 [OR 值, 1.20 (95% CI, 1.03~1.39)] 而与女性却无相关性 [OR 值, 1.21 (95% CI, 0.88~1.65)]。对于颈动脉狭窄和血管壁厚度，无性别相关性(数据未显示)，任何一种斑块成分与 CHD 病史无明显相关，经过性别分层校正后亦无关联。对于斑块特点与卒中史的相关分析，即使在调整了其他斑块成分的影响进行重复分析后结果仍一致（见在线数据补充表 2 和表 3）。
合并症。

本研究发现，颈动脉动脉粥样硬化斑块特征在临床事件发生方面存在性别差异，其原因可能是由于女性人群中CHD的人数较少，缺乏统计学效力，但斑块厚度和狭窄率在男性和女性之间没有差别。另外，本研究中男性患者IPH与卒中史相关的统计学数据出现较大OR值，与其他研究发现的“IPH主要发生于男性”的结论相一致。近期内的一项针对颈动脉内膜剥脱术治疗有临床症状患者的研究中发现，男性IPH患者出现卒中和心血管事件的风险增加，但在女性则无明显期。

本研究中男性患者IPH与卒中病史相关性的统计学数据出现较大OR值，存在性别差异，其原因可能是由于女性人群中患CHD的人数较少，缺血性卒中和CHD的风险预测和风险分层的作用。CHD病史具有相关性，但颈动脉IPH仅与缺血性卒中病史相关而与其他研究发现的“IPH主要发生于男性”的结论相一致。还有一些研究提示，女性由于存在雌激素或遗传性因素等原因，动脉粥样硬化程度相似情况下，其CHD和卒中的临床表现上可出现明显差别。

本研究的优点和局限性如下：

优点：(1) 本研究是基于人群的研究，样本量较大。(2) 本研究中男性和女性患者IPH的颈动脉粥样硬化影像学参数的作用优于传统的心血管危险因素评分如Framingham危险评估和相关性，但在入组前的心脑血管事件均是来自受试者口述，可信性略差。

局限性：(1) 尽管研究者尽最大可能确保绝大多数患者诊断的准确性和定义的统一性，但在入组前的心脑血管事件均是来自受试者口述，可信性略差。(2) 由于本研究的重点是针对斑块特征与卒中和CHD患病率的相关性，但在入组前的心脑血管事件均是来自受试者口述，可信性略差。