Retinal Vascular Calibers and the Risk of Intracerebral Hemorrhage and Cerebral Infarction
The Rotterdam Study

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Background and Purpose—Narrower retinal arteriolar calibers and wider venular calibers are associated with cardiovascular disease, including cerebral infarction. We investigated the association between retinal vascular calibers and the long-term risk for stroke and its subtypes with particular focus on intracerebral hemorrhage.

Methods—We included 5518 participants (aged ≥55 years) from the prospective population-based Rotterdam Study who were stroke-free at baseline (1990–1993) and of whom digital retinal images were available. Follow-up for incident stroke was complete up to January 1, 2007. Data were analyzed with Cox proportional hazards models adjusted for age and sex and additionally for potential confounders. Arteriolar and venular calibers were entered both separately and simultaneously in the models.

Results—During an average follow-up of 11.5 years, 623 participants developed a first-ever stroke (50 hemorrhagic, 361 ischemic, 212 unspecified). Larger venular caliber was independently associated with an increased risk for stroke (hazard ratio [HR] per SD increase: 1.20; 95% confidence interval [CI]: 1.09 to 1.33), cerebral infarction (HR: 1.28; 95% CI: 1.13 to 1.46), and intracerebral hemorrhage (HR: 1.53; 95% CI: 1.09 to 2.15). Much weaker, only borderline significant associations were found between arteriolar caliber and risk for stroke (HR per SD decrease: 1.12; 95% CI: 0.99 to 1.23), cerebral infarction (HR: 1.12; 95% CI, 0.98 to 1.27), and intracerebral hemorrhage (HR: 1.25; 95% CI: 0.87 to 1.79). Retinal vascular calibers were strongly associated with lobar hemorrhages and oral anticoagulant-related hemorrhages.

Conclusion—Larger retinal venular caliber is associated with an increased risk for stroke in the general population and, in particular, with an increased risk for intracerebral hemorrhage. (Stroke. 2010;41:2757-2761.)

Key Words: intracerebral hemorrhage ■ cerebral infarction ■ retinal microcirculation ■ risk factors ■ epidemiology

Intracerebral hemorrhage accounts for ≈10% to 15% of strokes and leads to high rates of death and disability in elderly people.1 Only a few risk factors of intracerebral hemorrhage have been identified, of which hypertension is the most frequent and the most important.2 Because the outcome of intracerebral hemorrhage is poor and present treatment results are disappointing, prevention seems the most effective approach.3,4 To identify people at risk for intracerebral hemorrhage, detection of new risk factors and risk indicators is extremely important.

Pathological studies have shown that the majority of intracerebral hemorrhages result from rupture of small arteries and arterioles affected by either hypertension-related degenerative changes or cerebral amyloid angiopathy.5,6 These pathological vascular changes, which may develop asymptptomatically until the sudden onset of intracerebral hemorrhage, are difficult to assess in vivo. The retinal vasculature, which shares many morphological and physiological properties with the cerebral vasculature, can be visualized directly and noninvasively with digitized fundus photography. Retinal vascular caliber changes are considered markers of cerebral microvascular changes and can be used as a model to study the relationship between cerebral microvascular pathology and intracerebral hemorrhage.7,8

Retinal arteriolar and retinal venular caliber changes are considered to mark different pathological processes, because they are related differently to cardiovascular risk factors and disease. High blood pressure is the major systemic determinant of narrower arteriolar caliber,9 whereas wider venular caliber is related to smoking, glucose levels, and markers of atherosclerosis and inflammation.10–12 Both narrower arteriolar caliber and wider venular caliber have been associated with an increased risk for coronary heart disease.13 In contrast, only wider venular caliber was reportedly associated
with the risk for stroke, cerebral infarction, and progression of cerebral small vessel disease.\textsuperscript{14–16} Data on the association between retinal vascular calibers and intracerebral hemorrhage are limited. Recently, a hospital-based cross-sectional study among acute stroke patients found that retinal vascular calibers were similar in patients with deep intracerebral hemorrhage and lacunar infarction, but patients with deep intracerebral hemorrhage were more likely to have narrower arterioles and wider venules than patients with nonlacunar stroke.\textsuperscript{17} The longitudinal relationship between retinal vascular calibers and incident intracerebral hemorrhage has not been investigated.

The aim of the present study was to investigate the association between retinal vascular calibers and the long-term risk for stroke and its subtypes in the general elderly population. We particularly focused on the association between retinal vascular calibers and intracerebral hemorrhage.

**Source Population**

This study is part of the Rotterdam Study, a prospective population-based cohort study, which started in 1990 an is still ongoing.\textsuperscript{18} All inhabitants who were 55 years of age or older and living in Ommoord, a district in the city of Rotterdam in the Netherlands, were invited to participate, and 7983 persons agreed (response rate 78%). Invitation into the study occurred in random order. Baseline examinations consisted of an interview at home and 2 visits to the research center for physical examination and blood sampling. Because the ophthalmologic part of the study became operational after the main study had begun, a smaller number of participants (n = 6780) underwent the ophthalmologic examination. All participants were followed for a variety of diseases that are common in the elderly, including stroke.\textsuperscript{18} The study was approved by the Medical Ethics Committee of the Erasmus University Medical Center in Rotterdam. Written informed consent was obtained from all participants.

**Assessment of Stroke**

History of stroke at baseline was assessed during the baseline interview and verified by reviewing medical records. After enrollment, participants were continuously monitored for incident stroke through automated linkage of the study database with files from general practitioners and the municipality. Nursing home physicians files and files from general practitioners of participants who moved out of the district were examined as well. Additional information was obtained from hospital records. Potential strokes were reviewed by research physicians and verified by an experienced stroke neurologist (P.J.K.). Examinations were classified as cerebral infarction or intracerebral hemorrhage on the basis of neuroimaging reports. If neuroimaging was lacking, strokes were classified as unspecified. Intracerebral hemorrhages were further categorized into 1 of 2 categories: lobar, when arising in the frontal, parietal, temporal, or occipital lobes; and deep, when occurring in the basal ganglia, thalamus, brain stem, or cerebellum. Very large hematomas with ventricular extension were also categorized as deep. Purely intraventricular hemorrhages and hemorrhages of undetermined localization were not categorized. Data on the use of oral anticoagulants at time of stroke were collected from medical records to classify hemorrhages as anticoagulation-related or non–anticoagulation-related. Cerebral infarctions were further categorized as cortical or lacunar based on clinical symptoms alone, or, when visible on CT or MRI, based on clinical and imaging features.\textsuperscript{19} Subarachnoid hemorrhages were excluded. Participants were followed from baseline to stroke; death; last health status update where they were known to be free of stroke; or January 1, 2007, whichever came first. Follow-up was complete up to January 1, 2007 for 96.2% of potential person years.\textsuperscript{20}

**Methods**

**Retinal Vascular Caliber Measurement**

Participants underwent a full eye examination at baseline, including simultaneous stereoscopic fundus color photography of the optic disc (20° field, Topcon Optical Company, Tokyo, Japan) after pharmacological mydriasis. The transparencies from both eyes were digitized with a high-resolution scanner (Nikon LS-4000, Nikon Corporation), and, for each participant, the digitized image with the best quality (left or right eye) was analyzed with the Retinal Vessel Measurement System (Retinal Analysis Optimize; Department of Ophthalmology & Visual Science, University of Wisconsin-Madison).\textsuperscript{21} The rationale and procedures to measure and summarize retinal vascular calibers have been described.\textsuperscript{10,21} Summary measures for arteriolar and venular calibers were based on improved Parr–Hubbard formulas and were corrected for magnification changes attributable to refractive errors of the eye. Four trained graders performed the assessments, blinded to the clinical characteristics of the participants. In a random subsample of 100 participants, we found no differences between the right and left eyes for the arteriolar and venular calibers. Pearson’s correlation coefficients for intergrader agreement were 0.67 to 0.80 for arteriolar caliber and 0.91 to 0.94 for venular caliber. Corresponding figures for intra-grader agreement were 0.69 to 0.88 and 0.90 to 0.95.\textsuperscript{10}

**Cardiovascular Risk Factors at Baseline**

Blood pressure was calculated as the mean of 2 measurements with the random-zero sphygmomanometer at the right brachial artery while the subject was in a sitting position. Hypertension was defined as a diastolic blood pressure of $\geq 90$ mm Hg and/or a systolic blood pressure of $\geq 140$ mm Hg and/or the use of antihypertensive medication. Diabetes mellitus was defined as a nonfasting or postload serum glucose level of $\geq 11.1$ mmol/L and/or the use of glucose-lowering drugs. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and C-reactive protein (CRP) were measured in nonfasting serum with an automated enzymatic procedure. Prevalent heart failure and left ventricular hypertrophy were determined as described previously.\textsuperscript{22,23} Smoking behavior, alcohol intake, and current medication use were assessed during a standardized interview.\textsuperscript{24}

**Study Population**

From the 6780 participants who underwent the ophthalmologic examination, we excluded participants who had had a stroke before baseline (n = 199) or had refused informed consent for the collection of follow-up data from general practitioners (n = 34). Of the remaining 6547 participants at risk for stroke, 1029 persons could not be included in the analyses because fundus transparencies were not available or not gradable. In total, 5518 participants were included in the analyses.

**Statistical Analysis**

We used Cox proportional hazards regression to determine hazard ratios and 95% confidence intervals for the associations between baseline retinal vascular calibers and any incident stroke, intracerebral hemorrhage, and cerebral infarction. Only first-ever strokes were included in the analyses. Hazard ratios for stroke and its subtypes were calculated by analyzing arteriolar calibers per SD decrease and venular calibers per SD increase. To verify the linearity of associations, we also categorized vessel calibers in quartiles. We constructed 4 models: (1) age and sex plus either the arteriolar or the venular caliber; (2) age and sex plus both the arteriolar and the venular caliber; (3) age, sex, both vascular calibers, and cardiovascular risk factors (hypertension, diabetes, smoking, total cholesterol, HDL-cholesterol, CRP, body mass index); and (4) as model 3, plus additional putative confounders (systolic blood pressure, blood pressure–lowering medication use, alcohol intake, left ventricular hypertrophy, and heart failure). Missing values in covariates were imputed with a linear regression model based on age and sex.

We further explored the relationship between retinal vascular calibers and intracerebral hemorrhage by categorizing intracerebral hemorrhages as lobar or deep and by classifying hemorrhages as...
anticoagulation-related or non-anticoagulation-related. Associations were adjusted for age, sex, and the fellow-vessel caliber.

**Results**

During 63,306 person years of follow-up (mean 11.5 years), 623 participants developed a stroke, of which 50 were classified as intracerebral hemorrhage, 361 as cerebral infarction, and 212 as unspecified. The localization of intracerebral hemorrhage was lobar in 25 and deep in 22 (3 did not fit in either of the categories). Among the 50 intracerebral hemorrhages, 13 were related to anticoagulation use and 37 were not. Baseline characteristics of the study population are shown in Table 1. At baseline, the mean age was 67.8 years, and 59.1% of the participants were women.

Associations between retinal arteriolar caliber and stroke and its major subtypes are shown in Table 2. When adjusted for age and sex only, narrower arteriolar caliber was nonsignificantly associated with the risk for any stroke, cerebral infarction, and intracerebral hemorrhage, independent of cardiovascular risk factors. Narrower arteriolar caliber was nonsignificantly associated with the risk for any stroke or cerebral infarction, although we did find a trend toward an increased risk for anticoagulation-related or non-anticoagulation-related. Associations were adjusted for age, sex, and the fellow-vessel caliber.

**Table 1. Baseline Characteristics of the Study Population (n=5518)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>67.8 (8.1)</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>59.1</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>23.4</td>
</tr>
<tr>
<td>Non-fasting glucose level, mmol/L</td>
<td>6.8 (2.6)</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>10.7</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>55.4</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>138.3 (22.0)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>73.7 (11.3)</td>
</tr>
<tr>
<td>Antihypertensive medication use, %</td>
<td>30.1</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.3 (3.7)</td>
</tr>
<tr>
<td>Serum total cholesterol level, mmol/L</td>
<td>6.6 (1.2)</td>
</tr>
<tr>
<td>Serum HDL-cholesterol level, mmol/L</td>
<td>1.4 (0.4)</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>3.1 (6.1)</td>
</tr>
<tr>
<td>Alcohol intake, gram/day</td>
<td>10.3 (15.0)</td>
</tr>
<tr>
<td>Heart failure, %</td>
<td>3.0</td>
</tr>
<tr>
<td>Left ventricular hypertrophy, %</td>
<td>3.8</td>
</tr>
<tr>
<td>Retinal arteriolar caliber, μm</td>
<td>146.9 (14.4)</td>
</tr>
<tr>
<td>Retinal venular caliber, μm</td>
<td>220.0 (20.8)</td>
</tr>
</tbody>
</table>

Values are means (SD) or percentages.

We further found a strong association between venular widening and risk for lobar hemorrhage (hazard ratio [HR] per SD increase: 2.02; 95% confidence interval [CI]: 1.28 to 3.19) but not deep hemorrhage (HR: 0.90; 95% CI: 0.53 to 1.55). Arteriolar narrowing was associated with neither type of hemorrhage. Retinal vascular calibers were also strongly associated with risk for anticoagulation-related hemorrhage. The hazard ratio per SD decrease in arteriolar caliber was 2.59 (95% CI: 1.28 to 5.23) and 2.48 per SD increase in venular caliber (95% CI: 1.30 to 4.76).

**Table 2. Association Between Retinal Arteriolar Caliber and Stroke**

<table>
<thead>
<tr>
<th>Arteriolar Caliber</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All strokes (n=623)</td>
<td>Model 1</td>
</tr>
<tr>
<td>Quartile IV*</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Quartile III</td>
<td>1.06 (0.85–1.32)</td>
</tr>
<tr>
<td>Quartile II</td>
<td>0.97 (0.77–1.21)</td>
</tr>
<tr>
<td>Quartile I</td>
<td>1.03 (0.82–1.29)</td>
</tr>
<tr>
<td>Per SD decrease†</td>
<td>1.00 (0.93–1.08)</td>
</tr>
<tr>
<td>Intracerebral hemorrhages (n=50)</td>
<td>Model 1</td>
</tr>
<tr>
<td>Quartile IV</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Quartile III</td>
<td>0.59 (0.25–1.43)</td>
</tr>
<tr>
<td>Quartile II</td>
<td>1.12 (0.53–2.36)</td>
</tr>
<tr>
<td>Quartile I</td>
<td>1.02 (0.48–2.18)</td>
</tr>
<tr>
<td>Per SD decrease†</td>
<td>0.95 (0.72–1.25)</td>
</tr>
<tr>
<td>Cerebral infarctions (n=361)</td>
<td>Model 1</td>
</tr>
<tr>
<td>Quartile IV</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Quartile III</td>
<td>1.08 (0.81–1.43)</td>
</tr>
<tr>
<td>Quartile II</td>
<td>0.86 (0.63–1.16)</td>
</tr>
<tr>
<td>Quartile I</td>
<td>0.91 (0.68–1.23)</td>
</tr>
<tr>
<td>Per SD decrease†</td>
<td>0.97 (0.88–0.97)</td>
</tr>
</tbody>
</table>

*Range of arteriolar calibers (μm): quartile I: 92.2–137.4; II: 137.4–146.2; III: 146.2–155.6; IV: 155.6–235.7.

†Per SD (14.4 μm) decrease in retinal arteriolar caliber.

In this prospective cohort study, we found that wider retinal venular caliber was associated with an increased risk for stroke and its subtypes cerebral infarction and intracerebral hemorrhage, independent of cardiovascular risk factors. Narrower retinal arteriolar caliber was nonsignificantly associated with the risk for any stroke or cerebral infarction, although we did find a trend toward an increased risk for

**Discussion**

In this prospective cohort study, we found that wider retinal venular caliber was associated with an increased risk for stroke and its subtypes cerebral infarction and intracerebral hemorrhage, independent of cardiovascular risk factors. Narrower retinal arteriolar caliber was nonsignificantly associated with the risk for any stroke or cerebral infarction, although we did find a trend toward an increased risk for
intracerebral hemorrhage when we took venular caliber into account. Wider venular caliber was strongly associated with lobar intracerebral hemorrhage. Both narrower arterioles and wider venules increased the risk for anticoagulation-related hemorrhage.

In interpreting these findings, we have to consider some methodological issues. The strengths of this study are its prospective and population-based design, the large number of participants, the standardized procedures for retinal vascular caliber measurements, and the long duration of follow-up. Thorough stroke monitoring procedures and the nearly complete follow-up (loss of potential years only 3.8%) allowed us to identify virtually all incident stroke events, even in participants who had not been referred to a hospital, for example, people living in nursing homes or participants who had a fatal stroke. Nevertheless, we may have missed some strokes presenting with symptoms too subtle for the participant to visit a physician. Because the outcome measure of the study was symptomatic stroke, we have not collected data on the occurrence of asymptomatic stroke before baseline or during follow-up. Another implication of our stroke monitoring approach was that neuroimaging was often lacking. As a result, 33% of strokes were classified as unspecified. Intra- cerebral hemorrhages were further categorized as lobar or deep based on their localization on CT. Likewise, we aimed to categorize cerebral infarctions as cortical or lacunar. Unfortunately, because most infarctions were not visible on CT and subtyping of infarctions based on clinical symptoms alone is vulnerable to misclassification, we decided not to perform analysis on subtypes of infarctions.

This study describes the association between retinal vascular calibers and risk for intracerebral hemorrhage. We found that larger retinal venular caliber was associated with an increased risk for intracerebral hemorrhage. The association was stronger in lobar than in deep intracerebral hemorrhages. The mechanism underlying the association is unclear. Previous studies have shown that wider retinal venules are associated with an increased risk for stroke, including cerebral infarction. Furthermore, studies have shown that larger retinal venular caliber is associated with cardiovascular risk factors, such as cigarette smoking, serum glucose levels, and serum cholesterol levels and with markers of atherosclerosis, inflammation, and obesity. In the present study, adjustment for these factors only minimally influenced the results, suggesting that other mechanisms must be involved. Other possible mechanisms underlying retinal venular dilation include retinal hypoxia, venous insufficiency, and endothelial dysfunction. Whether any of these proposed mechanisms underlies the association between retinal venular caliber and intracerebral hemorrhage requires additional investigations.

A priori we had expected to find an association between smaller retinal arteriolar caliber and risk for intracerebral hemorrhage, given that hypertension is the major established risk factor of intracerebral hemorrhage and known to lead to retinal arteriolar narrowing. Remarkably, however, the association between retinal arteriolar caliber and intracerebral hemorrhage was not significant and smaller than the association we found between retinal venular caliber and intracerebral hemorrhage. However, when we classified intracerebral hemorrhages as anticoagulation-related or non–anticoagulation-related, we found that both arteriolar narrowing and venular widening strongly increased the risk for anticoagulation-related hemorrhage. Although this finding was based on a small number of events, it may have important clinical implications. Intracerebral hemorrhage is a major concern when prescribing oral anticoagulants to elderly people, and clinical decision making would benefit from additional risk predictors to identify those at risk for bleeding complications. However, further research is needed to establish the association and to investigate possible implications of retinal vascular caliber measurements.

We have previously shown that wider retinal venular caliber, but not narrower arteriolar caliber, is associated with an increased risk for stroke and cerebral infarction. In the present analysis, following more recent insights on how to adjust for confounding, we corrected for the confounding effect of the complementary retinal vessel by entering both vascular calibers simultaneously in the regression models. In comparison with the previously reported results, these additional adjustments resulted in somewhat stronger associations between retinal vascular calibers and risk for cerebral infarction. However, they did not affect our previous conclusion that larger retinal venular caliber is associated with an
increased risk for cerebral infarction, whereas narrower arteriolar caliper is not.15

The present study suggests that retinal venular caliber is a novel risk determinant for intracerebral hemorrhage. Because of the poor prognosis after intracerebral hemorrhage, identification of people at risk and treatment of risk factors is extremely important. To date, only a limited number of detectable and modifiable risk factors and risk indicators have been identified. Our finding that retinal vascular caliber is a strong risk determinant of intracerebral hemorrhage may help the early identification of people at risk for intracerebral hemorrhage, and in particular of people at risk for anticoagulation-related hemorrhage, but may also provide new directions for further research into the pathophysiology of intracerebral hemorrhage.

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Disclosures
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