Cerebral Vasomotor Reactivity and Risk of Mortality

The Rotterdam Study

Marileen L.P. Portegies, MD*; Renée F.A.G. de Bruijn, MD*; Albert Hofman, MD, PhD; Peter J. Koudstaal, MD, PhD; M. Arfan Ikram, MD, PhD

Background and Purpose—Accumulating vascular pathology in cerebral arteries leads to impaired cerebral vasomotor reactivity. In turn, impaired cerebral vasomotor reactivity is a risk factor for stroke in clinical populations. It remains unclear whether impaired cerebral vasomotor reactivity also reflects more systemic vascular damage. We investigated whether cerebral vasomotor reactivity is associated with the risk of mortality, focusing particularly on cardiovascular mortality independent from stroke.

Methods—Between 1997 and 1999, 1695 participants from the Rotterdam Study underwent cerebral vasomotor reactivity measurements using transcranial Doppler. Follow-up was complete until January 1, 2011. We assessed the associations between cerebral vasomotor reactivity and mortality using Cox proportional hazards models, adjusting for age, sex, and blood pressure changes and subsequently for cardiovascular risk factors. We additionally censored for incident stroke.

Results—During 17,004 person-years, 557 participants died, of whom 181 due to a cardiovascular cause. In the fully adjusted model, the hazard ratio per SD decrease in vasomotor reactivity was 1.10 (95% confidence interval [CI], 1.01–1.19) for all-cause mortality, 1.09 (95% CI, 0.94–1.26) for cardiovascular mortality, and 1.10 (95% CI, 0.99–1.21) for noncardiovascular mortality. These associations remained unchanged after censoring for incident stroke.

Conclusions—We found that lower cerebral vasomotor reactivity is associated with an increased risk of death. Incident stroke does not affect this association, suggesting that a lower cerebral vasomotor reactivity reflects a generally impaired vascular system. (Stroke. 2014;45:42-47.)

Key Words: epidemiology ■ mortality ■ risk factors ■ stroke

Vascular diseases are the main cause of mortality worldwide and lead to considerable societal burden, both in terms of care and cost. The World Health Organization estimated that by 2030, >23 million people will die yearly from vascular diseases.1 Despite the acute clinical presentation, an important feature of vascular diseases is the long preclinical phase, during which various pathologies interact leading to accumulating vascular damage. These pathologies include atherosclerosis, arterial stiffening, inflammation, and endothelial damage.2,4 In the brain, this pathological process ultimately manifests itself as either ischemic or hemorrhagic stroke.7

A cornerstone of preventive research has been to identify markers that reflect such preclinical vascular pathology and thus may predict shorter survival. For cerebrovascular damage, diminished vasomotor reactivity has been identified in recent years as a prognostic marker.6 Cerebral vasomotor reactivity reflects the ability of the cerebral arterioles to dilate in the event of hypercapnia to improve cerebral blood flow.9,10 Clinically, cerebral vasomotor reactivity can be measured using transcranial Doppler. Most studies investigating vasomotor reactivity were in clinical populations of patients with carotid artery stenosis. In these studies, impaired vasomotor reactivity was associated with an increased risk of stroke and transient ischemic attack.8,11–16 However, its role in the general, community-dwelling population is less clear. Vasomotor reactivity has been measured within the population-based Rotterdam Study, but no association between vasomotor reactivity and stroke was found.7,17

Still, the question remains whether impaired cerebral vasomotor reactivity associates with poorer survival in a general elderly population. Specifically, it is unknown whether any such associations are driven by stroke, or whether cerebral vasomotor reactivity actually reflects more systemic vascular damage. Therefore, we investigated the association of cerebral vasomotor reactivity with all-cause mortality and cardiovascular mortality in a community-dwelling elderly population. Furthermore, we studied whether any associations were independent of incident stroke.

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Drs Portegies and de Bruijn contributed equally.

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Materials and Methods

Setting
This study is part of the Rotterdam Study, a prospective population-based cohort study that started in 1990 among inhabitants aged ≥25 years residing in Ommoord, a suburb of Rotterdam, the Netherlands. Of the 10,215 eligible inhabitants, 7,983 agreed to participate in the baseline examinations. Until 2013, there have been 4 follow-up examinations. Details of the study have been described elsewhere.19 The medical ethics committee at Erasmus University of Rotterdam approved the study, and written informed consent was obtained from all participants. For the present study, the second follow-up examination from 1997 to 1999 was used as baseline, because transcranial Doppler measurements were performed only at that visit.

Transcranial Doppler Assessment
At the examination in 1997 to 1999, participants underwent transcranial Doppler ultrasonography (Multi-Dop X-4; DWL, Sipplingen, Germany). Vasomotor reactivity was measured as follows17: Cerebral blood flow velocity was measured at the middle cerebral artery continuously. End-diastolic, peak systolic, and mean cerebral blood flow velocities were recorded automatically. Mean blood flow velocity was calculated automatically as (1/3*(peak systolic flow velocity+2*end-diastolic flow velocity)).18 Blood pressure was measured automatically (Dynamap; Datascopc, Hoeveraken, the Netherlands) before and during transcranial Doppler recordings. Participants first breathed room air through an anesthetic mask, tightly fit over mouth and nose, until a steady expiratory end-tidal CO2 was obtained. One-way valves were placed in the tubes for inspiration and expiration. End-tidal CO2 pressure (kPa), measured in the exhaled air, was recorded continuously with a CO2 analyzer (Multinex; Datascopc). End-expiratory CO2 was assumed to reflect arterial CO2.20 Participants then inhaled a mixture of 5% CO2 in 95% O2 for 2 minutes. Vasomotor reactivity was defined as the percentage increase in mean cerebral blood flow velocity during inspiration of 5% CO2, divided by the absolute increase in end-tidal CO2 in the same time period (%/kPa). TCD-8 DWL special software (VMR–CO2) was used. All transcranial Doppler data were stored on hard disk for offline analysis.

Assessment of Mortality
Deaths were continuously reported through automatic linkage of general practitioner files. In addition, municipal records were checked bi-monthly for information on vital status. Information about cause and circumstances of death was obtained from general practitioner and hospital records. Research physicians reviewed all available information and coded the events according to the International Classification of Diseases, 10th edition (ICD-10). If the cause of death was coded as I20–25, 146, 150, 161, 163, 164, 166, 168–70, or 836, the cause of death was labeled as cardiovascular. A consensus panel, led by a physician with expertise in cardiovascular disease, adjudicated the final cause of death according to ICD-10 codes using standardized definitions, as described in detail previously.21 The follow-up was complete until January 1, 2011, for 97.1% of potential person-years.

Assessment of Stroke
At study entry, history of stroke was assessed using home interviews and confirmed by reviewing medical records. Once participants enter the Rotterdam Study, they are continuously followed up for stroke using Cox proportional hazards models. We used these models because we investigated time-to-event data. The underlying time-scale in these models was the follow-up time in years, which was complete until January 1, 2011. Participants were censored with in this follow-up period at date of death, date of loss to follow-up, or January 1, 2011, whichever date came first. The proportional hazards assumption was met.

Because of a right skewed distribution of vasomotor reactivity, we first performed a natural logarithmic transformation to obtain a roughly normal distribution of the data. Logarithmic-transformed vasomotor reactivity was entered continuously per SD decrease into the models, because a decrease reflects an impaired reactivity. We presented the results per SD merely for a uniform representation of data; this presentation was also used by Bos et al.23 Furthermore, we studied vasomotor reactivity in quartiles taking the upper quartile as reference. All models were adjusted for age, sex, and blood pressure.

Other Measurements
Covariates were measured during the same examination round as transcranial Doppler measurements were performed (1997–1999). Smoking status and medication use were assessed using a home interview. Smoking was classified into current smoking, former smoking, or never smoking. Diabetes mellitus was defined as having a fasting glucose level of ≥7.0 mmol/L or using blood glucose-lowering medication. Total cholesterol and HDL-cholesterol levels were acquired by an automated enzymatic procedure. Blood pressure was measured at the research center twice in the sitting position on the right arm with a random zero sphygmomanometer. The average of the 2 measurements was used in the analyses. Blood pressure was also measured before and during vasomotor reactivity measurements. We used the difference between these 2 measurements in the analyses because changes in blood pressure caused by CO2 inhalation can influence vasomotor reactivity measurements.22 Prevalent vascular disease (myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, heart failure, and peripheral arterial disease) was, except for peripheral arterial disease, assessed through active follow-up and adjudicated using standardized definitions, as described in detail previously.21 Peripheral arterial disease was assessed using the ankle-brachial index. Ankle-brachial index was assessed by computing the ratio of systolic blood pressure at the right and left ankle to the systolic blood pressure at the right arm. The lowest value was used in the analyses. Values of ankle-brachial index >1.4 were excluded because high ankle-brachial index might represent a different underlying pathology. Peripheral arterial disease was defined as an ankle-brachial index of ≤0.9.24 To measure carotid intima-media thickness (cIMT), ultrasonography of the left and right carotid arteries was performed with a 7.5-MHz linear array transducer (ATL UltraMark IV; Advanced Technology Lab, Tustin, CA). The maximal cIMT, summarized as the mean of maximal measurements from the near and far walls of both the left and right sides, was used for analysis.24,25

Study Population
Of the 5909 participants who were alive in 1997 to 1999, 4797 persons participated in the examination used as baseline for this study. Of these, 4215 visited the study center. Because of lack of technical support, vasomotor reactivity measurements started later in the examination round (from July 1, 1997) and could only be offered to 2732 random participants. After excluding participants with prevalent stroke at time of transcranial Doppler assessment (N=100), 2632 participants were eligible for transcranial Doppler assessment. Of these, 937 participants were excluded because of window failure on both sides (N=656), restlessness, anxiety, and discomfort (N=56), or missing data for other reasons (N=125). This left 1695 participants eligible for the analysis of this study. Participants with a prevalent stroke (i.e., stroke before vasomotor reactivity measurement) have a higher probability of vascular damage of the middle cerebral artery where vasomotor reactivity was measured. Moreover, these persons are both at a higher risk of a recurrent stroke and at a higher risk of mortality compared with persons without prevalent stroke. Including persons with prevalent stroke into our analysis, even if they had a remote stroke, would bias our results.

Statistical Analyses
We investigated the associations of vasomotor reactivity with all-cause mortality, cardiovascular mortality, noncardiovascular mortality, and stroke using Cox proportional hazards models. We used these models because we investigated time-to-event data. The underlying time-scale in these models was the follow-up time in years, which was complete until January 1, 2011. Participants were censored within this follow-up period at date of death, date of loss to follow-up, or January 1, 2011, whichever date came first. The proportional hazards assumption was met.

However, we studied vasomotor reactivity in quartiles taking the upper quartile as reference. All models were adjusted for age, sex, and blood pressure.
changes during vasomotor reactivity measurement. We adjusted subsequently for current smoking, former smoking, use of blood pressure–lowering medication, systolic blood pressure, diastolic blood pressure, diabetes mellitus, total cholesterol, HDL-cholesterol, use of statins, history of vascular disease, and cIMT for being potential confounders. Missing data on covariates (≤8.4%) were imputed based on sex and age using linear regression models.

To investigate whether vasomotor reactivity within normal ranges was associated with mortality, we repeated the analysis after excluding participants with an exhausted vasomotor reactivity (<5.3%/kPa, as described previously).12

To assess the role of stroke on these associations, we related vasomotor reactivity to stroke as well as to mortality after censoring for stroke. We performed an additional analysis to investigate whether diminished vasomotor reactivity acts as intermediate between various cardiovascular risk factors and risk of mortality. We associated the various cardiovascular risk factors with mortality and investigated whether adjustment for vasomotor reactivity affected these associations. All analyses were done using the IBM SPSS Statistics version 20.0 (IBM Corp., Armonk, NY).

**Results**

Table 1 shows baseline characteristics of the study population. Nonparticipants were older and majorly women compared with participants. Also, they smoked less; had a higher HDL-cholesterol, a larger cIMT, prevalent vascular disease; and often used blood pressure–lowering medication and statins, compared with participants.

The average follow-up duration for total mortality was 10.0 years, during which a total of 557 of 1695 participants died, of whom 181 due to a cardiovascular cause and 376 due to a noncardiovascular cause. The most important cardiovascular causes of death were stroke (N=41), heart failure (N=39), cardiac arrest (N=29), other sudden death with unknown cause (N=24), and acute myocardial infarction (N=26). The most important noncardiovascular causes of death were cancer (N=170, especially lung [N=45], colon [N=22], pancreas [N=15], and breast [N=10]), and dementia [N=40]). Of the 1037 nonparticipants, 457 (44.1%) died. This difference was statistically significant compared with the number of deaths in the study population.

A total of 168 participants had a stroke, of which 92 participants died because of either stroke or other causes. After censoring for stroke, a total of 465 participants died, 131 due to a cardiovascular cause and 334 due to a noncardiovascular cause. The most important cardiovascular causes of death in this latter group were heart failure (N=36), cardiac arrest (N=29), other sudden death with unknown cause (N=21), and acute myocardial infarction (N=24).

Table 2 shows the hazard ratios of all-cause mortality. A lower vasomotor reactivity was associated with a higher risk of all-cause mortality (hazard ratio [HR] per SD decrease in vasomotor reactivity, 1.12; 95% confidence interval [CI], 1.03–1.21). These associations remained unchanged after additional adjustments (HR, 1.10; 95% CI, 1.01–1.19). Also, persons in the lowest 2 quartiles had an increased risk of death compared with the upper quartile (Table 2). Figure shows the corresponding Kaplan–Meier curves for these associations.

Associations between vasomotor reactivity and mortality were stronger for cardiovascular mortality (HR per SD decrease, 1.15; 95% CI, 1.00–1.32), whereas the associations

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**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Participants (N=1695)</th>
<th>Nonparticipants (N=1037)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, (SD), y</td>
<td>70.7 (6.3)</td>
<td>73.2 (6.8)†</td>
</tr>
<tr>
<td>Follow-up time mortality, mean (SD), y</td>
<td>10.0 (3.0)</td>
<td>9.5 (3.3)†</td>
</tr>
<tr>
<td>Women, No. (%)</td>
<td>785 (46.3)</td>
<td>760 (73.3)†</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mmHg</td>
<td>142.7 (20.8)</td>
<td>145.1 (21.4)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean (SD), mmHg</td>
<td>75.9 (11.1)</td>
<td>75.2 (11.0)</td>
</tr>
<tr>
<td>Blood pressure–lowering medication, No. (%)</td>
<td>384 (23.2)</td>
<td>293 (29.2)†</td>
</tr>
<tr>
<td>Diabetes mellitus, No. (%)</td>
<td>158 (9.5)</td>
<td>111 (10.9)</td>
</tr>
<tr>
<td>Former smoking, No. (%)</td>
<td>990 (58.8)</td>
<td>447 (43.5)†</td>
</tr>
<tr>
<td>Current smoking, No. (%)</td>
<td>311 (18.5)</td>
<td>176 (17.1)</td>
</tr>
<tr>
<td>Total cholesterol, mean (SD), mmol/L</td>
<td>5.81 (0.99)</td>
<td>5.85 (1.01)</td>
</tr>
<tr>
<td>HDL-cholesterol, mean (SD), mmol/L</td>
<td>1.38 (0.38)</td>
<td>1.42 (0.39)†</td>
</tr>
<tr>
<td>Statins, No. (%)</td>
<td>216 (12.9)</td>
<td>154 (15.1)†</td>
</tr>
<tr>
<td>History of vascular disease, No. (%)</td>
<td>368 (23.3)</td>
<td>256 (27.1)†</td>
</tr>
<tr>
<td>Carotid intima-media thickness, mean (SD), mm</td>
<td>1.06 (0.18)</td>
<td>1.09 (0.20)†</td>
</tr>
<tr>
<td>Difference in systolic blood pressure before and during measurement, mean (SD), mmHg</td>
<td>14.9 (13.8)</td>
<td>NA</td>
</tr>
<tr>
<td>Difference in diastolic blood pressure before and during measurement, mean (SD), mmHg</td>
<td>5.7 (7.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Vasomotor reactivity, median (IQR)*, %/kPa</td>
<td>39.3 (28.1–54.0)</td>
<td>NA</td>
</tr>
</tbody>
</table>

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**Table 2. Vasomotor Reactivity and Risk of All-Cause Mortality**

<table>
<thead>
<tr>
<th>Vasomotor Reactivity*</th>
<th>n/N</th>
<th>Model I†, HR (95% CI)</th>
<th>Model II‡, HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile 1</td>
<td>182/423</td>
<td>1.40 (1.10–1.80)</td>
<td>1.30 (1.01–1.67)</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>154/424</td>
<td>1.36 (1.06–1.74)</td>
<td>1.33 (1.03–1.71)</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>117/424</td>
<td>1.04 (0.79–1.35)</td>
<td>1.07 (0.82–1.40)</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>104/424</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
</tbody>
</table>

Per SD decrease 557/1695 1.12 (1.03–1.21) 1.10 (1.01–1.19)

The range of vasomotor reactivity for each quartile was as follows: quartile 1, 0 to 28.1%/kPa; quartile 2, 28.1 to 39.3%/kPa; quartile 3, 39.3 to 54.0%/kPa; quartile 4, 54.0 to 229.3%/kPa. CI indicates confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; n, number of deaths; and N, number of persons at risk.

†Vasomotor reactivity was natural log-transformed.
‡Model I: adjusted for age, sex, and difference in blood pressure before and during vasomotor reactivity measurement.
§Model II: adjusted for age, sex, current smoking, former smoking, use of blood pressure–lowering medication, systolic blood pressure, diastolic blood pressure, diabetes mellitus, total cholesterol, high-density lipoprotein-cholesterol, use of statins, history of vascular disease, carotid intima-media thickness, and difference in blood pressure before and during vasomotor reactivity measurement.
We found that persons with a lower cerebral vasomotor reactivity have an increased risk of mortality. These associations were independent from cardiovascular risk factors and from incident stroke.

Strengths of this study are the population-based design, thorough collection of events, and long follow-up for both mortality and stroke. A potential limitation is selection bias because transcranial Doppler measurements failed in a large group of participants. The percentage of participants who died was significantly higher among the excluded participants, which might point toward selection bias. Transcranial Doppler measurements failed mainly because of window failure, which occurred more often in women and in older participants. Given that vasomotor reactivity decreases with age, coupled with higher risk of cardiovascular disease, this could have led to a dilution of the effect. Another consideration is potential survivor effect because transcranial Doppler measurements were only performed at the second follow-up examination of the Rotterdam Study. It is possible that unhealthy persons may have died during the intermediate time period. This would have resulted in an underestimation of the effect. A final remark is that we only assessed cMT but did not measure the lumen of the carotid artery and were, therefore, unable to assess extracranial carotid artery stenosis. In the general population, the prevalence of moderate extracranial carotid artery stenosis ranges from 2.0% to 7.5% in persons aged ≥60 years. Given that it affects both cerebral vasomotor reactivity measurements and stroke, extracranial carotid artery stenosis could have influenced our results.

We found that a lower vasomotor reactivity was associated with higher risk of mortality, especially cardiovascular mortality. These results suggest that a low vasomotor reactivity is a marker of accumulating vascular damage. We did find a dose–response relation between vasomotor reactivity and all-cause mortality; however, this relation was not found for cardiovascular mortality. Moreover, no clear cut-off between normal and abnormal vasomotor reactivity values can be obtained from these analyses, because the cut-off points for the quartiles are based on this study population and cannot be generalized to other study populations. Vasomotor reactivity is measured in the cerebral vessels, and previous studies have shown that in patients with carotid artery stenosis, those

### Table 3. Vasomotor Reactivity and Risk of Cardiovascular and Noncardiovascular Mortality

<table>
<thead>
<tr>
<th>Vasomotor Reactivity*</th>
<th>Cardiovascular Mortality</th>
<th>Noncardiovascular Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>Model I†, HR (95% CI)</td>
</tr>
<tr>
<td>Quartile 1</td>
<td>56/423</td>
<td>1.62 (1.01–2.59)</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>59/424</td>
<td>1.99 (1.26–3.15)</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>39/424</td>
<td>1.30 (0.79–2.13)</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>27/424</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Per SD decrease</td>
<td>181/1695</td>
<td>1.15 (1.00–1.32)</td>
</tr>
</tbody>
</table>

*The range of vasomotor reactivity for each quartile was as follows: quartile 1, 0 to 28.1%/kPa; quartile 2, 28.1 to 39.3%/kPa; quartile 3, 39.3 to 54.0%/kPa; quartile 4, 54.0 to 229.3%/kPa. CI indicates confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; n, number of deaths; and N, number of persons at risk.
†Model I: adjusted for age, sex, and difference in blood pressure before and during vasomotor reactivity measurement.
‡Model II: adjusted for age, sex, current smoking, former smoking, use of blood pressure–lowering medication, systolic blood pressure, diastolic blood pressure, diabetes mellitus, total cholesterol, high-density lipoprotein-cholesterol, use of statins, history of vascular disease, carotid intima-media thickness, and difference in blood pressure before and during vasomotor reactivity measurement.
Although associations with cardiovascular mortality attenuated after adjustment for cardiovascular risk factors and became statistically nonsignificant, an effect size in excess of 1.3 remained for each of the lowest 3 quartiles compared with the upper quartile. This suggests that part of the effect of vasomotor reactivity is independent from cardiovascular risk factors. Also, it is questionable whether such an adjustment is a correction for potential confounders or actually an overadjustment for possible intermediates of the causal chain. Nevertheless, some remarks can be made on the results after these adjustments. First, previous studies have shown that hypertension, smoking, and dyslipidemia disrupt the vascular homeostasis. This might cause endothelial dysfunction, which eventually contributes to cardiovascular disease.3,32 Endothelial dysfunction leads to a lower excretion of dilatory factors, such as NO, and could also lead to a lower vasomotor reactivity. Second, it is possible that participants with unrecognized risk factors did not receive preventative treatment and, therefore, were more at risk for a cardiovascular event than those in whom cardiovascular risk factors were present and thus treated. This would lead to a minimal effect of adjusting for such risk factors. Third, we adjusted for baseline measurements of cardiovascular risk factors, which might be less representative for lifelong exposure. A final consideration is that vasomotor reactivity reflects a different mechanism of vascular damage, not explained by cardiovascular risk factors but by risk factors that we did not measure, such as genetic factors.33,34 Conversely, we found that the associations of cardiovascular risk factors with mortality remained unchanged after adjusting for vasomotor reactivity. It is likely that these factors exert their effect through many different mediators, among which is vasomotor reactivity.

Because vascular disease is the leading cause of mortality worldwide, there is an urgent need for preventive options. As such, markers of early vascular damage are of much interest. Our study on vasomotor reactivity and mortality is set in a community-dwelling population. Unlike in a clinical setting, our participants are relatively healthy and the amount of available in-depth data is limited. We, therefore, do not have additional data to clarify the potential cause of diminished vasomotor reactivity. The association between a lower vasomotor reactivity and higher risk of cardiovascular mortality, thus, merits further investigation. Specifically, unravelling the underlying mechanism and the possible contribution to identification of high-risk individuals is worthy of future research. Also, it

### Table 4. Vasomotor Reactivity and the Risk of Stroke

<table>
<thead>
<tr>
<th>Vasomotor Reactivity*</th>
<th>n/N</th>
<th>Model I†, HR (95% CI)</th>
<th>Model II‡, HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile 1</td>
<td>47/423</td>
<td>1.11 (0.72–1.71)</td>
<td>1.10 (0.71–1.70)</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>46/424</td>
<td>1.15 (0.75–1.77)</td>
<td>1.15 (0.74–1.77)</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>37/424</td>
<td>0.90 (0.57–1.43)</td>
<td>0.92 (0.58–1.45)</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>38/424</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Per SD decrease</td>
<td>168/1695</td>
<td>1.06 (0.91–1.23)</td>
<td>1.06 (0.91–1.23)</td>
</tr>
</tbody>
</table>

The range of vasomotor reactivity for each quartile was as follows: quartile 1, 0 to 28.1%/kPa; quartile 2, 28.1 to 39.3%/kPa; quartile 3, 39.3 to 54.0%/kPa; quartile 4, 54.0 to 229.3%/kPa. CI indicates confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; n, number of deaths; and N, number of persons at risk.

*Vasomotor reactivity was natural log-transformed.
†Model I: adjusted for age, sex, and difference in blood pressure before and during vasomotor reactivity measurement.
‡Model II: adjusted for age, sex, current smoking, former smoking, use of blood pressure-lowering medication, systolic blood pressure, diastolic blood pressure, diabetes mellitus, total cholesterol, high-density lipoprotein-cholesterol, use of statins, history of vascular disease, carotid intima-media thickness, and difference in blood pressure before and during vasomotor reactivity measurement.

with a lower vasomotor reactivity have an increased risk of stroke.8,11–16 Consequently, our findings with all-cause and cardiovascular mortality could be explained by stroke and stroke-related deaths. However, we did not find vasomotor reactivity to be associated with stroke. This is consistent with what was found before within the same study population, with shorter follow-up.18 Furthermore, the association of lower vasomotor reactivity with both all-cause and cardiovascular mortality was independent from incident stroke. The main causes of cardiovascular death after censoring for strokes were heart failure, cardiac arrest, sudden death with unknown cause, and myocardial infarction. This supports the hypothesis that loss of cerebral vasomotor reactivity is a reflection of a more systemic dysfunction of the vascular system rather than only cerebrovascular damage. Further evidence comes from previous studies that have reported a link between peripheral artery endothelial dysfunction and cerebrovascular reactivity.26,29 Still, we note that some studies did not find an association between flow-mediated vasodilatation in the brachial artery, which is an indirect measure of peripheral endothelial dysfunction, and cerebrovascular reactivity.30,31 Inconsistencies across studies might be explained by methodological differences and differences in study population.

### Table 5. Vasomotor Reactivity and Risk of Mortality, After Censoring for Incident Stroke

<table>
<thead>
<tr>
<th>Vasomotor Reactivity*</th>
<th>n/N</th>
<th>All-Cause Mortality, HR (95% CI)</th>
<th>Cardiovascular Mortality, HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile 1</td>
<td>150/423</td>
<td>1.49 (1.13–1.96)</td>
<td>41/423</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>128/424</td>
<td>1.39 (1.05–1.83)</td>
<td>43/424</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>103/424</td>
<td>1.13 (0.85–1.51)</td>
<td>28/424</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>84/424</td>
<td>1 (reference)</td>
<td>19/424</td>
</tr>
<tr>
<td>Per SD decrease</td>
<td>465/1695</td>
<td>1.12 (1.03–1.22)</td>
<td>131/1695</td>
</tr>
</tbody>
</table>

The range of vasomotor reactivity for each quartile was as follows: quartile 1, 0 to 28.1%/kPa; quartile 2, 28.1 to 39.3%/kPa; quartile 3, 39.3 to 54.0%/kPa; quartile 4, 54.0 to 229.3%/kPa. Models are adjusted for age, sex, and difference in blood pressure before and during vasomotor reactivity measurement. CI indicates confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; n, number of deaths; and N, number of persons at risk.

*Vasomotor reactivity was natural log-transformed.
would be of interest to investigate the association of vasomotor reactivity and white matter lesions measured on MRI.

Conclusions
Our results indicate that loss of cerebral vasomotor reactivity is associated with an increased risk of mortality, especially cardiovascular mortality, independent of stroke. This suggests that impaired cerebral vasomotor reactivity reflects a systemically impaired vascular system.

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Disclosures
None.

References
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Cerebral vasomotor reactivity and the risk of mortality: the Rotterdam Study

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Itemized list of tables and figures:

- Supplementary Table I: Associations between cardiovascular risk factors and all-cause mortality, before and after adjustment for vasomotor reactivity.
Supplementary Table I. Associations between cardiovascular risk factors and all-cause mortality, before and after adjustment for vasomotor reactivity.

<table>
<thead>
<tr>
<th></th>
<th>All-cause mortality n/N 557/1695</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model I†</td>
</tr>
<tr>
<td>Age</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>1.12 (1.10; 1.13)</td>
</tr>
<tr>
<td>Sex</td>
<td>0.76 (0.61; 0.94)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>1.00 (0.99; 1.00)</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>1.00 (0.99; 1.01)</td>
</tr>
<tr>
<td>Blood pressure-lowering medication</td>
<td>1.17 (0.96; 1.43)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.20 (0.93; 1.54)</td>
</tr>
<tr>
<td>Former smoking</td>
<td>1.16 (0.94; 1.43)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>2.08 (1.65; 2.63)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.93 (0.85; 1.02)</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>0.86 (0.67; 1.11)</td>
</tr>
<tr>
<td>Statins</td>
<td>0.72 (0.55; 0.95)</td>
</tr>
<tr>
<td>History of vascular disease</td>
<td>1.55 (1.27; 1.88)</td>
</tr>
<tr>
<td>Carotid intima-media thickness</td>
<td>1.84 (1.13; 2.99)</td>
</tr>
</tbody>
</table>

Abbreviations: n, number of deaths; N, number of persons at risk; HR, hazard ratio; CI, confidence interval; HDL, high-density lipoprotein.

Values are hazard ratios with 95% confidence intervals.

† Model I: Adjusted for age, sex, current smoking, former smoking, use of blood pressure-lowering medication, systolic blood pressure, diastolic blood pressure, diabetes mellitus, total cholesterol, HDL-cholesterol, use of statins, history of vascular disease, and carotid intima-media thickness.

‡ Model II: Adjusted for age, sex, current smoking, former smoking, use of blood pressure-lowering medication, systolic blood pressure, diastolic blood pressure, diabetes mellitus, total cholesterol, HDL-cholesterol, use of statins, history of vascular disease, carotid intima-media thickness, and vasomotor reactivity (natural log transformed).