Transcranial Doppler Hemodynamic Parameters and Risk of Stroke
The Rotterdam Study

Michiel J. Bos, MD, MSc; Peter J. Koudstaal, MD, PhD; Albert Hofman, MD, PhD; Jacqueline C.M. Witteman, PhD; Monique M.B. Breteler, MD, PhD

Background and Purpose—We explored the association between transcranial Doppler hemodynamic parameters and the risk of stroke in the general population.

Methods—At baseline, we assessed mean flow velocity, peak systolic flow velocity, end diastolic flow velocity, and vasomotor reactivity with transcranial Doppler in 2022 Rotterdam Study participants aged 61 years and over in both middle cerebral arteries. All participants, who at baseline were free from previous stroke, were subsequently followed for occurrence of stroke (average follow-up time 5.1 years). We calculated hazard ratios for the association between hemodynamic parameters and risk of stroke using Cox proportional hazards models with adjustment for age, sex, systolic blood pressure, antihypertensive drug use, diabetes mellitus, ever smoking, current smoking, carotid intima media thickness, and carotid distensibility.

Results—Risk of stroke (n=122) and ischemic stroke (n=89) increased with increasing middle cerebral artery flow velocity; when comparing the tertile with highest velocity to the tertile with lowest velocity, the hazard ratio was 1.74 (95% CI: 1.09 to 2.77) for the association between mean flow velocity and stroke, 1.63 (95% CI: 1.03 to 2.58) for end diastolic flow velocity and stroke, and 1.33 (95% CI: 0.86 to 2.08) for peak systolic flow velocity and stroke. These estimates increased 10% to 26% when only ischemic strokes were included. The side of highest flow velocity was not associated with the side of stroke. We found no associations between vasomotor reactivity and risk of stroke.

Conclusions—Risk of stroke increased strongly with increasing middle cerebral artery flow velocity as measured with transcranial Doppler in the general population. (Stroke. 2007;38:2453-2458.)

Key Words: cerebral infarct ■ cerebrovascular disease ■ risk factors ■ stroke ■ TCD
measured with TCD and the risk of stroke in a population-based setting.

Materials and Methods

Population

The Rotterdam Study is a population-based cohort study on chronic and disabling diseases.9,10 All inhabitants of Ommoord, a district of the city of Rotterdam in The Netherlands, aged 55 years and over, were invited to participate. Participation rate of those invited for the study was 78%; in total, 7983 subjects participated in the first study survey (1990–1993). Baseline measurements for the present study were done during the third survey of the Rotterdam Study (1997–1999); at this time, participants were 61 years of age and over. The third study survey included only participants who had also participated in the first survey. The Medical Ethics Committee of Erasmus University Rotterdam approved the study. Written informed consent to retrieve information from treating physicians was obtained from all participants. Follow up was from TCD assessment to first-ever stroke, death, study end, or loss to follow up (whichever occurred first).

Assessment of Stroke

History of stroke at time of enrollment into the first Rotterdam Study survey (1990–1992) was positive if a stroke was reported during the interview and confirmed by medical records. After enrollment into the Rotterdam Study, participants were continuously monitored for strokes through automated linkage of the study database with files from general practitioners and the municipality. Also, nursery home physicians' files and files from general practitioners of participants who moved out of the district were scrutinized. For reported events, additional information (including brain imaging) was obtained from hospital records. Research physicians discussed information on all potential strokes with an experienced stroke neurologist (P.J.K.) to verify all diagnoses. Subarachnoid hemorrhages were excluded. A stroke was subclassified as ischemic when a CT or MRI scan, made within 4 weeks after the stroke occurred, ruled out other diagnoses or when indirect evidence (deficit limited to one limb or completely resolved within 72 hours, atrial fibrillation in the absence of anticoagulants) pointed at an ischemic nature of the stroke. Follow up was complete until January 1, 2005, for 99.0% of potential person-years.11

Transcranial Doppler Assessment

All participants underwent TCD ultrasonography monitoring in one session during the third Rotterdam Study survey, which was the baseline measurement for the present study. This monitoring (Multi-Dop X-4; DWL, Sipplingen, Germany) was performed to measure the cerebral blood flow velocity in the middle cerebral artery on both sides. End diastolic, peak systolic, and mean cerebral blood flow velocities were recorded automatically. If automatic recording was not possible, the participant was excluded from the study. All velocities were measured at a depth of 50 mm or as close as possible to this depth. The mean cerebral blood flow velocity was defined as: 1/3*(peak systolic flow velocity + 2*end diastolic flow velocity). If flow velocity was available for both sides, the average value was used. Cerebrovascular CO₂ reactivity was measured as follows: the cerebral blood flow velocity was measured continuously and the participants first breathed room air through an anesthetic mask, tightly fit over the mouth and nose, until a steady expiratory end tidal CO₂ was obtained. Participants were then asked to inhale a mixture of 5% carbon dioxide in 95% oxygen for 2 minutes. Cerebrovascular CO₂ reactivity was defined as the percentage increase in mean cerebral blood flow velocity during inspiration of 5% CO₂/the absolute increase in end tidal CO₂ in the same time period (Δ/kPa). End tidal CO₂ pressure (kPa) was recorded continuously with a CO₂ analyser (Multinex, Datascopc, Hoevelaken, The Netherlands). End expiratory CO₂ was assumed to reflect arterial CO₂.12 All measurements were performed with the participant in the supine position after 5 minutes of rest. TCD-8 DWL special software (VMR–CO₂) was used. All TCD data were stored on hard disk for offline analysis. The TCD studies were performed by one of 3 technicians who were specially trained for the present study.

Other Measurements

Blood pressure was measured twice in the sitting position on the right arm with a random-zero sphygmomanometer. We used the average of these 2 measurements in the analyses. We considered diabetes mellitus to be present if a fasting glucose level was 7.0 mmol/L or higher or if a person used antidiabetic medication. Smoking status was assessed during a home interview. Carotid intima media thickness was measured by longitudinal 2-dimensional ultrasound of the carotid artery.13 We calculated the mean common carotid artery intima media thickness as the mean of 4 locations: the near and far wall of both the right and left common carotid artery. Common carotid distensibility was assessed with a duplex scanner connected to a vessel wall movement detector system in the right common carotid artery as described previously.14

Population for Analysis

TCD flow velocity assessment was implemented in the protocol of the third Rotterdam Study survey starting April 8, 1997. From this date onward, 4215 participants visited the study center. Because of lacking technical support over a prolonged period, TCD measurements were only offered to 3118 participants. We excluded all participants who had previous stroke at the time of TCD assessment (n=110), which left 3008 participants eligible for TCD assessment. Of these, 986 participants had window failure on both sides (n=741) or difficulty to participate because of a variety of other reasons, most importantly restlessness, anxiety, and discomfort (n=245). This left 2022 stroke-free participants eligible for the analyses. VMR assessment was only performed from July 1, 1997, leaving 1695 participants eligible for VMR analyses.

Statistical Analysis

We used Cox proportional hazards models to calculate hazard ratios with 95% CIs for the associations between TCD parameters and risk of stroke. Hazard ratios were calculated for sex-specific TCD parameter tertiles (relative to the lowest tertile) and per SD increase in TCD parameter. We performed the analyses per participant, averaging parameters over both middle cerebral arteries if available, and associated this with risk of stroke. We looked separately at TCD mean flow velocity >100 cm/s because this cutoff has been found to correspond well with stenosis of >50%.15 We adjusted for confounding by age and sex, and additionally for confounding by other putative confounders (systolic blood pressure, antihypertensive drug use, diabetes mellitus, ever smoking, current smoking, carotid intima media thickness, and carotid distensibility). Missing values in carotid intima media thickness (n=163) and carotid distensibility (n=546) were imputed with a linear regression model based on age and sex. Analyses were performed with SPSS 11.0.1 for Windows.

Results

Baseline characteristics of the study population are described in Table 1. Flow velocity was available for both sides in 1354 participants and for one side in 668 participants. Measurements failed in 986 participants. TCD measurement failure occurred more often in women and in older participants who possibly had more diabetes mellitus and smoked less.

Average follow up from time of TCD measurement to stroke, death, or censoring was 5.1 years. During this period, 122 strokes occurred; 89 of these were subclassi-
A strong association was found between mean cerebral blood flow velocity and the risk of stroke: the age- and sex-adjusted hazard ratio (95% CI) for upper versus lower tertile of flow velocity was 1.75 (1.10 to 2.77) for the risk of stroke and 2.21 (1.26 to 3.88) for the risk of ischemic stroke (Table 2). End diastolic and peak systolic flow velocities were somewhat weaker but positively associated with the risk of stroke and ischemic stroke, although not statistically significant at α=0.05; hazard ratios for highest versus lowest tertile of end diastolic flow velocity were 1.47 (0.93 to 2.32) for stroke and 1.58 (0.92 to 2.72) for ischemic stroke, hazard ratios (95% CIs) for highest versus lowest tertile of peak systolic flow velocity were 1.42 (0.91 to 2.19) for stroke and 1.69 (1.00 to 2.87) for ischemic stroke. VMR was not associated with the risk of stroke or with risk of left hemispherical stroke in Cox models (P>0.25).

We found no difference in the associations between TCD parameters and stroke when we compared participants of different ages (P interaction=0.33 for all parameters). We also found no difference in the associations between TCD parameters and stroke when we compared men with women (P interaction=0.05 for interaction between end diastolic blood pressure and sex on risk of ischemic stroke; for all other parameters, P interaction>0.10).

In 27 participants (10 males, 17 females, median age 68.9 years), the mean flow velocity in the middle cerebral artery exceeded 100 cm/s; this was a unilateral finding in 24 participants and bilateral in 3 participants. Two strokes occurred in these participants; both strokes were ischemic and in the hemisphere contralateral to the artery with velocity >100 cm/s.

For most participants, the left mean flow velocity was very similar to the right mean flow velocity (Pearson’s correlation coefficient 0.79, P<0.001). In 96% of participants, the difference between left and right mean flow velocity was less than 1 SD of the mean flow velocity distribution. Of all participants with a difference >1 SD (N=134), 4 had a stroke at the side with highest flow velocity, 8 had a stroke at the side with lowest flow velocity, and one had a vertebrobasilar stroke. In addition, we found that the difference between left and right flow velocity was not associated with risk of right hemispherical stroke or with risk of left hemispherical stroke in Cox models (P>0.25).

**Discussion**

In this population-based study in stroke-free subjects aged 61 years and over, we found a strong, significant, and independent association between middle cerebral artery blood flow velocity measured with TCD and the risk of stroke, particularly ischemic stroke. Differences between left and right flow velocities were very small, and the side of highest flow velocity was not associated with the side of stroke. No associations were found between VMR and the risk of stroke.

Before these results can be interpreted, some methodological issues need to be discussed. The strengths of our study are the meticulous stroke case finding and the nearly complete follow up (loss of potential person-years, 1.0%). To our knowledge, ours is the first study that assessed TCD parameters in the general population. Our stringent stroke monitoring procedures allowed us to include also patients with stroke who were not referred to a hospital. A disadvantage is that in these...
cases, neuroimaging was often lacking so that 21% of strokes could not be subclassified into ischemic or hemorrhagic. A limitation of the technique of TCD is window failure. We had bilateral window failure in 33% of participants, which is comparable to other studies, although some studies had a lower failure rate. It is possible that healthy participants in a population study are less inclined to endure the discomfort of TCD investigations than hospital patients. Our decision to restrict ourselves to automated velocity recording increased measurement standardization but could have increased failure rate. As expected, window failure, which primarily depends on temporal bone thickness, occurred most frequently in older persons and in women. Because we found no difference in the associations between TCD parameters and stroke when we compared older with younger participants or when we compared men with women, we think the relative underrepresentation of older women in our study population compared with our source population has not biased our results. Several participants (n = 245) did not have successful TCD assessments because of anxiety or restlessness. To the extent that this could have reflected cerebrovascular dysfunction, it could have led to an underestimation of the true associations. TCD ultrasonography is not the gold standard method to assess intracranial atherosclerosis, but it is very well suited for population-based research on the basis of its noninvasiveness and its strong association with gold standard measurements.

We cannot directly compare our findings regarding the association between middle cerebral artery flow velocity and the risk of stroke with previous studies; in children with sickle cell disease, high flow velocity also predicted a high stroke risk, but the pathophysiological mechanism of stroke in sickle cell disease greatly differs from that in our study population. Another study reported that progression of symptomatic middle cerebral artery stenosis measured with TCD was associated with an increased risk of stroke. Although this study was conducted in patients with stroke and patients with transient ischemic attack rather than in stroke-free subjects and looked at progression of flow velocity rather than at flow velocity itself, we can regard the findings of this study as support for our finding that increased middle cerebral artery flow velocity is associated with an increased risk of stroke.

### TABLE 2. Middle Cerebral Artery Flow Velocity (N=2022) and Vasomotor Reactivity (N=1695) and Risk of Stroke

<table>
<thead>
<tr>
<th>TCD Hemodynamic Parameter*</th>
<th>All Strokes (n=122)</th>
<th>Ischemic Strokes (n=89)</th>
<th>All Strokes (n=122)</th>
<th>Ischemic Strokes (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean flow velocity</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Tertile 1</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>1.60 (1.03–2.48)</td>
<td>2.04 (1.19–3.49)</td>
<td>1.60 (1.03–2.48)</td>
<td>2.04 (1.19–3.49)</td>
</tr>
<tr>
<td>Tertile 3</td>
<td>1.75 (1.10–2.77)</td>
<td>2.21 (1.26–3.88)</td>
<td>1.74 (1.09–2.77)</td>
<td>2.20 (1.25–3.87)</td>
</tr>
<tr>
<td>Per SD</td>
<td>1.25 (1.05–1.49)</td>
<td>1.38 (1.13–1.67)</td>
<td>1.24 (1.04–1.49)</td>
<td>1.37 (1.12–1.68)</td>
</tr>
<tr>
<td><strong>End diastolic flow velocity</strong></td>
<td></td>
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<tr>
<td>Tertile 1</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>1.09 (0.70–1.69)</td>
<td>1.23 (0.73–2.06)</td>
<td>1.12 (0.72–1.75)</td>
<td>1.28 (0.76–2.16)</td>
</tr>
<tr>
<td>Tertile 3</td>
<td>1.47 (0.93–2.32)</td>
<td>1.58 (0.92–2.72)</td>
<td>1.63 (1.03–2.58)</td>
<td>1.80 (1.04–3.11)</td>
</tr>
<tr>
<td>Per SD</td>
<td>1.17 (0.98–1.40)</td>
<td>1.22 (0.99–1.50)</td>
<td>1.20 (1.01–1.43)</td>
<td>1.25 (1.02–1.53)</td>
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<tr>
<td><strong>Peak systolic flow velocity</strong></td>
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<td>Tertile 1</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>1.20 (0.77–1.86)</td>
<td>1.51 (0.89–2.55)</td>
<td>1.16 (0.74–1.80)</td>
<td>1.45 (0.85–2.45)</td>
</tr>
<tr>
<td>Tertile 3</td>
<td>1.42 (0.91–2.19)</td>
<td>1.69 (1.00–2.87)</td>
<td>1.33 (0.86–2.08)</td>
<td>1.58 (0.92–2.69)</td>
</tr>
<tr>
<td>Per SD</td>
<td>1.17 (0.99–1.38)</td>
<td>1.28 (1.06–1.54)</td>
<td>1.14 (0.97–1.35)</td>
<td>1.24 (1.02–1.50)</td>
</tr>
<tr>
<td><strong>Vasomotor reactivity‡</strong></td>
<td></td>
<td></td>
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<tr>
<td>Tertile 1</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>0.73 (0.43–1.24)</td>
<td>0.80 (0.43–1.47)</td>
<td>0.75 (0.44–1.27)</td>
<td>0.81 (0.44–1.51)</td>
</tr>
<tr>
<td>Tertile 3</td>
<td>1.04 (0.63–1.72)</td>
<td>1.17 (0.66–2.09)</td>
<td>1.04 (0.62–1.74)</td>
<td>1.15 (0.64–2.08)</td>
</tr>
<tr>
<td>Per SD</td>
<td>1.03 (0.83–1.28)</td>
<td>1.10 (0.88–1.38)</td>
<td>1.01 (0.82–1.25)</td>
<td>1.07 (0.85–1.33)</td>
</tr>
</tbody>
</table>

*Cut points for tertiles in men: 48 and 60 cm/s (mean flow velocity), 28 and 35 cm/s (end diastolic flow velocity), 76 and 92 cm/s (peak systolic flow velocity), 27 and 34%/kPa (VMR). Cut points for tertiles in women: 52 and 65 cm/s (mean flow velocity), 29 and 37 cm/s (end diastolic flow velocity), 79 and 96 cm/s (peak systolic flow velocity), 31 and 46%/kPa (VMR).

†Model 1: adjusted for age and sex; model 2: adjusted for age, sex, systolic blood pressure, antihypertensive drug use, diabetes mellitus, ever smoking, current smoking, carotid intima media thickness, carotid distensibility.

‡The vasomotor reactivity analyses included 87 incident strokes and 67 incident ischemic strokes.
It has been shown that middle cerebral artery flow velocity can locally be strongly increased by atheroma; in a study among patients with symptomatic intracranial stenosis, it was concluded that a mean flow velocity of >100 cm/s corresponds well with a middle cerebral artery stenosis of 50%.\textsuperscript{15} In our study population, 99% of participants had flow velocities <100 cm/s; therefore, high-grade middle cerebral artery stenoses probably do not account for the associations between flow velocity and stroke that we observed. However, it is possible that a more subtle increase in flow velocity reflects a more subtle, and likely a more generalized, arterial narrowing caused by atherosclerosis. Poiseuille’s law shows that an atherosclerotic decrease in arterial diameter (D) leads to a strong drop in total blood flow (which is proportional to D\textsuperscript{4}) and to a milder drop in flow velocity (which is proportional to D\textsuperscript{2}) unless the effect of arterial narrowing is counterbalanced by an increase in the pressure gradient over the stenosed trajectory. This pressure gradient can be increased by a decrease in pressure downstream to the stenosis or by an increase in blood pressure. If the increase in pressure gradient is large enough to result in a constant total flow, it results in an increased flow velocity. As such, increased flow velocity may be a marker of subtle generalized atherosclerosis. An alternative explanation for our findings is based on the observation that cerebral blood flow is kept constant over a wide blood pressure range by compensatory constriction or dilatation of cerebral arteries and arterioles.\textsuperscript{20} Because this compensatory mechanism is balanced to keep total flow constant and, as described, its effect on total flow is much larger than on flow velocity, the cerebral vasomotor response to increasing blood pressure leads to increasing flow velocity. As such, increased flow velocity may be a marker of increased blood pressure. However, adjusting for systolic blood pressure did not attenuate the observed associations between flow velocity and stroke, which is not in line with the latter hypothesis but could be attributable to residual confounding.

Left and right flow velocity were very similar and the side of highest flow velocity was not associated with the side of stroke. These observations support the hypothesis that moderately increased flow velocity reflects a generalized process rather than a local atheroma causing stenosis and embolus or poor distal flow.

Whereas we found no association between VMR and stroke risk, previous studies reported that patients with impaired vasomotor reactivity were at increased stroke risk.\textsuperscript{6–8} In one of these studies,\textsuperscript{8} arterial CO\textsubscript{2} was raised with a method similar to the one we used, whereas in others,\textsuperscript{6,7} arterial CO\textsubscript{2} was raised with breathholding. However, all these studies were conducted in patients with severe stenocclusive carotid disease, and VMR is strongly influenced by stenocclusive carotid disease; the mean VMR was 16%/kPa in a previous study in 117 patients with >70% carotid stenosis or occlusion,\textsuperscript{8} whereas in the general elderly population, we found a mean VMR of 44%/kPa (median VMR 39%/kPa). Therefore, the contrast between our findings and previous findings might be explained by the much more severe exhaustion of VMR in previous studies among patients with carotid stenosis compared with that in our study population. In conclusion, middle cerebral artery flow velocity is strongly and independently associated with the risk of stroke in the general population. The pathophysiological mechanisms that underlie this association are most likely mild diffuse middle cerebral artery atherosclerosis or middle cerebral artery vasocostriction in response to systemic hypertension. Whereas exhausted VMR is a risk factor for stroke in patients with carotid artery disease, it is not in our study in the general population.

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Disclosures
None.

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