Arterial Stiffness and Cerebral Small Vessel Disease

The Rotterdam Scan Study

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Background and Purpose—Aging and vascular risk factors contribute to arterial stiffening. Increased arterial stiffness exposes the small vessels in the brain to abnormal flow pulsations and, as such, may contribute to the pathogenesis of cerebral small vessel disease. In a population-based study, we investigated the association between arterial stiffness, as measured by aortic pulse wave velocity (aPWV), and small vessel disease.

Methods—Overall, 1460 participants (mean age, 58.2 years) underwent aPWV measurement and brain MRI scanning. We calculated aPWV by measuring time differences and distances between pulse waves in the carotid and femoral arteries. Using automated MRI analysis, we obtained white matter lesion volumes. Infarcts and microbleeds were rated visually. We used linear and logistic regression models to associate aPWV with small vessel disease, adjusting for age, sex, mean arterial pressure, and heart rate and additionally for cardiovascular risk factors. Subsequently, we explored associations in strata of hypertension.

Results—In the study group, higher aPWV was associated with larger white matter lesion volume (difference in volume per SD increase in aPWV 0.07; 95% CI, 0.02–0.12) but not with lacunar infarcts or microbleeds. In persons with uncontrolled hypertension, higher aPWV was significantly associated with larger white matter lesion volume (difference in volume per SD increase in aPWV 0.09; 95% CI, 0.00–0.18), deep or infratentorial microbleeds (OR, 2.13; 95% CI, 1.16–3.91), and to a lesser extent also with lacunar infarcts (OR, 1.63; 95% CI, 0.98–2.70). No such associations were present in persons with controlled hypertension or without hypertension.

Conclusions—In our study, increased arterial stiffness is associated with a larger volume of white matter lesions. (Stroke. 2012;43:00-00.)

Key Words: arterial stiffness ■ epidemiology ■ pulse wave velocity ■ small vessel disease ■ vascular aging

Aging, hypertension, and other cardiovascular risk factors contribute to structural and functional changes of the arterial wall.

These changes result in decreased elasticity and increased stiffness of the arteries. Arterial stiffness, as measured by pulse wave velocity, has been associated with increased risk of cardiovascular disease including clinical stroke.

It has further been suggested that arterial stiffening exposes the small vessels in the brain to highly pulsatile pressure and flow and, as such, may contribute to the pathogenesis of cerebral small vessel disease.

Several studies have indeed shown an association between arterial stiffness and subclinical cerebral small vessel disease, visualized on MRI as white matter lesions (WMLs), lacunar infarcts, or cerebral microbleeds (CMBs).

Some previous studies furthermore suggested that arterial stiffness may be influenced differentially by blood pressure with the strongest effects in subjects with hypertension.

Most of the aforementioned studies, however, used proxy markers for arterial stiffness, including the brachial–ankle pulse wave velocity and arterial pulse waves, or were performed in selected populations with high cardiovascular risk. Carotid–femoral pulse wave velocity is considered as the “gold standard” measurement of arterial stiffness and allows direct investigation of the association between arterial stiffness and small vessel disease.

We investigated in the large population-based Rotterdam Scan Study whether arterial stiffness, as measured by carotid–femoral pulse wave velocity, was related to the presence of...
cerebral small vessel disease, that is, WML, lacunar infarcts, and CMBs, and explored these associations in strata of hypertension.

Methods

Study Population

This study is embedded within the Rotterdam Study, a large population-based cohort study in The Netherlands that started in 1990 and aims to investigate determinants of various chronic diseases among elderly participants. The present study is based on Rotterdam Study III, the second expansion of the Rotterdam Study. In total, Rotterdam Study III comprised 3932 persons (≥45 years of age) of whom 1873 participants had arterial stiffness measurements available. Missing information on arterial stiffness measurement was almost entirely due to logistic reasons, in particular malfunctioning equipment or unavailability of technicians. We excluded individuals who were demented (n=7) or had MRI contraindications (including claustrophobia, n=105). Consequently, 1644 persons were eligible for brain MRI, of whom 1470 (89%) participated. Due to physical inabilities (eg, back pain), imaging could not be performed or completed in 10 individuals, yielding 1460 persons for the analyses. The Medical Ethics Committee of Erasmus Medical Center approved the study, and written informed consent was obtained from all participants.

Measurement of Arterial Stiffness

Carotid–femoral pulse wave velocity (aPWV), a measure of arterial stiffness, was measured with the subjects in the supine position. After 5 minutes of rest, blood pressure was measured twice using an automatic blood pressure recorder (Omron). Subsequently, aPWV was measured. The time delay between the feet of simultaneously recorded pulse waves in the carotid artery and the femoral artery was measured using an automatic device (Compilior Artech Medicla, Pantin, France). The distance traveled by the pulse wave was measured between the sternal notch and the femoral artery using a tape measure. aPWV was calculated as the ratio of the distance traveled by the pulse wave and the foot-to-foot time delay and was expressed in meters per second. The average of 10 successive measurements, to cover a complete respiratory cycle, was used in the analyses.

Brain MRI

Brain MRI was performed on a 1.5-T scanner (GE Healthcare, Milwaukee, WI) with an 8-channel head coil and included T1-weighted, proton-density weighted, fluid-attenuated inversion recovery, and T2*-weighted gradient echo sequences.

WML volume was quantified with a validated tissue classification technique and was calculated by summing all voxels of the WML class across the whole brain. Rating of CMBs and infarcts was performed according to a previously described protocol. Infarcts were divided into cortical or lacunar. CMBs were categorized into one of 3 locations: lobar, deep, or infratentorial. We made separate categories of persons who had one or more microbleeds restricted to a lobar location (strictly lobar microbleeds) and persons with microbleeds in a deep or infratentorial location with or without one or more lobar microbleeds (deep or infratentorial microbleeds).

Cardiovascular Risk Factors

Based on previous literature, we considered the following cardiovascular risk factors as covariates in the models. Information on medical history, smoking habits, and medication use was obtained during the home interview. Smoking status was divided into 3 categories: current, former, and never smokers. The waist and hip circumference were measured, and the waist–hip ratio was computed (waist circumference divided by the hip circumference in centimeters). Blood pressure measurements were obtained as described previously. Pulse pressure was defined as the difference between systolic and diastolic blood pressure. We calculated mean arterial pressure as diastolic blood pressure plus one third of the pulse pressure. Diabetes mellitus was defined as a history of diabetes mellitus and/or the use of blood glucose-lowering medication and/or a fasting serum glucose level ≥7.0 mmol/L. Serum total cholesterol and high-density lipoprotein cholesterol values were determined by an automated enzymatic procedure (Boehringer Mannheim System).

Statistical Analysis

We investigated the association of aPWV per SD increase with WML volume using linear regression models. WML volumes were natural log transformed because of skewness of the untransformed measure. Logistic regression models were used for the association of aPWV per SD increase with lacunar infarcts, deep or infratentorial microbleeds, and strictly lobar microbleeds.

All analyses were initially adjusted for age, sex, mean arterial pressure, and heart rate and additionally for blood pressure-lowering medication, diabetes mellitus, body mass index, current smoking status, total cholesterol, high-density lipoprotein cholesterol, and lipid-lowering medication. Analyses regarding WML volumes were additionally adjusted for intracranial volume to correct for differences in individual head size.

In line with previous studies suggesting differential effects of arterial stiffness according to blood pressure, we defined 3 categories of hypertension: (1) no hypertension (systolic blood pressure <140 mm Hg and a diastolic blood pressure <90 mm Hg without use of antihypertensive medication); (2) controlled hypertension (systolic blood pressure <140 mm Hg and a diastolic blood pressure <90 mm Hg with use of antihypertensive medication); and (3) uncontrolled hypertension (systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg with or without use of antihypertensive medication) and repeated the analyses stratified for these categories.

To create a more robust measure of cerebral small vessel disease, we combined different markers of arteriolar/sclerotic small vessel disease into one variable. Because it was previously shown that CMBs in deep or infratentorial brain regions are indicative of hypertensive or arteriolar/sclerotic vasculopathy, we included microbleeds in these locations in this combined variable along with the highest quartile of WML volume and presence of lacunar infarcts. In the analysis using this combined variable as the outcome, persons in the lowest quartile of arterial stiffness (indicating best state of the arteries) were taken as the reference category.

We added interaction terms to the models to test differences between categories of hypertension (aPWV×[un]controlled hypertension) regarding the association of arterial stiffness with small vessel disease.

Previous studies have described an association between arterial stiffness and large artery disease. Therefore, we performed additional analyses excluding persons with cortical infarcts (n=44) to rule out that associations in our study are driven by cortical infarcts. All analyses were performed using the statistical package SPSS 17.0 (SPSS Inc, Chicago, IL).

Results

Table 1 presents the characteristics of the study population. Mean age of the study population was 58.2 years, and 809 (55%) were women. Carotid–femoral pulse wave velocity increased with age (difference in aPWV per year increase in age, 0.11; 95% CI, 0.10–0.12). Table 2 shows the association between aPWV per SD increase and markers of cerebral small vessel disease. Persons with higher aPWV had a larger volume of WML (difference in WML volume per SD increase in aPWV, 0.07; 95% CI, 0.02–0.12) independent of age, sex, mean arterial pressure, heart rate, intracranial volume, and other vascular risk factors. No significant associations were found between aPWV and lacunar infarcts or microbleeds (Table 2).
In this cross-sectional population-based study, we found that persons with high arterial stiffness, as measured by aPWV, had a larger volume of WMLs.

Strengths of our study include the population-based setting, the large sample size, and our focus on various subclinical manifestations of cerebral small vessel disease, including CMBs, which are a relatively new marker of cerebral vasculopathy. Furthermore, we measured arterial stiffness with aPWV, which is generally accepted as the most simple, noninvasive, robust, and reproducible method to determine arterial stiffness.17,24

The present study, however, has also limitations. First, our study has a cross-sectional design in which association does not imply causation. Future studies are clearly needed to further clarify the found association and elucidate possible underlying mechanisms. Moreover, if reversible, arterial stiffness may be a target for preventive therapies. Second, information on measures of arterial stiffness was available for somewhat less than half of the study cohort. When we compared persons with and without arterial stiffness measurements, we found that persons with arterial stiffness measurements were older and more often male, but other characteristics did not differ significantly after correction for differences in age and sex (online-only Data Supplement). Therefore, we do not think that this has led to any selection biases. Nevertheless, any residual selection bias due to missing data cannot be fully ruled out. Third, WML volumes were natural log transformed because of skewness of the untransformed measure. When back transformed, we note that the effect size seen of aPWV per SD increase in persons with uncontrolled hypertension corresponds with a white

### Table 1. Baseline Characteristics of the Study Population (N=1460)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58.2 (7.2)</td>
</tr>
<tr>
<td>Women</td>
<td>809 (55.4%)</td>
</tr>
<tr>
<td>Aortic pulse wave velocity, m/s</td>
<td>9.0 (SD 1.6)</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>96.5 (SD 11.7)</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>64.5 (SD 13.5)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>130.0 (SD 17.6)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>79.8 (SD 9.7)</td>
</tr>
<tr>
<td>Blood pressure-lowering medication</td>
<td>393 (27.2%)</td>
</tr>
<tr>
<td>Smoking, ever</td>
<td>1005 (69.3%)</td>
</tr>
<tr>
<td>Waist–hip ratio</td>
<td>0.86 (SD 0.09)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>111 (7.8%)</td>
</tr>
<tr>
<td>Serum total cholesterol, mmol/L</td>
<td>5.52 (SD 1.04)</td>
</tr>
<tr>
<td>Serum HDL cholesterol, mmol/L</td>
<td>1.43 (SD 0.42)</td>
</tr>
<tr>
<td>Lipid-lowering medication</td>
<td>320 (22.2%)</td>
</tr>
<tr>
<td>White matter lesions on MRI, mL, median (interquartile range)</td>
<td>2.2 (1.4–3.8)</td>
</tr>
<tr>
<td>Lacunar infarcts on MRI</td>
<td>63 (4.3%)</td>
</tr>
<tr>
<td>Strictly lobar cerebral microbleeds on MRI</td>
<td>147 (10.1%)</td>
</tr>
<tr>
<td>Deep or infratentorial microbleeds on MRI</td>
<td>48 (3.3%)</td>
</tr>
</tbody>
</table>

Values are means with SD or numbers with percentages, unless specified otherwise. Data are missing for smoking (n=10), waist–hip ratio (n=32), diabetes (n=32), serum cholesterol (n=23), medication use (n=17), cerebral microbleeds (n=6), lacunar infarcts (n=6), and white matter lesions (n=34).

HDL indicates high-density lipoprotein.

### Table 2. The Association of Arterial Stiffness, as Measured by Aortic Pulse Wave Velocity, With Cerebral Small Vessel Disease

<table>
<thead>
<tr>
<th>Pulse Wave Velocity</th>
<th>White Matter Lesions*†</th>
<th>Lacunar Infarcts</th>
<th>Deep or Infratentorial Microbleeds‡</th>
<th>Strictly Lobar Microbleeds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Differences in WML Volume (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
</tbody>
</table>

Per SD increase, Model I

| 0.08 (0.03–0.13) | 1.25 (0.92–1.69) | 1.27 (0.91–1.76) | 0.98 (0.79–1.21) |

Per SD increase, Model II

| 0.07 (0.02–0.12) | 1.26 (0.92–1.73) | 1.25 (0.90–1.75) | 0.99 (0.79–1.23) |

Values represent difference in white matter lesion (WML) volumes per SD increase in pulse wave velocity or ORs with 95% CIs.

Model I: adjusted for age, sex, mean arterial pressure, and heart rate. Model II: adjusted for age, sex, mean arterial pressure, heart rate, smoking, waist–hip ratio, diabetes, cholesterol, high-density lipoprotein cholesterol, use of lipid-lowering drugs, and use of blood pressure-lowering drugs. Values of white matter lesions are natural log-transformed. To obtain volumes in milliliters, back transformation is needed.

*Log-transformed.
†Additionally adjusted for intracranial volume.
‡With or without lobar microbleeds.

### Discussion

Studying the population in strata of hypertension, as shown in Table 3, revealed that in persons with uncontrolled hypertension, high aPWV was associated both with larger WML volume and with CMBs in deep or infratentorial locations. Furthermore, although not significant, these persons also tended to have a higher prevalence of lacunar infarcts when arterial stiffness values were higher (OR per SD increase in aPWV, 1.63; 95% CI, 0.98–2.70). Among persons without hypertension or with controlled hypertension, no associations were found between arterial stiffness and presence of cerebral small vessel disease (Figure A–B), yet in persons with uncontrolled hypertension, we found that those in the highest quartiles of aPWV had a higher prevalence of cerebral small vessel disease compared with the reference group (Figure C). All statistical interaction terms testing differential effects of (un)controlled hypertension versus no hypertension were nonsignificant. Repeating the analyses after excluding subjects with cortical infarcts did not change any of the results.

The Figure shows the association between quartiles of aPWV and presence of cerebral small vessel disease. In persons without hypertension or with controlled hypertension, no associations were found between arterial stiffness and presence of cerebral small vessel disease (Figure A–B), yet in persons with uncontrolled hypertension, we found that those in the highest quartiles of aPWV had a higher prevalence of cerebral small vessel disease compared with the reference group (Figure C). All statistical interaction terms testing differential effects of (un)controlled hypertension versus no hypertension were nonsignificant. Repeating the analyses after excluding subjects with cortical infarcts did not change any of the results.

In this cross-sectional population-based study, we found that persons with high arterial stiffness, as measured by aPWV, had a larger volume of WMLs.

Strengths of our study include the population-based setting, the large sample size, and our focus on various subclinical manifestations of cerebral small vessel disease, including CMBs, which are a relatively new marker of cerebral vasculopathy. Furthermore, we measured arterial stiffness with aPWV, which is generally accepted as the most simple, noninvasive, robust, and reproducible method to determine arterial stiffness.17,24

The present study, however, has also limitations. First, our study has a cross-sectional design in which association does not imply causation. Future studies are clearly needed to further clarify the found association and elucidate possible underlying mechanisms. Moreover, if reversible, arterial stiffness may be a target for preventive therapies. Second, information on measures of arterial stiffness was available for somewhat less than half of the study cohort. When we compared persons with and without arterial stiffness measurements, we found that persons with arterial stiffness measurements were older and more often male, but other characteristics did not differ significantly after correction for differences in age and sex (online-only Data Supplement). Therefore, we do not think that this has led to any selection biases. Nevertheless, any residual selection bias due to missing data cannot be fully ruled out. Third, WML volumes were natural log transformed because of skewness of the untransformed measure. When back transformed, we note that the effect size seen of aPWV per SD increase in persons with uncontrolled hypertension corresponds with a white
matter volume increase of 1.1 mL. Lastly, a more integrative measure of blood pressure over time will be more reliable compared with a single or few measures due to regression to the mean. Unfortunately, integrative measures were not feasible in our population-based cohort.

Several other studies have been performed in the general population investigating the association between arterial stiffness and markers of cerebral small vessel disease.8,9,11–13 Our finding that arterial stiffness is associated with WML volume is in line with these studies.8,11,13 However, all of these studies used the brachial–ankle pulse wave velocity as a proxy for arterial stiffness. This is the first report on the association between arterial stiffness and cerebral small vessel disease in the general population using the carotid–femoral pulse wave velocity, the “gold standard” measurement of arterial stiffness. Nevertheless, even this combined measure may be feasible in our population-based cohort.

The associations found between arterial stiffness and microbleeds are indicative of hypertensive vasculopathy, whereas lobar microbleeds are thought to be a marker of underlying amyloid angiopathy.25 Furthermore, again in participants without hypertension, we found an association between arterial stiffness and WML volume and nonsignificantly with lacunar infarcts. Some other smaller studies performed in hypertensive subjects reported similar results1,16,26 However, we note that in our study, formal tests of statistical interaction were all nonsignificant. Possibly, our findings in this subgroup could be a chance finding due to multiple testing.

Several pathologies may contribute to the occurrence of lacunes and WMLs. However, small vessel disease is the major and most frequent underlying pathology. Conversely, WMLs, lacunar infaracts, and CMBs are considered the best available in vivo markers of cerebral small vessel disease. When we analyzed these different markers of cerebral small vessel disease separately, persons with higher aPWV had a larger volume of WML, whereas no significant associations were found between aPWV and lacunar infarcts or microbleeds. To create a more robust measure of cerebral small vessel disease, we constructed an overall measure of cerebral small vessel disease. This combined measure of cerebral small vessel disease was significantly associated with arterial stiffness. Nevertheless, even this combined measure may be driven primarily by WMLs.

The associations found between arterial stiffness and markers of cerebral small vessel disease were independent of other

### Table 3. The Association of Arterial Stiffness, as Measured by Aortic Pulse Wave Velocity, With Cerebral Small Vessel Disease in Strata of Hypertension

<table>
<thead>
<tr>
<th>Pulse Wave Velocity</th>
<th>White Matter Lesions*† Differences in WML Volume (95% CI)</th>
<th>Lacunar Infarcts OR (95% CI)</th>
<th>Deep or Infratentorial Microbleeds‡ OR (95% CI)</th>
<th>Strictly Lobar Microbleeds OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects without hypertension (n=808)§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per SD increase, Model I</td>
<td>0.07 (0.00 to 0.14)</td>
<td>0.91 (0.46 to 1.80)</td>
<td>1.24 (0.72 to 2.11)</td>
<td>0.84 (0.57 to 1.23)</td>
</tr>
<tr>
<td>Per SD increase, Model II</td>
<td>0.05 (−0.01 to 0.12)</td>
<td>0.97 (0.48 to 1.96)</td>
<td>1.20 (0.69 to 2.08)</td>
<td>0.83 (0.56 to 1.24)</td>
</tr>
<tr>
<td>Subjects with controlled hypertension (n=226)§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per SD increase, Model I</td>
<td>0.04 (−0.09 to 0.16)</td>
<td>1.05 (0.55 to 1.98)</td>
<td>0.59 (0.26 to 1.34)</td>
<td>0.83 (0.50 to 1.38)</td>
</tr>
<tr>
<td>Per SD increase, Model II</td>
<td>0.03 (−0.10 to 0.15)</td>
<td>1.24 (0.64 to 2.40)</td>
<td>0.50 (0.20 to 1.22)</td>
<td>0.86 (0.50 to 1.48)</td>
</tr>
<tr>
<td>Subjects with uncontrolled hypertension (n=414)§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per SD increase, Model I</td>
<td>0.10 (0.01 to 0.19)</td>
<td>1.48 (0.93 to 2.34)</td>
<td>1.80 (1.05 to 3.07)</td>
<td>1.18 (0.85 to 1.62)</td>
</tr>
<tr>
<td>Per SD increase, Model II</td>
<td>0.09 (0.00 to 0.18)</td>
<td>1.63 (0.98 to 2.70)</td>
<td>2.13 (1.16 to 3.91)</td>
<td>1.18 (0.84 to 1.65)</td>
</tr>
</tbody>
</table>

Subjects without hypertension: systolic blood pressure <140 mm Hg and a diastolic blood pressure <90 mm Hg without use of antihypertensive medication. Subjects with controlled hypertension: systolic blood pressure <140 mm Hg and a diastolic blood pressure <90 mm Hg with use of antihypertensive medication. Subjects with uncontrolled hypertension: systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg with or without use of antihypertensive medication. Values represent difference in white matter lesion volumes per SD increase in pulse wave velocity or ORs with 95% CIs. Model I: adjusted for age, sex, mean arterial pressure, and heart rate. Model II: adjusted for age, sex, mean arterial pressure, heart rate, smoking, waist–hip ratio, diabetes, cholesterol, high-density lipoprotein cholesterol, use of lipid-lowering drugs, and use of blood pressure-lowering drugs. Values of white matter lesions are natural log-transformed. To obtain volumes in milliliters, back transformation is needed.

*Ln-transformed.
†Additionally adjusted for intracranial volume.
‡With or without lobar microbleeds.
§Hypertension data missing for n=12.
vascular risk factors. This suggests that these associations are probably not mediated by these risk factors. An explanation could be that arterial stiffness reflects risk factors for cerebral small vessel disease that we did not measure in our study, for example, genetic factors or other biomarkers. For example, there is an increasing interest in the cardiovascular effects of plasma aldosterone levels. These biomarkers may give additional insights into the association of arterial stiffness with cerebral small vessel disease. Alternatively, arterial stiffness may be a better marker of small vessel disease than these concomitantly measured cardiovascular risk factors.

Structural and functional changes of the arterial wall, caused by aging and cardiovascular risk factors, result in decreased elasticity and increased stiffness of the arteries. Vascular resistance and pulse wave reflections are very low in the microcirculations of the brain and kidney. Arterial stiffening exposes, therefore, especially the small vessels in the brain and kidney, to highly pulsatile pressure and flow. It is hypothesized that these abnormal flow pulsations contribute to the pathogenesis of cerebral small vessel disease. Shared underlying pathological mechanisms, however, may also be a possible explanation for the associations we found between arterial stiffness and markers of cerebral small vessel disease.

The associations we found between arterial stiffness and markers of cerebral small vessel disease were most pronounced in persons with uncontrolled hypertension. In the presence of hypertension, structural and functional changes of the arterial wall are thought to occur earlier. Moreover, it is known that subjects with hypertension have a higher prevalence of cerebral small vessel disease. Our results suggest that within this group of subjects with uncontrolled hypertension, those with stiffer large arteries are more prone to develop cerebral small vessel disease.

Conclusions

We found that arterial stiffness is associated with WML and that the associations were independent of cardiovascular risk factors. Our study emphasizes the importance of identifying persons with high arterial stiffness and to treat high blood pressure in these persons appropriately. Longitudinal studies on reduction of arterial stiffness, however, are needed to study whether this lowers the risk of cerebral small vessel disease and ultimately decreases risk of symptomatic cerebrovascular disease.

Sources of Funding

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Disclosures

None.

References


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Table A. Baseline characteristics of the study population stratified according to hypertension status.

<table>
<thead>
<tr>
<th></th>
<th>Subjects without hypertension (n=808)*</th>
<th>Subjects with controlled hypertension (n=226)*</th>
<th>Subjects with uncontrolled hypertension (n=414)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>56.9 (SD 6.4)</td>
<td>60.1 (SD 7.6)</td>
<td>60.1 (SD 7.8)</td>
</tr>
<tr>
<td>Women</td>
<td>469 (58.0%)</td>
<td>120 (53.1%)</td>
<td>210 (50.7%)</td>
</tr>
<tr>
<td>Aortic Pulse Wave Velocity, m/s</td>
<td>8.5 (SD 1.3)</td>
<td>9.1 (SD 1.5)</td>
<td>10.0 (SD 1.7)</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>90.3 (SD 7.7)</td>
<td>93.4 (SD 7.0)</td>
<td>110.6 (SD 7.9)</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>65.0 (SD 11.9)</td>
<td>61.3 (SD 16.1)</td>
<td>65.4 (SD 14.8)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>120.4 (SD 10.7)</td>
<td>124.6 (SD 9.3)</td>
<td>151.8 (SD 12.1)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>75.2 (SD 7.0)</td>
<td>77.7 (SD 7.1)</td>
<td>90.1 (SD 7.9)</td>
</tr>
<tr>
<td>Blood pressure lowering medication</td>
<td>--</td>
<td>226 (100.0%)</td>
<td>167 (40.8%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>--</td>
<td>57 (25.2%)</td>
<td>42 (10.1%)</td>
</tr>
<tr>
<td>Betablocking agents</td>
<td>--</td>
<td>117 (51.8%)</td>
<td>81 (19.6%)</td>
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<td>43 (19.0%)</td>
<td>29 (7.0%)</td>
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<td>110 (48.7%)</td>
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<tr>
<td>Smoking, ever</td>
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<td>Waist-hip ratio</td>
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<tr>
<td>Diabetes</td>
<td>32 (4.0%)</td>
<td>31 (13.7%)</td>
<td>48 (11.9%)</td>
</tr>
<tr>
<td>Serum total cholesterol, mmol/L</td>
<td>5.6 (SD 1.0)</td>
<td>5.2 (SD 1.2)</td>
<td>5.6 (SD 1.0)</td>
</tr>
<tr>
<td>Serum HDL cholesterol, mmol/L</td>
<td>1.5 (SD 0.4)</td>
<td>1.3 (SD 0.4)</td>
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</tr>
<tr>
<td>Lipid lowering medication</td>
<td>112 (13.9%)</td>
<td>107 (47.3%)</td>
<td>101 (24.7%)</td>
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<tr>
<td>White matter lesions on MRI, mL, median (interquartile range)</td>
<td>1.9 (IR 1.3-3.3)</td>
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<td>Lacunar infarcts on MRI</td>
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<tr>
<td>Strictly lobar cerebral microbleeds on MRI</td>
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<tr>
<td>Deep or infratentorial microbleeds on MRI</td>
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<td>10 (4.4%)</td>
<td>16 (3.9%)</td>
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</table>

* Hypertension data missing for n=12.

Subjects without hypertension: Systolic blood pressure <140 mmHg and a diastolic blood pressure <90 mmHg without use of antihypertensive medication.

Subjects with controlled hypertension: Systolic blood pressure <140 mmHg and a diastolic blood pressure <90 mmHg with use of antihypertensive medication.

Subjects with uncontrolled hypertension: Systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg with or without use of antihypertensive medication.

Values are means with standard deviation (SD) or numbers with percentages (%), unless specified otherwise.

Data are missing for medication use (n=17), smoking (n=10), diabetes (n=32), serum cholesterol (n=23), cerebral microbleeds (n=6), lacunar infarcts (n=6), and white matter lesions (n=3).
Table B. Baseline characteristics of the study population stratified according to presence or absence of cerebral small vessel disease.

<table>
<thead>
<tr>
<th></th>
<th>Subjects with absence of cerebral small vessel disease (n=1048)</th>
<th>Subjects with presence cerebral small vessel disease (n=412)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>56.8 (SD 6.0)</td>
<td>62.1 (SD 8.5)</td>
</tr>
<tr>
<td>Women</td>
<td>574 (54.8%)</td>
<td>235 (57.0%)</td>
</tr>
<tr>
<td>Aortic Pulse Wave Velocity, m/s</td>
<td>8.8 (SD 1.4)</td>
<td>9.6 (SD 1.8)</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>96.0 (SD 11.6)</td>
<td>97.8 (SD 12.0)</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>64.7 (SD 13.0)</td>
<td>64.1 (SD 14.8)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>128.7 (SD 17.2)</td>
<td>133.2 (SD 18.2)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>79.7 (SD 9.7)</td>
<td>80.0 (SD 9.9)</td>
</tr>
<tr>
<td>Blood pressure lowering medication</td>
<td>244 (23.6%)</td>
<td>149 (36.5%)</td>
</tr>
<tr>
<td>Smoking, ever</td>
<td>699 (67.3%)</td>
<td>306 (74.3%)</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>0.9 (SD 0.1)</td>
<td>0.9 (SD 0.1)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>71 (6.9%)</td>
<td>40 (9.9%)</td>
</tr>
<tr>
<td>Serum total cholesterol, mmol/L</td>
<td>5.5 (SD 1.0)</td>
<td>5.5 (SD 1.1)</td>
</tr>
<tr>
<td>Serum HDL cholesterol, mmol/L</td>
<td>1.4 (SD 0.4)</td>
<td>1.4 (SD 0.4)</td>
</tr>
<tr>
<td>Lipid lowering medication</td>
<td>204 (19.7%)</td>
<td>116 (28.4%)</td>
</tr>
<tr>
<td>White matter lesions on MRI, mL, median (interquartile range)</td>
<td>1.7 (IR 1.2-2.5)</td>
<td>5.7 (IR 4.2-9.0)</td>
</tr>
<tr>
<td>Lacunar infarcts on MRI</td>
<td>--</td>
<td>63 (15.3%)</td>
</tr>
<tr>
<td>Strictly lobar cerebral microbleeds on MRI</td>
<td>96 (9.2%)</td>
<td>51 (12.4%)</td>
</tr>
<tr>
<td>Deep or infratentorial microbleeds on MRI</td>
<td>--</td>
<td>48 (11.7%)</td>
</tr>
</tbody>
</table>

* Presence of small vessel disease (n=412) was defined as persons in the highest quartile of white matter lesion volume, or presence of lacunar infarcts, or presence of deep or infratentorial microbleeds. Values are means with standard deviation (SD) or numbers with percentages (%), unless specified otherwise. Data are missing for medication use (n=17), smoking (n=10), diabetes (n=32), serum cholesterol (n=23), cerebral microbleeds (n=6), lacunar infarcts (n=6), and white matter lesions (n=34).
Table C. Baseline characteristics of Rotterdam Study III (n=3932) stratified according to presence or absence of arterial stiffness measurements.

<table>
<thead>
<tr>
<th></th>
<th>Subjects without arterial stiffness measurements (n=2099)</th>
<th>Subjects with arterial stiffness measurements (n=1833)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>56.1 (SD 6.6)</td>
<td>58.3 (SD 7.6)*</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>1212 (57.7%)</td>
<td>1040 (56.7%)*</td>
</tr>
<tr>
<td><strong>Systolic blood pressure, mmHg</strong></td>
<td>131.7 (SD 18.2)</td>
<td>133.6 (SD 20.0)</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure, mmHg</strong></td>
<td>82.3 (SD 10.8)</td>
<td>82.9 (SD 11.2)</td>
</tr>
<tr>
<td><strong>Blood pressure lowering medication</strong></td>
<td>560 (26.7%)</td>
<td>516 (28.2%)</td>
</tr>
<tr>
<td><strong>Smoking, ever</strong></td>
<td>1497 (71.6%)</td>
<td>1267 (69.5%)</td>
</tr>
<tr>
<td><strong>Waist-hip ratio</strong></td>
<td>0.9 (SD 0.1)</td>
<td>0.9 (SD 0.1)</td>
</tr>
<tr>
<td><strong>Serum total cholesterol, mmol/L</strong></td>
<td>5.6 (SD 1.1)</td>
<td>5.5 (SD 1.0)</td>
</tr>
<tr>
<td><strong>Serum HDL cholesterol, mmol/L</strong></td>
<td>1.4 (SD 0.5)</td>
<td>1.4 (SD 0.4)</td>
</tr>
</tbody>
</table>

*Age and sex-adjusted (when applicable) difference between groups is $P<0.05$. Values are means with standard deviation (SD) or numbers with percentages (%). Data are missing for blood pressure (n=290), blood pressure lowering medication (n=38), smoking (n=18), and cholesterol (n=378).
### Table A. Baseline characteristics of the study population stratified according to hypertension status.

<table>
<thead>
<tr>
<th></th>
<th>Subjects without hypertension (n=808)*</th>
<th>Subjects with controlled hypertension (n=226)*</th>
<th>Subjects with uncontrolled hypertension (n=414)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>56.9 (SD 6.4)</td>
<td>60.1 (SD 7.6)</td>
<td>60.1 (SD 7.8)</td>
</tr>
<tr>
<td>Women</td>
<td>469 (58.0%)</td>
<td>120 (53.1%)</td>
<td>210 (50.7%)</td>
</tr>
<tr>
<td>Aortic Pulse Wave Velocity, m/s</td>
<td>8.5 (SD 1.3)</td>
<td>9.1 (SD 1.5)</td>
<td>10.0 (SD 1.7)</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>90.3 (SD 7.7)</td>
<td>93.4 (SD 7.0)</td>
<td>110.6 (SD 7.9)</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>65.0 (SD 11.9)</td>
<td>61.3 (SD 16.1)</td>
<td>65.4 (SD 14.8)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>120.4 (SD 10.7)</td>
<td>124.6 (SD 9.3)</td>
<td>151.8 (SD 12.1)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>75.2 (SD 7.0)</td>
<td>77.7 (SD 7.1)</td>
<td>90.1 (SD 7.9)</td>
</tr>
<tr>
<td>Blood pressure lowering medication</td>
<td>--</td>
<td>226 (100.0%)</td>
<td>167 (40.8%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>--</td>
<td>57 (25.2%)</td>
<td>42 (10.1%)</td>
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<tr>
<td>Serum total cholesterol, mmol/L</td>
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<td>5.5 (SD 1.0)</td>
</tr>
<tr>
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</tr>
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*Age and sex-adjusted (when applicable) difference between groups is P<0.05. Values are means with standard deviation (SD) or numbers with percentages (%). Data are missing for blood pressure (n=290), blood pressure lowering medication (n=38), smoking (n=18), and cholesterol (n=378).