Higher Ambulatory Blood Pressure Relates to New Cerebral Microbleeds
2-Year Follow-Up Study in Lacunar Stroke Patients

Pim Klarenbeek, MD; Robert J. van Oostenbrugge, MD, PhD; Rob P.W. Rouhl, MD, PhD; Iris L.H. Knottnerus, MD, PhD; Julie Staals, MD, PhD

Background and Purpose—Elevated blood pressure (BP) is associated with the presence of cerebral microbleeds (CMBs) in cross-sectional studies. However, longitudinal studies did not show a convincing relationship. We aimed to determine the association between elevated BP levels and the occurrence of new CMBs after a 2-year follow-up in first-ever lacunar stroke patients using ambulatory BP monitoring.

Methods—Ninety-six first-ever lacunar stroke patients underwent brain MRI and ambulatory BP monitoring at baseline and after 2-year follow-up. We used logistic regression analyses to assess the association of BP levels with new CMBs.

Results—We found new CMBs in 17 patients (18%). Higher 24-hour, day and night systolic BP (odds ratio, 2.69; 95% confidence interval, 1.40–5.21 per SD increase for 24-hour BP) and diastolic BP (odds ratio, 2.13; 95% confidence interval, 1.15–3.90 per SD increase for 24-hour BP) at baseline were associated with the development of new CMBs independent of age and sex. BP levels decreased during follow-up in both patients with and without new CMBs. Unlike BP levels at baseline, there was no difference in BP levels at follow-up between patients with and without new CMBs.

Conclusions—Both higher systolic and diastolic BP levels were associated with the development of new CMBs in a population of lacunar stroke patients. Decrease of BP levels during follow-up did not halt progression of CMBs; however, it remains to be determined whether (early) intervention with antihypertensive drugs can slow down progression of CMBs. (Stroke. 2013;44:00-00.)

Key Words: ambulatory blood pressure monitoring ■ blood pressure ■ cerebral microbleeds ■ cerebral small vessel disease

Cerebral microbleeds (CMBs) are old (micro) hemorrhages from small blood vessels affected by lipohyalinosis (a blood pressure [BP]-related vascular pathology) or cerebral amyloid angiopathy.1,2 CMBs are more prevalent in hemorrhagic and ischemic stroke, especially in lacunar stroke subtype.3–5 Clinically, CMBs are associated with worse cognitive function, gait disturbances, increased stroke risk, and increased mortality. Therefore, CMBs can be considered a marker for poor outcome.6–12

In cross-sectional studies, higher age and elevated BP levels were most consistently associated with the prevalence of CMBs.3,5,13,14 However, longitudinal studies did not show a convincing association between elevated BP and the appearance of new CMBs.15–19 Three studies found that higher systolic BP levels predict the development of new CMBs, but in only 1 study was this relationship independent of age.15–17 No study found an association between new CMBs and diastolic BP levels. An explanation could be the universal use of office BP measurements instead of ambulatory BP monitoring (ABPM), which is proven to be superior in predicting BP-related end-organ damage.20,21 Furthermore, no information about BP and its treatment during follow-up was provided.

In the current study, we investigated the incidence of CMBs after 2-year follow-up in first-ever lacunar stroke patients. We investigated the association of clinical risk factors and MRI characteristics with the development of new CMBs, with special emphasis on BP, because this is the only previously identified modifiable risk factor associated with CMBs. We used 24-hour ABPM at baseline and after 2 years of follow-up.

Methods

Patients
From May 2003 to January 2008, patients with a first-ever lacunar stroke were prospectively recruited for a lacunar stroke research project at Maastricht University Medical Center and Orbis Medical Center Sittard, the Netherlands. This study was approved by the local ethics committee, and informed consent was obtained from all patients. We defined lacunar stroke as an acute lacunar stroke syndrome with a recent, small (diameter <20 mm) infarct on MRI.
(basal ganglia, internal capsule, or brain stem) compatible with the clinical findings. We used established criteria of specific clinical lacunar syndromes, if no symptomatic lesion was visible. Exclusion criteria and documented vascular risk factors are described in detail previously. Baseline evaluation included brain MRI and 24-hour ABPM. Patients were reinvited for follow-up MRI and 24-hour ABPM, after a prespecified time interval of 2 years after baseline imaging (mean 25.0±2.1 months).

### MRI Scoring

We acquired standard axial T2-weighted fast-spin echo images, axial fluid attenuated inversion recovery images, and T2-weighted gradient echo images at baseline and follow-up on a 1.5T or 3.0T MRI scanner. Only patients that were scanned with the same field strength at baseline and follow-up were included. CMBs were defined as rounded hypointense lesions on T2-weighted gradient echo sequences, with a diameter <10 mm. Symmetrical hypointensities in the basal ganglia, likely to represent calcification, sulcal flow voids from cortical vessels, and hypointensities possibly because of partial volume artifacts from bone were disregarded. All images were independently rated by 2 vascular neurologists (J.S. and R.R.). Side-by-side comparison of baseline and follow-up scans was used to assess the presence of new CMBs. In case of disagreement, a consensus meeting was held. Interobserver agreement for new CMBs was excellent (Cohen κ, 0.91).

Baseline MRI scans were graded for asymptomatic lacunar infarcts and white matter lesions as well. Asymptomatic lacunar infaracts were defined as hyperintense lesions on T2-weighted images with corresponding hypointense lesions with a hyperintense rim on fluid attenuated inversion recovery in the basal ganglia, internal capsule, or brain stem (diameter <20 mm), and not compatible with clinical findings. Deep and periventricular white matter lesions were graded according to the Fazekas scale from 0 to 3. For the present study, we only counted (early) confluent, deep white matter hyperintensities. (Fazekas score 2 and 3) and irregular periventricular hyperintensities extending into the deep white matter (Fazekas score 3). We used these scores because they are histopathologically related to cerebral small vessel disease.

### Blood Pressure Measurements

At baseline and follow-up, ABPM (using Mobil O Graph equipment, IEM GbmH, Stolberg, Germany) was performed over a 24-hour period with an appropriately sized cuff on the nondominant arm. Measurements were obtained every 15 minutes during 7 AM to 11 PM and every 30 minutes during night (11 PM to 7 AM). At baseline, ABPM was performed after the acute stroke phase, between 1 and 6 months poststroke (mean 110±52 days). Patients continued their prescribed medications, which were registered. Patients kept a record of rising and retiring times. We determined day and night periods by excluding a 2-hour transition period around the reported rising and retiring times. Measurement data were not edited manually. Valid recordings required a minimum of 15 daytime and 8 nighttime measurements. At both time points, we calculated mean 24-hour, day, and night systolic and diastolic BP. The absolute change of BP levels at follow-up was determined by subtracting the baseline BP level from the follow-up BP level. During follow-up, BP was treated according to the judgment of the treating physician, who was aware of the results of the BP measurements, without interference or monitoring of the researchers.

### Statistical Analysis

Analyses were performed using SPSS version 20 (SPSS Inc, Chicago, IL). To detect group differences, we applied independent samples t test, Mann–Whitney U test, or χ² test, where appropriate. We used univariable logistic regression analyses to assess which cardiovascular risk factors, BP levels, and MRI characteristics at baseline are risk factors for the presence of new CMBs at follow-up. All analyses were then adjusted for age and sex, because these were considered elementary demographic factors. Main regression analyses of BP levels were additionally adjusted for other cardiovascular risk factors (ie, diabetes mellitus, smoking, body mass index, hypercholesterolemia), medication (statin use, antithrombotic use, and number of antihypertensives), and scan interval (exploratory analyses, factors were added one by one separately to the model). Statistical significance was considered at P<0.05.

### Results

#### Study Sample

Of 281 first-ever lacunar stroke patients at Maastricht University Medical Center, 108 had a complete baseline work-up (35 were excluded because of carotid artery stenosis or possible cardioembolic source, 116 refused to participate or had contraindications for MRI, and 22 had inadequate MRI or ABPM data). In Orbis Medical Center Sittard, 26 patients completed baseline work-up (nonincluded patients were not listed). Follow-up was completed in 96/134 (72%) patients. Twenty-six patients had inadequate or different field strength follow-up MRI, 12 patients were lost to follow-up (5 died of non-neurological causes, 5 refused follow-up, and 2 could not be contacted). Age, sex, and baseline 24-hour systolic and diastolic BP did not differ significantly between patients who were included (n=98) and patients who did not complete adequate follow-up (n=38). Most patients (96%; 92/96) had baseline and follow-up MRI at 1.5T. Four patients (4%) underwent both MRI scans at 3.0T. In 23 (28%) patients, lacunar stroke was defined clinically, and MRI did not show a symptomatic lacunar infarct.

#### Incident CMBs

Table 1 presents baseline characteristics of all 96 patients. Seventeen patients (18%) developed new CMBs of whom 12 already had CMBs at baseline. Of the 17 patients with new CMBs, 8 (47%) had multiple new CMBs at follow-up (median 3, range 2–6). CMBs were present at baseline in 33 (34%) patients, and this increased to 38 (40%) patients at follow-up. In 2 patients (6% of patients with CMBs at baseline), a CMB had disappeared at follow-up. Age, sex, body mass index, diabetes mellitus, hypercholesterolemia, and smoking were not associated with the development of new CMBs (Table 1). The use of statins, antithrombotic, or antihypertensive drugs was also not associated with new CMBs.

#### Ambulatory Blood Pressure Levels

Table 2 presents baseline ambulatory BP levels. Higher 24-hour, day, and night systolic and diastolic BP were all associated with the development of new CMBs, after adjustment for age and sex (Table 2). Exploratory analyses with additional adjustment for any one of the cardiovascular risk factors (diabetes mellitus, body mass index, smoking, or hypercholesterolemia), use of medication at baseline or follow-up (statins, antihypertensive, or antithrombotic drugs), or MRI scan interval did not change the odds ratios substantially.

Table 3 presents ambulatory BP data at 2-year follow-up (n=91). Follow-up BP data were missing for 5 patients; none of these patients developed new CMBs. Both systolic and diastolic BP levels decreased significantly during follow-up for the entire group (P=0.003; paired samples t test). Patients...
with new CMBs had more BP decrease during follow-up than those without new CMBs (Table 3); this difference was significant for 24-hour, day, and night systolic BP and diastolic BP. Unlike ambulatory BP levels at baseline, there was no difference in BP levels at follow-up between patients with and without new CMBs. None of the follow-up BP levels were associated with incident CMBs during follow-up, or with the prevalence of CMBs at follow-up (logistic regression analyses; results not shown).

Although ABPM was always performed >1 month after acute stroke, we additionally ensured that the observed BP decrease during follow-up was not influenced by (too early) timing of baseline BP measurement by performing a correlation analysis between the time interval to baseline BP measurement and the absolute BP change (diastolic and systolic) during follow-up (Spearman ρ P value 0.42 and 0.20, respectively).

Antihypertensive Treatment

Of patients with new CMBs, 71% (12/17) were treated with ≥1 antihypertensive drug at baseline (most commonly a β-blocker), and 6 (35%) of these received multiple drugs (median 3, range 2–4). Of patients without new CMBs, 63% (50/79) were treated with antihypertensives at baseline and 27% (21/79) received multiple drugs (median 2, range 2–5).

At follow-up, the use of antihypertensive drugs increased to 82% (14/17) in patients with new CMBs versus 74% (55/74) in patients without new CMBs. The number of patients using multiple drugs also increased in both groups to 59% (10/17) in patients with new CMBs (median 3, range 2–4) versus 47% (35/74) in patients without new CMBs (median 2, range 2–4).

Use of antihypertensive drugs at baseline or at follow-up was not associated with incidence of CMBs during follow-up (Table 1) or prevalence of CMBs at follow-up (logistic regression analyses; results not shown). We have no information about (change of) medication use in-between baseline and follow-up, nor about alternative treatments, such as diet and weight loss.

Baseline MRI Characteristics

Table 4 presents the baseline MRI characteristics. Patients with new CMBs at follow-up had more often CMBs or lacunar infarcts at baseline than patients without new CMBs. After correction for age and sex, presence of CMBs at baseline was
associated with the development of new CMBs. Multiple CMBs at baseline had an even stronger association. The presence of asymptomatic lacunar infarcts on baseline MRI was also associated with new CMBs, whereas white matter lesions were not.

### Discussion

In this study, in 96 first-ever lacunar stroke patients, we found new CMBs in 18% of patients after a 2-year follow-up period. Higher 24-hour, day, and night systolic and diastolic BP levels were all associated with the development of new CMBs independent of age and sex. The presence of CMBs and asymptomatic lacunar infarcts at baseline were also associated with CMB incidence, after adjustment for age and sex.

The incidence of CMBs in our cohort was 18% over a 2-year follow-up period. No other longitudinal studies of CMBs in lacunar stroke patients are available for comparison. In the general population, an incidence of CMBs over a 3-year period of 10% was reported, whereas in a memory clinic population, an incidence rate of 12% was found with a follow-up interval of 1.9 years. The incidence rate in our study is slightly higher, probably reflecting the manifest small vessel pathology present in all our patients. In small series of patients with primary intracerebral hemorrhage, even higher incidence rates are reported. We found disappearance of CMBs at follow-up in 2 patients (6% of patients with CMBs at baseline), which is comparable to previous series. Whether this is a result of some biological process like resorption or because of imaging techniques remains unclear.

We found a clear association of both higher systolic and diastolic BP levels with CMB incidence. We analyzed BP as a continuous variable instead of dichotomizing BP levels at an arbitrary hypertensive cut-off value. Furthermore, 24-hour ABPM provided information regarding diurnal BP levels. In our population, both higher day and night BP levels were associated with new CMBs. Only 1 other longitudinal study found an independent association of office systolic BP with new CMBs.

A possible explanation for the different associations of BP with CMB incidence is that we used 24-hour ABPM, which provides a more accurate estimate of actual BP levels and is proven to be superior to office BP measurements in predicting BP-related end-organ damage. Moreover, because our cohort consisted of patients with lacunar stroke, which is a BP-related small vessel pathology, the effect of BP on the incidence of CMBs might be more pronounced compared with other populations.

Based on the observation that higher BP levels are associated with the development of CMBs, strict BP control may potentially halt or slow down progression of CMBs. In our cohort, antihypertensive treatment was intensified in both groups during follow-up. BP levels decreased in both patients with and without new CMBs, and BP levels were equal after 2 years. It seems that BP was treated more intensively in patients with higher baseline BP. This might explain the larger BP decrease in patients with new CMBs at follow-up. However, we do not have information about BP treatment inbetween baseline and follow-up, and other factors such as

### Table 3. Blood Pressure Characteristics at 2-Year Follow-Up

<table>
<thead>
<tr>
<th>BP Characteristics at Follow-Up (mm Hg)</th>
<th>All Patients (n=91, 5 missing)</th>
<th>Incident CMBs (n=17)</th>
<th>Absolute BP Change From Baseline</th>
<th>No Incident CMBs (n=74)</th>
<th>Absolute BP Change From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h SBP</td>
<td>132±13</td>
<td>134±14</td>
<td>−17±21*</td>
<td>132±13</td>
<td>−5±16*</td>
</tr>
<tr>
<td>DBP</td>
<td>78±9</td>
<td>78±8</td>
<td>−8±11</td>
<td>77±9</td>
<td>−3±9</td>
</tr>
<tr>
<td>Day SBP</td>
<td>136±15</td>
<td>138±14</td>
<td>−17±22*</td>
<td>136±15</td>
<td>−5±17*</td>
</tr>
<tr>
<td>DBP</td>
<td>80±9</td>
<td>81±8</td>
<td>−8±13</td>
<td>80±10</td>
<td>−3±10</td>
</tr>
<tr>
<td>Night SBP</td>
<td>120±14</td>
<td>123±15</td>
<td>−17±22†</td>
<td>120±13</td>
<td>−3±15†</td>
</tr>
<tr>
<td>DBP</td>
<td>69±9</td>
<td>68±9</td>
<td>−9±12†</td>
<td>69±9</td>
<td>−3±9†</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; CMBs, cerebral microbleeds; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

†P<0.01.

### Table 4. Baseline MRI Characteristics, Association With New CMBs

<table>
<thead>
<tr>
<th>MRI Characteristics at Baseline</th>
<th>All Patients (n=96)</th>
<th>Incident CMBs (n=17)</th>
<th>No Incident CMBs (n=79)</th>
<th>Unadjusted OR (95% CI)</th>
<th>OR Adjusted for Age and Sex (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CMBs</td>
<td>33 (34.4%)</td>
<td>12 (70.6%)</td>
<td>21 (26.6%)</td>
<td>6.63 (2.09–21.1)†</td>
<td>5.91 (1.83–19.1)†</td>
</tr>
<tr>
<td>Multiple CMBs</td>
<td>11 (11.5%)</td>
<td>6 (35.3%)</td>
<td>5 (6.3%)</td>
<td>8.07 (2.10–31.1)†</td>
<td>7.43 (1.82–30.4)†</td>
</tr>
<tr>
<td>Asymptomatic lacunar infarcts</td>
<td>63 (65.6%)</td>
<td>16 (94.1%)</td>
<td>47 (59.5%)</td>
<td>10.9 (1.38–86.3)*</td>
<td>8.64 (1.05–71.1)*</td>
</tr>
<tr>
<td>White matter lesions</td>
<td>36 (37.5%)</td>
<td>10 (58.8%)</td>
<td>26 (32.9%)</td>
<td>2.91 (1.00–8.52)</td>
<td>2.44 (0.78–7.62)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and CMBs, cerebral microbleeds.

Data presented as number (%). OR for incident vs no incident CMBs.

*P<0.05.

†P<0.01.
weight loss, diet, or different classes of medication might also have influenced BP decrease. It appears that BP reduction is ineffective in preventing progression of CMBs, perhaps because the vessel damage has already occurred, or because other mechanisms besides BP are responsible for progression of CMBs. Furthermore, other prognostic factors may have influenced antihypertensive treatment decisions, and this may also bias the relationship between BP course and CMB progression. We cannot exclude that the observed BP decrease indeed slowed down or prevented some progression. It may be that with a longer treatment and follow-up, progression may finally be halted. We also cannot exclude that the progression of CMBs occurred quite early, before BP decrease was achieved. To investigate the true effect of antihypertensive drugs on the progression of CMBs, an intervention trial would be needed.

Like previous studies, we found that (multiple) CMBs and asymptomatic lacunar infarcts on baseline MRI are associated strongly with the occurrence of new CMBs.\(^15\)–\(^19\),\(^20\),\(^27\) White matter lesions were not associated with new CMBs in our study, possibly because of limited sample size or scoring method (perhaps volumetric analysis of white matter lesions would yield different results). The majority of our patients (n=12/17; 71%) developed new CMBs in a deep or mixed (deep and lobar) location, which is in line with previous evidence suggesting that BP-related cerebral small vessel disease gives rise to CMBs preferentially in a deep location.\(^2\) Of 5 patients with new lobar CMBs, 2 patients had all CMBs strictly lobar at follow-up, a distribution that indicates amyloid angiopathy. Repeating analyses excluding these 2 patients did not change results.

The major strength of our study is that we collected a very homogeneous patient group with symptomatic cerebral small vessel disease. Second, we had a strict interval between baseline and follow-up MRI, which makes the incidence rate solid. However, our study also has some limitations. First, we were unable to identify a symptomatic lacunar lesion on MRI in some patients (n=23). Diffusion-weighted imaging was not standard in the imaging protocol, and when MRI was done after acute stroke phase, the distinction between recent and old lacunar infarcts may be difficult. However, because all patients had a distinct clinical lacunar stroke syndrome, and we excluded every patient with a possible cardioembolic or large vessel source of infarct, we feel that this did not lead to unrightfully included patients. Furthermore, a repeated analysis selecting only those patients in whom a symptomatic MRI lesion was visible (n=73) did not substantially change our results. Second, because of the observational nature of our study, conclusions regarding the effect of BP decrease on progression of CMBs should be interpreted with caution, and a randomized controlled trial is desired to truly evaluate the effect of BP intervention on the natural course and progression of CMBs.

In conclusion, our results show that both systolic and diastolic BP levels are associated with the development of new CMBs in lacunar stroke patients, independent of age and sex. Although decrease of BP levels during follow-up did not halt progression of CMBs, it remains to be determined whether (early) intervention with BP-lowering drugs can slow down progression of CMBs.

Disclosures
None.

References
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24時間自由行動下血圧の上昇と新規微小脳出血の関係
ラクナ梗塞患者の2年間追跡調査

Higher Ambulatory Blood Pressure Relates to New Cerebral Microbleeds
2-Year Follow-Up Study in Lacunar Stroke Patients

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Abstract

背景および目的: 血圧(BP)上昇が微小脳出血(CMB)の存在と関連があることが横断研究で明らかになっている。しかし、総合研究ではその関連が立証されていない。本研究では、初めてラクナ梗塞を発症した患者を24時間自由行動下BP測定によって2年間追跡し、BPの上昇と新たなCMB発生の関係を明確にすることを目的とした。

方法: ラクナ梗塞初発患者96例にベースライン時と2年間追跡調査終了後に脳MRIと24時間自由行動下BP測定を行った。ロジスティック回帰分析を用いて新たに発生したCMBとBPの関連を評価した。

結果: 17例(18%)に新規CMBが認められた。ベースライン時の24時間収縮期BPオッズ比(OR) = 2.69, 95%信頼区間(24時間BPの1SD増加ごとに1.40 〜 5.21)と拡張期BP(OR = 2.13, 95% CI: 24時間BPの1SD増加ごとに1.15 〜 3.90)は、年齢と性別に関わらず、新規CMB発生と関連していた。新規CMBの発生の有無とは無関係に追跡期間中患者のBPは低下した。ベースライン時のBPとは異なり、追跡調査時は、新規CMBが発生した患者としなかった患者の間にBPの差はなかった。

結論: ラクナ梗塞患者で収縮期BPも拡張期BPも高い場合は、新規CMBが発生していた。追跡期間中にBPが低下してもCMBの進行は止まらなかった。ただし、降圧剤による(早期)介入がCMBの進行を遅らせる可能性についてはまだ不明である。

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表4 ベースライン時のMRIの特徴、新規発生したCMBとの関連

<table>
<thead>
<tr>
<th>ベースライン時のMRIの特徴</th>
<th>全患者 (n = 96)</th>
<th>CMB 発生あり (n = 17)</th>
<th>CMB 発生なし (n = 79)</th>
<th>未調整 OR (95% CI)</th>
<th>年齢および性別で調整 したOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ベースライン時のCMB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMBあり</td>
<td>33 (34.4%)</td>
<td>12 (70.6%)</td>
<td>21 (26.6%)</td>
<td>6.63 (2.09 〜 21.1)†</td>
<td>5.91 (1.83 〜 19.1)†</td>
</tr>
<tr>
<td>複数のCMB</td>
<td>11 (11.5%)</td>
<td>6 (35.3%)</td>
<td>5 (6.3%)</td>
<td>8.07 (2.10 〜 31.1)†</td>
<td>7.43 (1.82 〜 30.4)†</td>
</tr>
<tr>
<td>無症状性ラクナ梗塞</td>
<td>63 (65.6%)</td>
<td>16 (94.1%)</td>
<td>47 (59.5%)</td>
<td>10.9 (1.38 〜 86.3)*</td>
<td>8.64 (1.05 〜 71.1)*</td>
</tr>
<tr>
<td>白質病変</td>
<td>36 (37.5%)</td>
<td>10 (58.8%)</td>
<td>26 (32.9%)</td>
<td>2.91 (1.00 〜 8.52)</td>
<td>2.44 (0.78 〜 7.62)</td>
</tr>
</tbody>
</table>

CI: 信頼区間、CMB: 微小脳出血。
データは数値（%）で表示、ORはCMB発生あり対CMB発生なし。
* p < 0.05
† p < 0.01