Microbleeds, Mortality, and Stroke in Alzheimer Disease
The MISTRAL Study

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IMPORTANCE Microbleeds are more prevalent in patients with Alzheimer disease (AD) compared with the general elderly population. In addition, microbleeds have been found to predict mortality in AD.

OBJECTIVE To investigate whether microbleeds in AD increase the risk for mortality, stroke (including intracerebral hemorrhage), and cardiovascular events.

DESIGN, SETTING AND PARTICIPANTS The MISTRAL (do Microbleeds predict STRoke in ALzheimer’s disease) Study is a longitudinal cohort study within the memory clinic–based Amsterdam Dementia Cohort. We selected all patients with AD with a baseline visit between January 2, 2002, and December 16, 2009, and microbleeds (n = 111) and matched those (1:2) for age, sex, and magnetic resonance imaging scanner to 222 patients with AD without microbleeds. After a minimal follow-up of 3 years, information on all-cause mortality, stroke-related mortality, and cardiovascular mortality was obtained between November 1, 2012, and May 1, 2014. In addition, we obtained information on the occurrence of incident stroke or transient ischemic attack, cardiovascular events, and nursing home admittance.

MAIN OUTCOMES AND MEASURES Stroke-related mortality, incident stroke, and intracerebral hemorrhage.

RESULTS Patients had a mean (SD) age of 71.2 (7.8) years and 127 (42%) were female. Compared with having no microbleeds, microbleeds in lobar locations were associated with an increased risk for stroke-related mortality (hazard ratio [HR], 33.9; 95% CI, 2.5-461.7), whereas nonlobar microbleeds were associated with an increased risk for cardiovascular mortality (HR, 12.0; 95% CI, 3.2-44.7). In addition, lobar microbleeds were associated with an increased risk for incident stroke (HR, 3.8; 95% CI, 1.5-10.1) and nonlobar microbleeds with an increased risk for cardiovascular events (HR, 6.2; 95% CI, 1.5-25.0). Even higher risks for incident stroke and cardiovascular events were found in patients using antithrombotic medication. All 5 patients with an intracerebral hemorrhage had lobar microbleeds at baseline; 4 of them used antithrombotics.

CONCLUSIONS AND RELEVANCE In patients with AD, the presence of nonlobar microbleeds was associated with an increased risk for cardiovascular events and cardiovascular mortality. Patients with lobar microbleeds had an increased risk for stroke and stroke-related mortality, indicating that these patients should be treated with the utmost care.
Microbleeds are considered indicative of small-vessel blood leakage and have been more frequently observed in patients with Alzheimer disease (AD) compared with the general elderly population. In patients with AD, microbleeds are mostly seen in lobar locations. Epidemiological data suggest that lobar microbleeds reflect cerebral amyloid angiopathy (CAA), whereas nonlobar microbleeds are associated with hypertensive vasculopathy.

We previously found that the presence of multiple microbleeds predicts mortality in patients with AD. In populations enriched for vascular disease, lobar microbleeds have been found to increase the risk for stroke-related mortality and, more specifically, mortality due to intracerebral hemorrhage (ICH). It is tempting to assume that an increased incidence of ICH accounts for increased mortality in patients with AD with microbleeds, but longitudinal data are largely lacking.

We designed the MISTRAL (do Microbleeds predict STRoke in AD) study to investigate whether microbleeds in AD are associated with mortality, stroke or transient ischemic attack (TIA), cardiovascular events, and nursing home admittance. As antithrombotic therapy may augment the bleeding risk associated with microbleeds, we also assessed whether antithrombotic medication influenced the associations between microbleeds and future events.

Methods

Patients

In this longitudinal study, we included patients from the memory clinic–based Amsterdam Dementia Cohort. We selected patients with a baseline visit between January 2, 2002, and December 16, 2009; a diagnosis of AD; and available T2*-weighted magnetic resonance imaging (MRI). We included all patients with microbleeds, resulting in a data set of 111 patients with AD with microbleeds. We matched those (1:2) for age, sex, and MRI scanner to 222 patients with AD without microbleeds. At baseline, all patients underwent a standardized dementia screening, including physical and neurologic examination, laboratory tests, electroencephalography, and brain MRI. Cognitive assessment included the Mini-Mental State Examination and extensive neuropsychological testing. All results were discussed in a multidisciplinary meeting, after which the diagnosis of probable AD was made according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association criteria and all patients fulfilled the core clinical criteria of the National Institute on Aging-Alzheimer’s Association (more details can be found in the study by van der Flier et al). Antithrombotic medication use (antiplatelet or anticoagulant) was recorded. The presence of hypertension, hypercholesterolemia, and diabetes mellitus was determined based on self-reported medical history and medication use. Smoking was defined as current smoking and body mass index was calculated as weight in kilograms divided by height in meters squared. Laboratory testing included apolipoprotein ε4 genotyping performed using a QIAxcel DNA Fast Analysis kit (Qiagen); patients were categorized into carriers (heterozygous or homozygous) or noncarriers. Cerebrospinal fluid β-amyloid 1-42 (Aβ42), total tau (tau), and hyperphosphorylated tau-181 (pTau) were determined with Innogenetics sandwich enzyme-linked immunosorbent assay, as described previously.

The medical ethics committee of the VU University Medical Center approved the study. At baseline, all patients provided written informed consent to use their clinical data for research purposes.

Magnetic Resonance Imaging

Magnetic resonance imaging scans were obtained on 1-T (n = 171), 1.5-T (n = 57), or 3-T (n = 105) scanners. The scan protocol included T1-weighted, T2-weighted, fluid-attenuated inversion recovery, and gradient echo T2*-weighted images and was essentially unchanged over the years. The raters were blinded to the patients’ clinical data. Microbleeds were defined as small round foci of hypointense signal, measuring up to 10 mm in brain parenchyma on T2*-weighted images. The total number of microbleeds was counted and microbleed presence was defined as the presence of at least 1 microbleed. Microbleeds were also categorized according to their location: no microbleeds; strictly nonlobar microbleeds; and any lobar microbleed (including microbleeds in mixed locations). On the fluid-attenuated inversion recovery sequence, white matter hyperintensities were assessed using the Fazekas et al scale (0 = none; 1 = punctuate; 2 = early confluent; and 3 = confluent) and dichotomized into absent (0) or present (≥1). Lacunes were defined as deep lesions (3-15 mm) with cerebrospinal fluid–like signal on all sequences; lacunes were scored as absent (0) or present (≥1).

Follow-up

Follow-up information was retrieved between November 1, 2012, and May 1, 2014, allowing a minimal follow-up duration of 3 years. As a first step, we obtained information on mortality (deceased: yes or no) from the Dutch Municipal Population Register. Next, this information was used to obtain mortality causes from the national register, Statistics Netherlands. In this anonymized national register, up to 4 causes of death (1 primary and 3 optional secondary) are registered according to the International Statistical Classification of Diseases, Tenth Revision. In the analyses, we only examined the primary cause of death. We considered all-cause mortality, stroke-related mortality (codes I60-I69, including ICH-related mortality), and cardiovascular mortality (codes I10-I15, I20-I25, I30-I52, and I70-I79). For specific mortality causes, patients were followed up from the date of the baseline visit until the date of death or November 1, 2012, whichever came first.

In addition to mortality and mortality causes, we also gathered information on the incidence of stroke or TIA, a cardiovascular event, nursing home admittance, and antithrombotic medication (ie, antiplatelet or anticoagulant) use by sending questionnaires to all patients’ general practitioners. Incident stroke included ICH, ischemic stroke, and unspecified stroke. A cardiovascular event included myocardial infarction, heart failure, cardiac arrhythmias, and aortic aneurysm. When additional information was needed, hospitals and pharmacologists were addressed. For the occurrence of events, patients were followed up from the date of the baseline visit until the date of event, date of death, or last date of survival. Follow-up infor-
Results

Overall Description of Cohort

We included 111 patients with AD with 1 or more microbleeds (mean [SD] age, 71.6 [7.8] years; 36% female) and 222 patients with AD without microbleeds (mean [SD] age, 71.1 [7.8] years; 45% female) (Figure 1). Patients with microbleeds had a lower Mini-Mental State Examination score ($P < .05$), had white matter hyperintensities ($P < .01$) and lacunes ($P < .05$) more often, and had lower levels of cerebrospinal fluid Aβ42 ($P < .01$) than patients without microbleeds (Table 1). Moreover, patients with microbleeds tended to have a higher systolic blood pressure and more often tended to have a history of hypertension (both $P < .07$). Patients did not differ with regard to other aspects.

Risk for Mortality

In the group without microbleeds, 85 patients died during follow-up (38%; 76 cases per 1000 person-years) compared with 62 in the group with microbleeds (56%; 134 cases per 1000 person-years) (Table 2). Adjusted Cox proportional hazard models showed that compared with no microbleeds, microbleed presence, in particular in lobar locations, was associated with an increased risk for all-cause mortality (HR for any lobar microbleed, 1.7; 95% CI, 1.2-2.5).

Stroke was the cause of mortality in 1 patient without microbleeds (0.5%; 1 case per 1000 person-years) and in 6 patients with microbleeds (5%; 13 cases per 1000 person-years). Microbleed presence was strongly associated with an increased risk for stroke-related mortality (HR, 14.6; 95% CI, 1.6-134.7). This increased risk appeared entirely attributable to lobar microbleeds (HR, 33.9; 95% CI, 2.5-461.7), as no patients with strictly nonlobar microbleeds died of stroke.

Stroke-related mortality was unspecified in most cases ($n = 4$); however, 3 patients died of an ICH and they all had lobar microbleeds at baseline (3%; 8 cases [95% CI, 2.2-24] per 1000 person-years). Stroke-related mortality was never classified as ischemic stroke. The low event rate prohibited calculation of HRs.

Data Analysis

We used SPSS version 20.0 (IBM) to perform statistical analyses. Data sets on mortality causes and incident events have been analyzed separately, as the anonymized data from the national register prohibited merging of both data sets. Baseline characteristics of patients with and without microbleeds were compared using χ² test for categorical variables and t test for continuous variables.

Incidence rates were determined per 1000 person-years of follow-up. The error factor was calculated with the formula: $e^{(1.96 \times \sqrt{n} \text{[events]})}$ and was used to calculate the lower (incidence/error factor) and upper (incidence × error factor) limits of the 95% CIs.

Cox proportional hazard analyses were used to calculate the hazard ratios (HRs) of microbleed presence (no or yes) and microbleed location (no, strictly nonlobar, or any lobar) for all-cause mortality, stroke-related mortality, and cardiovascular mortality. Patients without microbleeds were the reference category. Similarly, we calculated HRs for incident stroke or TIA, a cardiovascular event, and nursing home admittance. Antiplatelet medication use (no or yes) was defined as any use of antiplatelets or anticoagulants at baseline or during follow-up before the occurrence of events. We constructed a new predictor variable combining antithrombotic treatment with microbleed location (6 levels): (1) no microbleeds without antithrombotics (reference); (2) no microbleeds with antithrombotics; (3) strictly nonlobar microbleeds without antithrombotics; (4) strictly nonlobar microbleeds with antithrombotics; (5) any lobar microbleed without antithrombotics; and (6) any lobar microbleed with antithrombotics. All analyses were adjusted for age, sex, Mini-Mental State Examination score, vascular risk factors, and the presence of white matter hyperintensities and lacunes.
A cardiovascular event was the cause of mortality in 11 patients without microbleeds (5%; 10 cases per 1000 person-years) and in 8 patients with microbleeds (7%; 17 cases per 1000 person-years). Although the risk for cardiovascular mortality was not increased by the presence of microbleeds in general (HR, 2.1; 95% CI, 0.8-5.7), the presence of strictly nonlobar microbleeds was associated with an increased risk for cardiovascular mortality (HR, 12.0; 95% CI, 3.2-44.7).

**Risk for Stroke or Transient Ischemic Attack**

Information on the risk for stroke or TIA, cardiovascular events, and nursing home admittance was available for 200 patients without microbleeds and 101 patients with microbleeds (Figure 1). Incident stroke occurred in 9 patients without microbleeds (5%; 9 cases per 1000 person-years) and in 14 patients with microbleeds (14%; 33 cases per 1000 person-years) (Table 3). Microbleed presence was associated with an increased risk for incident stroke (HR, 3.3; 95% CI, 1.3-8.4). Compared with no microbleeds, the risk for incident stroke was only increased for lobar microbleeds (HR, 3.8; 95% CI, 1.5-10.1) and not for strictly nonlobar microbleeds (HR, 1.3; 95% CI, 0.2-11.5) (Figure 2A).

Incident stroke was not specified in all cases but the eTable in the Supplement shows the incidence of known ICHs (n = 5) and ischemic strokes (n = 12) according to microbleed presence and location. All patients with incident ICH had lobar microbleeds. In addition, whereas ischemic stroke was more frequent than ICH in the total group and in patients without microbleeds, ICH was more frequently observed in patients with (lobar) microbleeds. Calculation of HRs for stroke subtypes was not possible because of low event rates.

Transient ischemic attack occurred in 14 patients without microbleeds (7%; 14 cases [95% CI, 8-24] per 1000 person-years) and in 6 patients with microbleeds (6%; 14 cases [95% CI, 6-31] per 1000 person-years). Microbleeds were not associated with an increased risk for TIA (data not shown).

**Risk for Cardiovascular Events**

A cardiovascular event occurred in 12 patients without microbleeds (6%; 12 cases per 1000 person-years) and in 9 patients with microbleeds (9%; 21 cases per 1000 person-years) (Table 3). Compared with no microbleeds, microbleed presence and microbleed load were not associated with an increased risk for a cardiovascular event. However, the presence of strictly nonlobar microbleeds was associated with an increased risk for a cardiovascular event (HR for strictly nonlobar, 6.2; 95% CI, 1.5-25.0) (Figure 2B).

**Risk for Nursing Home Admittance**

Among patients without microbleeds, 119 were admitted to a nursing home (60%; 153 cases [95% CI, 128-183] per 1000 person-years) compared with 56 patients with microbleeds (55%; 164 cases [95% CI, 127-214] per 1000 person-years). Microbleeds were not associated with an increased risk for nursing home admittance (data not shown).

**Influence of Antithrombotic Medication**

A total of 122 patients used any antithrombotic medication (93 antiplatelet, 16 anticoagulant, and 13 both). When we combined antithrombotic treatment with microbleed location (Table 3), stroke occurred in 5 patients with neither micro-

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**Table 1. Baseline Characteristics of the Total Cohort and According to Microbleed Presence**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Cohort (n = 333)</th>
<th>Microbleeds (n = 111)</th>
<th>No Microbleeds (n = 222)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>71.2 (7.8)</td>
<td>71.6 (1.8)</td>
<td>71.1 (7.8)</td>
</tr>
<tr>
<td>Female</td>
<td>140 (42)</td>
<td>40 (36)</td>
<td>100 (45)</td>
</tr>
<tr>
<td>MMSE score, mean (SD)</td>
<td>20 (5)</td>
<td>20 (5)</td>
<td>22 (5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>76 (23)</td>
<td>32 (29)</td>
<td>44 (20)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>23 (7)</td>
<td>6 (5)</td>
<td>17 (7)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20 (6)</td>
<td>7 (6)</td>
<td>13 (6)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>48 (16)</td>
<td>18 (18)</td>
<td>30 (15)</td>
</tr>
<tr>
<td>Blood pressure, mean (SD), mm/Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>146 (18)</td>
<td>150 (18)</td>
<td>144 (16)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>84 (9)</td>
<td>86 (9)</td>
<td>84 (9)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>24 (4)</td>
<td>24 (4)</td>
<td>25 (4)</td>
</tr>
<tr>
<td>Lacunae presence</td>
<td>104 (31)</td>
<td>53 (47)</td>
<td>51 (23)</td>
</tr>
<tr>
<td>WMH presence</td>
<td>100 (30)</td>
<td>53 (47)</td>
<td>47 (21)</td>
</tr>
<tr>
<td>CSF, mean (SD), pg/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aβ42</td>
<td>479 (185)</td>
<td>404 (111)</td>
<td>509 (199)</td>
</tr>
<tr>
<td>Total tau</td>
<td>686 (401)</td>
<td>743 (470)</td>
<td>662 (368)</td>
</tr>
<tr>
<td>pTau</td>
<td>94 (45)</td>
<td>101 (53)</td>
<td>91 (42)</td>
</tr>
<tr>
<td>ApoE ε4 status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noncarriers</td>
<td>89 (31)</td>
<td>28 (3)</td>
<td>61 (19)</td>
</tr>
<tr>
<td>Heterozygous</td>
<td>135 (47)</td>
<td>35 (40)</td>
<td>100 (51)</td>
</tr>
<tr>
<td>Homozygous</td>
<td>60 (21)</td>
<td>24 (28)</td>
<td>36 (18)</td>
</tr>
</tbody>
</table>

Abbreviations: Aβ42, β-amyloid42; ApoE, apolipoprotein; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; pTau, hyperphosphorylated tau-181; WMH, white matter hyperintensity.

* Availability for incomplete data: smoking: microbleeds, 102 of 111, no microbleeds, 204 of 222; CSF: microbleeds, 68 of 111, no microbleeds, 170 of 222; and ApoE ε4 status: microbleeds, 87 of 111, no microbleeds, 197 of 222. The t and x² tests were performed.

**p < .05 compared with microbleeds.

**p < .01 compared with microbleeds.

**p < .05 compared with microbleeds.

**p < .05 compared with microbleeds.

**p < .1 compared with microbleeds.
bleeds nor antithrombotics (4%; 9 cases per 1000 person-years) and in 10 patients with lobar microbleeds and antithrombotics (27%; 67 cases per 1000 person-years). Compared with patients with neither microbleeds nor antithrombotics, only patients with lobar microbleeds and antithrombotics had an increased risk for stroke (HR, 6.7; 95% CI, 1.9-23.8). When we repeated these analyses in patients using antiplatelet agents, the results remained essentially unchanged (data not shown). The group using anticoagulants was too small to analyze.

A cardiovascular event occurred in 6 patients with neither microbleeds nor antithrombotics (5%; 10 cases per 1000 person-years) and in 2 patients with strictly nonlobar microbleeds and antithrombotics (33%; 94 cases per 1000 person-years). Compared with patients with neither microbleeds nor antithrombotics, only patients with strictly nonlobar microbleeds and antithrombotics had an increased risk for a cardiovascular event (HR, 13.1; 95% CI, 2.2-78.9).

The incidence of ICH and ischemic stroke for patients classified according to microbleed location and antithrombotic treatment can be found in the eTable in the Supplement. Of the 5 lobar microbleed patients who had an ICH, 4 used antithrombotics (1 anticoagulants, 2 antiplatelets, and 1 both). In addition, only in patients with lobar microbleeds and antithrombotics was ICH more frequently observed than ischemic stroke.

### Discussion

We found that microbleeds in lobar locations increased the risk for incident stroke and stroke-related mortality, whereas nonlobar microbleeds were associated with an increased risk for cardiovascular events and cardiovascular mortality. In patients using antithrombotics, the risks associated with lobar and nonlobar microbleeds were even stronger.

A strength of the current study was that we routinely performed T2*-weighted MRI in all patients who came to our memory clinic since 2002. This unique feature of the Amsterdam Dementia Cohort allows a systematic study of the clinical relevance and prognostic value of microbleeds in AD. In addition, we selected patients who had a minimal follow-up of 3
years, allowing a sufficient number of events. Another strength was that we not only looked at causes of mortality, but also took the occurrence of events during life into account.

A limitation was that we performed a longitudinal study in a clinical setting rather than an epidemiological population-based study. In addition, although our findings are relevant for patients with AD, the selection of patients does impede generalizability of the results. Despite the substantial total number of patients in our cohort, the event rate was rather low. This resulted in wide confidence intervals and a low incidence of stroke. In addition, stroke was unspecified in many cases, which is mainly owing to the population (elderly patients who are often admitted to a nursing home). This may have resulted in an underestimation of the risk for ICH or ischemic stroke. Although we gathered information on the presence and history of vascular risk factors, information on vascular risk factor control was not available. Owing to small numbers, we had to combine antiplatelet and anticoagulant agents into one single antithrombotic medication category; this may be considered a limitation as well.

In line with our previous findings, microbleeds were associated with an increased risk for all-cause mortality in patients with AD. In addition, we found that the presence of lobar microbleeds was strongly associated with stroke-related mortality and incident stroke. Previously, lobar microbleeds had been found to predict stroke,\(^{18}\) stroke-related mortality,\(^{8}\) and ICH-related mortality\(^{9}\) in populations enriched for vascular disease. However, in the general population, nonlobar, but not lobar, microbleeds have been associated with stroke-related mortality.\(^{19}\) The differences in findings can be explained by the different (patient) populations: most of the microbleeds in patients with AD are located in lobar brain regions (CAA related),\(^{4}\) indicating a higher amyloid burden in the brain. Cerebral amyloid angiopathy is clinically characterized by frequent lobar ICHs. Although we were not able to specify all stroke subtypes, all patients with an ICH had microbleeds in lobar locations. The risks for ICH could not be formally calculated; however, these findings seem to support the idea that in patients with AD, lobar microbleeds reflect the presence of CAA, which increases the risk for ICH.

Microbleed presence in general was not associated with an increased risk for cardiovascular mortality; however, the specific observation of nonlobar microbleeds inferred an increased risk for cardiovascular mortality and events. This is in line with findings in a vascular population and in the general elderly population.\(^{4,19}\) Nonlobar microbleeds are suggested to reflect hypertensive vasculopathy. Together with literature, our findings support the concept that such a vasculopathy is not restricted to the brain\(^{20}\) and may be responsible for the increased risk for cardiovascular mortality and events.

We found no association between microbleeds and future TIA. A possible association between microbleeds and TIA has thus far not received much attention; however, Werring et al\(^{21}\) did show that microbleeds are relatively rare in patients with TIA. Microbleeds were also not associated with an increased risk for institutionalization. This may be explained by the strong predictive value of (lobar) microbleeds for future stroke-related mortality. In line with our previous findings,\(^{22}\) our current results indicate that patients with AD with microbleeds are in particular vulnerable for future (fatal) events rather than for more rapid gradual cognitive or functional decline.

We found that the risks for stroke and a cardiovascular event were highest in microbleed patients taking antithrombotic medication. Confounding by indication may explain these findings. A more severe underlying vascular disease may explain the high risk for cardiovascular events, especially in antithrombotic drug users with nonlobar microbleeds. In these patients, treatment of vascular disease should be continued because the risk for events is in fact not a complication of the treatment but a consequence of the underlying, more severe, vascular disease. Alternatively, the use of antithrombotics, especially in patients with lobar microbleeds, may increase the risk for future stroke.\(^{10,11,23,24}\) Circumstantial evidence for this notion comes from our finding that ICH seems to be more frequent than ischemic stroke in these patients. If antithrombotics indeed augment bleeding risk in patients with lobar microbleeds, their prescription in these patients depends on a complicated balance that weighs the benefits of a decreased risk for ischemic stroke or cardiovascular events against the increased risk for ICH. Currently, several risk scores are available to estimate the risk of ischemic stroke (CHA\(_2\)DS\(_2\)-VASc [congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, female sex, vascular disease])\(^{25}\) or ICH (HAS-BLED [hyp-
pertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly) in patients with atrial fibrillation. Our results indicated that microbleed presence may also be a relevant factor contributing to stroke risk. Ongoing trials (eg, Clinical Relevance of Microbleeds in Stroke) are expected to help tailor treatment of vascular disease in the presence of microbleeds. Meanwhile, individualized risk prediction combining existing risk scores with neuroimaging findings and genetic factors is recommended.

Conclusions

Our study showed that in patients with AD, lobar microbleeds increase the risk for stroke, whereas nonlobar microbleeds are associated with an increased risk for cardiovascular events. As the presence of lobar microbleeds indicates a group particularly vulnerable to stroke, these patients should be treated with the utmost care, not only regarding treatment of vascular disease, but also in β-amyloid immunotherapy trials.