Chapter 2.2

Microbleeds, mortality and stroke in Alzheimer’s disease: the MISTRAL study

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Abstract

**Importance:** Microbleeds are more prevalent in patients with Alzheimer’s 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 of mortality, stroke (including intracerebral haemorrhage, ICH), and cardiovascular events.

**Design, setting, and participants:** The MISTRAL study is a longitudinal cohort study within the memory clinic based Amsterdam Dementia Cohort. We selected all AD patients with a baseline visit between 2002-2009 and microbleeds (n=111) and matched those (1:2) for age, gender, and scanner to 222 AD patients without microbleeds. After a minimal follow-up of 3 years, information on all-cause mortality, stroke-related mortality, and cardiovascular mortality was obtained. In addition, we obtained information on the occurrence of incident stroke or TIA, cardiovascular events, and nursing home admittance.

**Main outcome measures:** Stroke-related mortality, incident stroke, and ICH.

**Results:** Patients had a mean 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 of stroke-related mortality (HR 33.9; 95%CI 2.5-461.7), whereas non-lobar microbleeds were associated with an increased risk of cardiovascular mortality (HR 12.0; 95%CI 3.2-44.7). In addition, lobar microbleeds were associated with an increased risk of incident stroke (HR 3.8; 95%CI 1.5-10.1) and non-lobar microbleeds with an increased risk of 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 ICH had lobar microbleeds at baseline; 4 of them used antithrombotics.

**Conclusion and relevance:** In AD patients, the presence of non-lobar microbleeds was associated with an increased risk of cardiovascular events and cardiovascular mortality. Patients with lobar microbleeds had an increased risk of stroke and stroke-related mortality, indicating that these patients should be treated with the utmost care.
Introduction

Microbleeds are considered indicative of small vessel blood leakage and they have been more frequently observed in patients with Alzheimer disease (AD) compared with the general elderly population. In AD patients, microbleeds are mostly seen in lobar locations. Epidemiological data suggests that lobar microbleeds reflect cerebral amyloid angiopathy (CAA), whereas non-lobar 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 of stroke-related mortality and, more specifically, mortality due to intracerebral haemorrhage (ICH). It is tempting to assume that an increased incidence of ICH accounts for increased mortality in AD patients with microbleeds, but longitudinal data are largely lacking.

We designed the MISTRAL study (do Microbleeds predict STROKE in ALzheimer's disease) to investigate whether microbleeds in AD are associated with mortality, stroke or 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 2002-2009, a diagnosis of AD and available T2*-weighted MRI. We included all patients with microbleeds, resulting in a dataset of 111 AD patients with microbleeds. We matched those (1:2) for age, gender, and MRI scanner, to 222 AD patients without microbleeds. At baseline all patients underwent a standardized dementia screening, including physical and neurologic examination, laboratory tests, electroencephalography (EEG), and brain magnetic resonance imaging (MRI). Cognitive assessment included the Mini-Mental State Examination (MMSE) and extensive neuropsychological testing. All results were discussed in a multidisciplinary meeting, after which the diagnosis ‘probable AD’ was made according to the NINCDS-ADRDA criteria and all patients fulfilled the core clinical criteria of the NIA-AA (more details can be found in van der Flier et al). Antithrombotic medication use (antiplatelet or anticoagulant) was recorded. Presence of hypertension, hypercholesterolaemia, and diabetes mellitus was determined based on self-reported medical history and medication use. Smoking was defined as current smoking and body...
mass index (BMI) was calculated. Laboratory testing included Apoe ε4 genotyping performed using a QIAxcel DNA Fast Analysis kit (Qiagen, Venlo, the Netherlands); patients were categorized into carriers (heterozygous or homozygous) or non-carriers. Cerebrospinal fluid (CSF) Amyloid-Beta 1-42 (Aβ42), total Tau (Tau), and hyperphosphorylated Tau-181 (pTau) were determined with Innotest sandwich ELISA as described previously.12

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.

MRI
MRI scans were obtained at 1.0T (n= 171), 1.5T (n=57) or 3.0T scanners (n=105). The scan protocol included T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), 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, up to 10mm 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 one microbleed. Microbleeds were also categorized according to their location: no microbleeds; strictly non-lobar microbleeds; any lobar microbleed (including microbleeds in mixed locations). On the FLAIR sequence, white matter hyperintensities (WMH) were assessed using the Fazekas scale (0:none; 1:punctuate; 2:early confluent; and 3:confluent)16 and dichotomized into absent (0-1) or present (2-3). Lacunes were defined as deep lesions (3-15mm) with CSF-like signal on all sequences; lacunes were scored as absent (0) or present (≥1).

Follow-up
Follow-up information was retrieved between November 2012-May 2014, allowing a minimal follow-up duration of 3 years. As a first step, we obtained information on mortality (deceased: yes/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 classification of diseases, 10th edition (ICD-10; WHO, 1992). In the analyses we only examined 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 from date of baseline visit until date of death or November 1st 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 (i.e. antiplatelet or anticoagulants) use, by sending questionnaires to all patients' general practitioners (GPs). Incident stroke included intracerebral haemorrhage (ICH), ischaemic stroke, and unspecified stroke. A cardiovascular event included myocardial infarction (MI), 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 from date of baseline visit until date of event, date of death, or last date of survival. Follow-up information on incident events was not available for all patients (see figure 1). Patients who were lost to follow-up were more often deceased (81% vs. 47%, p<0.01), but groups did not differ with regard to other aspects (data not shown).

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

Incidence rates were determined per 1000 person-years of follow-up. The error factor (EF) was calculated with the formula: \( e^{(1.96*\sqrt{n \text{ events}})} \) and was used to calculate the lower (incidence/EF) and upper (incidence*EF) limit of the 95% confidence interval (CI).

Cox proportional-hazard analyses were used to calculate the hazard ratios (HR) of microbleed presence (no/yes) and microbleed location (no/strictly non-lobar/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. Antithrombotic medication use (no/yes) was defined as any use of antiplatelet 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 non-lobar microbleeds without antithrombotics; 4) strictly non-lobar microbleeds with antithrombotics; 5) any lobar microbleed without antithrombotics; 6) any lobar microbleed with antithrombotics. All analyses were adjusted for age, gender, MMSE, vascular risk factors, and presence of WMH and lacunes.
Results

Overall description of cohort

We included 111 AD patients with one or more microbleed (71.6±7.8 years, 36% female) and 222 AD patients without microbleeds (71.1±7.8 years, 45% female) (see figure 1). Patients with microbleeds had a lower MMSE score (p<0.05), more often WMH (p<0.01) and lacunes (p<0.05), and lower levels of CSF Aβ42 (p<0.01) than patients without microbleeds (table 1). Moreover, patients with microbleeds tended to have a higher systolic blood pressure and tended to have more often a history of hypertension (both p<0.07). Patients did not differ with regard to other aspects.

Risk of 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 of all-cause mortality (HR any lobar microbleed: 1.7; 95%CI 1.2-2.5).
Table 1. Baseline characteristics of the total cohort and according to microbleed presence

<table>
<thead>
<tr>
<th></th>
<th>Total cohort</th>
<th>Microbleeds</th>
<th>No Microbleeds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=333</td>
<td>N=111</td>
<td>N=222</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>140 (42%)</td>
<td>40 (36%)</td>
<td>100 (45%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>71.2±7.8</td>
<td>71.6±1.8</td>
<td>71.1±7.8</td>
</tr>
<tr>
<td>MMSE</td>
<td>21±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>Hypercholesterolaemia</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, systolic, mm/Hg</td>
<td>146±18</td>
<td>150±18</td>
<td>144±16&quot;</td>
</tr>
<tr>
<td>Blood pressure, diastolic, mm/Hg</td>
<td>84±9</td>
<td>86±9</td>
<td>84±9</td>
</tr>
<tr>
<td>Body mass index</td>
<td>24±4</td>
<td>24±4</td>
<td>25±4</td>
</tr>
<tr>
<td>Lacune presence</td>
<td>44 (13%)</td>
<td>21 (19%)</td>
<td>23 (10%) #</td>
</tr>
<tr>
<td>WMH presence</td>
<td>100 (30%)</td>
<td>53 (47%)</td>
<td>47 (21%) **</td>
</tr>
<tr>
<td>CSF Aβ42, pg/ml</td>
<td>479±185</td>
<td>404±111</td>
<td>509±199 **</td>
</tr>
<tr>
<td>CSF Tau, pg/ml</td>
<td>686±40</td>
<td>743±470</td>
<td>662±368</td>
</tr>
<tr>
<td>CSF pTau, pg/ml</td>
<td>94±45</td>
<td>101±53</td>
<td>91±42</td>
</tr>
<tr>
<td><strong>ApoE ε4 status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-carriers</td>
<td>89 (31%)</td>
<td>28 (3%)</td>
<td>61 (93%)</td>
</tr>
<tr>
<td>Heterozygous carriers</td>
<td>135 (47%)</td>
<td>35 (40%)</td>
<td>100 (53%)</td>
</tr>
<tr>
<td>Homozygous carriers</td>
<td>60 (21%)</td>
<td>24 (28%)</td>
<td>36 (18%)</td>
</tr>
</tbody>
</table>

Availability for incomplete data: Smoking: microbleeds 102/111; no microbleeds 204/222; CSF: microbleeds 68/111; no microbleeds 170/222; ApoE ε4 status: microbleeds 87/111.; no microbleeds 197/222.

Data are represented as mean±SD or number of patients with variable present (%). Student t-test and χ² test were performed respectively.

Key: MMSE: mini-mental state examination; WMH: white matter hyperintensities; CSF: cerebrospinal fluid.

**: p<0.01 compared with microbleeds; *: p<0.05 compared with microbleeds; #: p=0.07 compared with microbleeds.

Stroke was 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 of 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 non-lobar microbleeds died from stroke. Stroke-related mortality was unspecified in most (n=4) cases, but 3 patients died from an ICH and they all had lobar microbleeds at baseline (3%; 8 cases [95%CI 2-24] per 1000 person-years). Stroke-related mortality was never classified as ischaemic stroke. Unfortunately, the low event rate prohibited calculation of HRs.
### Table 2. Microbleeds and risk of mortality

<table>
<thead>
<tr>
<th></th>
<th>All-cause mortality</th>
<th>Stroke-related mortality</th>
<th>Cardiovascular mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no/1000 person-yrs (95% CI)</td>
<td>HR (95% CI)</td>
<td>no/1000 person-yrs (95% CI)</td>
</tr>
<tr>
<td>MB presence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No MBs</td>
<td>76 (62-94)</td>
<td>reference</td>
<td>1 (0-6)</td>
</tr>
<tr>
<td>Any MB</td>
<td>134 (104-171)</td>
<td>1.7 (1.2-2.4)</td>
<td>13 (6-29)</td>
</tr>
<tr>
<td>MB location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strictly non-lobar MBs</td>
<td>95 (48-191)</td>
<td>1.6 (0.7-3.4)</td>
<td>0</td>
</tr>
<tr>
<td>Any lobar MBs</td>
<td>142 (109-186)</td>
<td>1.7 (1.2-2.5)</td>
<td>16 (7-35)</td>
</tr>
</tbody>
</table>

Values represent incidence per 1000 person-years with 95% confidence intervals (CI) and hazard ratios (HR) with 95% CI. HRs are adjusted for age, gender, MMSE, vascular risk factors, white matter hyperintensities, and lacunes. No microbleeds are the reference category. Key: MB: microbleeds.

### Figure 2. Survival curves for incident stroke (A) according to microbleed location and for a cardiovascular event (B) according to microbleed location.
A cardiovascular event was 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 of 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 non-lobar microbleeds was associated with an increased risk of cardiovascular mortality (HR 12.0; 95%CI 3.2-44.7).

Risk of stroke or TIA
Incident stroke occurred in 9 patients without microbleeds (4%; 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 of incident stroke (HR 3.3; 95%CI 1.3-8.4). Compared with no microbleeds, the risk of incident stroke was only increased for lobar microbleeds (HR 3.8; 95%CI 1.5-10.1) and not for strictly non-lobar microbleeds (HR 1.3; 95%CI 0.2-11.5) (figure 2a).

Incident stroke was not specified in all cases, but eTable 4 shows the incidence of known ICHs (n=5) and ischaemic strokes (n=12) according to microbleed presence and location. All patients with incident ICH had lobar microbleeds. In addition, whereas ischaemic 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.

TIA 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 of TIA (data not shown).

Risk of 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 was not associated with an increased risk of a cardiovascular event. However, the presence of strictly non-lobar microbleeds was associated with an increased risk of a cardiovascular event (HR strictly non-lobar: 6.2; 95%CI 1.5-25.0) (figure 2b).

Risk of nursing home admittance
Among patients without microbleeds, 119 were admitted to a nursing home (59%; 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 of nursing home admittance (data not shown).
Influence of antithrombotic medication

Hundred twenty-two 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 microbleeds 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 of stroke (HR 6.7; 95%CI 1.9-23.8). When we repeated these analyses in patients using antiplatelet agents, results remained essentially unchanged (data not shown). The group using anticoagulants was too small to analyse.

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 non-lobar microbleeds and antithrombotics (33%; 94 cases per 1000 person-years). Compared with patients with neither microbleeds nor antithrombotics, only patients with strictly non-lobar microbleeds and antithrombotics had an increased risk of a cardiovascular event (HR 13.1; 95%CI 2.2-78.9).

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

Discussion

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

A strength of the current study is 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 three years, allowing a sufficient number of events. Another strength is that we not only looked at causes of mortality, but also took the occurrence of events during life into account.
Table 3. Microbleeds and risk of incident stroke and cardiovascular events

<table>
<thead>
<tr>
<th>MB presence</th>
<th>Stroke</th>
<th>Cardiovascular event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no/1000 person-yrs (95%CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>No MBs</td>
<td>9 (5-17)</td>
<td>reference</td>
</tr>
<tr>
<td>Any MB</td>
<td>33 (20-56)</td>
<td>3.3 (1.3; 8.4)</td>
</tr>
<tr>
<td>MB location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strictly non-lobar MBs</td>
<td>12 (2-85)</td>
<td>1.3 (0.2;11.5)</td>
</tr>
<tr>
<td>Any lobar MBs</td>
<td>38 (22-66)</td>
<td>3.8 (1.5;10.1)</td>
</tr>
<tr>
<td>MB location and antithrombotic treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No MBs, no antithrombotics</td>
<td>9 (4-21)</td>
<td>reference</td>
</tr>
<tr>
<td>No MBs, antithrombotics</td>
<td>10 (4-26)</td>
<td>0.9 (0.2;3.7)</td>
</tr>
<tr>
<td>Strictly non-lobar MBs, no antithrombotics</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Strictly non-lobar MBs, antithrombotics</td>
<td>47 (7-335)</td>
<td>5.5 (0.6;51.8)</td>
</tr>
<tr>
<td>Any lobar MB, no antithrombotics</td>
<td>16 (5-49)</td>
<td>1.8 (0.4; 8.1)</td>
</tr>
<tr>
<td>Any lobar MB, antithrombotics</td>
<td>67 (36-125)</td>
<td>6.7 (1.9; 23.8)</td>
</tr>
</tbody>
</table>

Values represent incidence per 1000 person-years with 95% confidence intervals (CI) and hazard ratios (HR) with 95% CI. HRs are adjusted for age, gender, MMSE, vascular risk factors, white matter hyperintensities and lacunes. No microbleeds are the reference category. Key: MB: microbleeds.
A limitation is that we performed a longitudinal study in a clinical setting, rather than an epidemiological population-based study. In addition, although our findings are extremely relevant for AD patients, the selection of patients does impede generalizability of the results. Despite the substantial total number of patients in our cohort, 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 due to the population (elderly patients who are often admitted to a nursing home). This may have resulted in an underestimation of the risk of ICH or ischaemic stroke. Although we gathered information on presence and history of vascular risk factors, information on vascular risk factor control was not available. Due 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,7 microbleeds were associated with an increased risk of 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 have been found to predict stroke,7 stroke-related mortality,8 and ICH-related mortality9 in populations enriched for vascular disease. In the general population, however, non-lobar, but not lobar, microbleeds have been associated with stroke-related mortality.18 Differences in findings can be explained by the different (patient) populations: the majority of the microbleeds in AD patients are located in lobar brain regions (CAA-related)4 indicating a higher amyloid burden in the brain. CAA 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. Risks for ICH could not be formally calculated, but these findings seem to support the idea that in AD patients, lobar microbleeds reflect the presence of CAA, which increases the risk of ICH.

Microbleed presence in general was not associated with an increased risk of cardiovascular mortality, but the specific observation of non-lobar microbleeds inferred an increased risk of cardiovascular mortality and events. This is in line with findings in a vascular population and in the general elderly population.818 Non-lobar microbleeds are suggested to reflect hypertensive vasculopathy. Together with literature our findings support the concept that such a vasculopathy is not restricted to the brain19 and may be responsible for the increased risk of 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, but Werring et al20 did show that microbleeds are relatively rare in patients with TIA. Microbleeds were also not associated with an increased risk of institutionalization. This may be explained by
the strong predictive value of (lobar) microbleeds for future stroke-related mortality. In line with our previous findings, our current results indicate that AD patients 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 of stroke and a cardiovascular event were highest in microbleed-patients using antithrombotic medication. Confounding by indication may explain these findings; especially in antithrombotic drug users with non-lobar microbleeds, a more severe underlying vascular disease may explain the high risk of cardiovascular events. In these patients, treatment of vascular disease should be continued, as the risk of 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 of future stroke. Circumstantial evidence for this notion comes from our finding that ICH seems to be more frequent than ischaemic 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 of ischaemic stroke or cardiovascular events, against the increased risk of ICH. Currently, several risk scores are available to estimate the risk of ischaemic stroke (CHA₂DS₂-VASc) or ICH (HAS-BLED) in patients with atrial fibrillation. Our results indicate that microbleed presence may also be a relevant factor contributing to stroke risk. Ongoing trials (e.g. CROMIS-2) are expected to help tailoring 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.

In conclusion, our study shows that in AD patients, lobar microbleeds increase the risk of stroke, whereas non-lobar microbleeds are associated with an increased risk of 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 Aβ immunotherapy trials.
References


### eTable 4. Incidence of intracerebral haemorrhage and ischaemic stroke

<table>
<thead>
<tr>
<th></th>
<th>Intracerebral haemorrhage</th>
<th>Ischaemic stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>no/1000 person-yrs (95%CI)</td>
</tr>
<tr>
<td>Total group</td>
<td>5/301</td>
<td>3 (1-8)</td>
</tr>
<tr>
<td><strong>MB presence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No MBs</td>
<td>0/200</td>
<td>-</td>
</tr>
<tr>
<td>Any MB</td>
<td>5/101</td>
<td>12 (5-28)</td>
</tr>
<tr>
<td><strong>MB location</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strictly non-lobar MBs</td>
<td>0/18</td>
<td>-</td>
</tr>
<tr>
<td>Any lobar MBs</td>
<td>5/83</td>
<td>15 (6-35)</td>
</tr>
<tr>
<td><strong>MB location and antithrombotic treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No MBs, no antithrombotics</td>
<td>0/121</td>
<td>-</td>
</tr>
<tr>
<td>No MBs, antithrombotics</td>
<td>0/79</td>
<td>-</td>
</tr>
<tr>
<td>Strictly non-lobar MBs, no antithrombotics</td>
<td>0/12</td>
<td>-</td>
</tr>
<tr>
<td>Strictly non-lobar MBs, antithrombotics</td>
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<td>-</td>
</tr>
<tr>
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<td>1/46</td>
<td>5 (1-37)</td>
</tr>
<tr>
<td>Any lobar MB, antithrombotics</td>
<td>4/37</td>
<td>27 (10-71)</td>
</tr>
</tbody>
</table>

Key: MB: microbleeds; n/N: events/number of subjects.