Cerebral Microbleeds Are Predictive of Mortality in the Elderly

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Background and Purpose—To investigate the prognostic value of cerebral microbleeds (CMB) regarding overall, cardiovascular-related, and stroke-related mortality and to investigate possible differences based on a cerebral amyloid angiopathy-type and nonlobar distribution of microbleeds.

Methods—We included 435 subjects who were participants from the nested MRI substudy of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). Cox proportional hazard models were applied to estimate the risk of overall, cardiovascular-related, and stroke-related death associated with microbleeds in general and microbleeds with a lobar distribution suggestive of the presence of cerebral amyloid angiopathy. The corresponding Kaplan-Meier survival curves were calculated.

Results—Subjects with $>1$ CMB had a 6-fold risk of stroke-related death compared to subjects without CMB (hazard ratio, 5.97; 95% CI, 1.60–22.26; $P=0.01$). The diagnosis of nonlobar microbleeds was associated with $>2$-fold risk of cardiovascular death compared to subjects without microbleeds (hazard ratio, 2.67; 95% CI, 1.23–5.81; $P=0.01$). Subjects with probable cerebral amyloid angiopathy-type microbleeds had $>7$-fold risk of stroke-related death compared to subjects without CMB (hazard ratio, 7.20; 95% CI, 1.44–36.10; $P=0.02$).

Conclusions—This is the first study investigating the association between microbleeds and risk of overall, cardiovascular-related, and stroke-related mortality in an elderly population. Our findings indicate that the diagnosis of microbleeds is potentially of clinical relevance. Larger studies are needed to expand our observations and to address potential clinical implications and cost-benefits of such a policy. (Stroke. 2011;42:638-644.)

Key Words: cerebral amyloid angiopathy ■ hemorrhage ■ neuroradiology

Cerebral microbleeds (CMB) are focal hemosiderin deposits that result from minimal blood leakage from damaged small vessels and can be regarded as markers of pathological vascular changes. Concerning histopathology, the 2 most common types of underlying small vessel damage are hypertensive vasculopathy and cerebral amyloid angiopathy (CAA). The location and distribution of CMB depend on the type of underlying vasculopathy; whereas hypertensive CMB preferentially occur in deep brain regions such as the basal ganglia, thalamus, or brain stem, CAA-type CMB are mainly located in the cerebral lobes but never in deep brain regions. CMB are commonly seen in patients with ischemic stroke, intracerebral hemorrhage, Alzheimer’s disease, traumatic brain injury-associated diffuse axonal injury, and also in healthy elderly individuals. The prevalence of CMB in the general population increases from $\approx 20\%$ in subjects aged 60 to 69 years to $\approx 40\%$ in subjects aged 80 years and older.

Presence of CMB was the strongest predictor of overall mortality among a range of MRI markers of vascular damage in a memory clinic population. It remains to be elucidated whether CMB are predictive of mortality in the general population. Furthermore, it is not known to what extent CMB are specifically associated with cardiovascular mortality or noncardiovascular disease.

In the present study, we investigated the prognostic value of CMB regarding overall, cardiovascular-related, and stroke-related mortality in a population enriched for or at high risk for cardiovascular disease. Moreover, we
investigated possible differences in prognostic value based on a CAA-type and nonlobar distribution of CMB.

Subjects and Methods

Study Participants

All subjects are participants from the nested MRI substudy of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). Inclusion criteria for the PROSPER were men or women aged 70 to 82 years with a total cholesterol of 4.0 to 9.0 mmol/L and a history of either ischemic or hemorrhagic stroke, transient ischemic attack, myocardial infarction, arterial surgery, or amputation for vascular disease, or 1 of the following risk factors for vascular disease: current smoker, hypertension diagnosed, diabetes mellitus, or fasting blood glucose >7 mmol/L. Of the included subjects, 43% had symptomatic vascular disease. These subjects experienced symptoms >6 months before entering the study. Exclusion criteria have been described in detail elsewhere. There were no specific inclusion criteria for the MRI study. All consenting subjects (646 of the 1100 eligible Dutch participants) were enrolled in the Netherlands from May 2, 1998. CMB were scored on MRI scans obtained at the end of the study. Ninety-two subjects did not undergo an MRI scan because of the following reasons: 44 subjects had died, 6 subjects had withdrawn informed consent, and 2 could not undergo a scan because of technical problems. T2*-weighted scans for the detection of CMB were available for 435 subjects. Baseline characteristics of these 435 subjects and the remaining 665 Dutch PROSPER participants were similar, except for the proportion of smokers, which was significantly higher among the 665 Dutch participants (26.8% vs 20.5%; P = 0.02). Mortality of study participants was continuously followed-up after the official end of the study until December 31, 2009. The individual causes of death were obtained through the Central Bureau of Statistics of the Netherlands. All end points were adjudicated by the independent clinical events committee of PROSPER. The protocols meet the criteria of the Declaration of Helsinki and were approved by the Medical Ethics Committees of each participating institution. Written informed consent was obtained from all participating patients.

MRI Scanning

All imaging was performed on an MR system operating at field strength of 1.5 T (Philips Medical Systems). Dual fast-spin echo (repetition time = 3000 ms; echo time = 27/120 ms; flip angle = 90°; slice thickness = 3 mm; 48 slices; no interslice gap; field of view = 220 × 220 mm; matrix = 512 × 512), fluid-attenuated inversion recovery (FLAIR) (repetition time = 8000 ms; echo time = 100 ms; inversion delay = 2000 ms; flip angle = 90°; slice thickness = 3 mm; 48 slices; no interslice gap; field of view = 220 × 176 mm; matrix = 256 × 153), and T2*-weighted images (multislice gradient echo sequence; repetition time = 2593 ms; echo time = 48 ms; flip angle = 60°; slice thickness = 6 mm; 22 slices; interslice gap = 6 mm; whole brain coverage; field of view = 220 × 198 mm; matrix = 256 × 176) were obtained from all subjects.

MRI Analysis: Microbleeds

All MRI scans were read in consensus by 2 experienced raters (A.C.G.M.v.E. and M.A.v.B.), who were blinded to the clinical history. CMB were defined as focal areas of signal loss on T2*-weighted images that increased in size on the T2*-weighted gradient-echo planar images (“blooming effect”). In this way, CMB were differentiated from areas of signal loss based on vascular flow void. Areas of symmetrical hypointensity in the basal ganglia likely to represent calcification or nonhemorrhagic iron deposits were disregarded. For each subject, number and location (corticosubcortical junction, deep white matter, basal ganglia, and infratentorial) of CMB were recorded. All study participants were assigned to one of the following groups accord-
tions: atrophy (\%)=([intracranial volume−parenchymal volume]/intracranial volume)×100\% and hippocampal atrophy (\%)=(hippocampal volume/intracranial volume)×100\%, respectively.\textsuperscript{19,20} Cortical infarcts were defined as cortical defects surrounded by a hyperintense zone on T2-weighted scans. Lacunar infarcts were defined as parenchymal defects, not extending into the cortex, surrounded by a hyperintense zone (\(≥3\) mm, \(<15\) mm in diameter) on a T2-weighted scan. Dilated perivascular spaces were distinguished from infarcts on the basis of their location, form, and the absence of a hyperintense zone around the parenchymal defect.

Statistical Analysis

For statistical analysis, SPSS software for windows (version 17.0.1; SPSS) was used. Kaplan-Meier survival curves for overall, cardiovascular-related, and stroke-related mortality were calculated for no, 1, and \(>1\) microbleed, possible and probable CAA-type CMB, and nonlobar microbleeds. We applied Cox proportional hazard models to estimate the risk of overall, cardiovascular-related, and stroke-related death associated with these microbleed categories in 2 different ways: adjusting for age, sex, and use of statins (model 1; \(n=435\) for overall mortality, \(n=434\) for cardiovascular-related and stroke-related mortality; the cause of death of 1 subject was missing) and additionally adjusting for cardiovascular risk factors (alcohol use, smoking, body mass index, high-density lipoprotein cholesterol, systolic and diastolic blood pressure, and history of hypertension/diabetes mellitus/ischemic or hemorrhagic stroke/transient ischemic attack; model 2; \(n=418\) for overall mortality, \(n=417\) for cardiovascular-related and stroke-related mortality; the cause of death of 1 subject was missing).

Results

Baseline characteristics of the study population are shown in Table 1. In total, 435 participants with a mean age of 75.0 years and a female fraction of 43.6\% were included in the present study. The mean follow-up duration for determining mortality was 7.0 (\(±2.1\) ) years. In this period, 153 subjects (34.9\%) died, of whom 57 (37.3\%) died of cardiovascular causes: 14 had an ischemic or hemorrhagic stroke, 43 subjects died of cardiovascular causes not affecting the brain, and the cause of death of 1 subject was missing. The individual amount of CMB was not significantly different between subjects treated with statins and subjects treated with placebo (data not shown). History of hypertension was significantly associated with the diagnosis of CMB independent of the other mentioned cardiovascular risk factors (\(P=0.005\); data not shown).

First, we investigated the risk of overall, cardiovascular-related, and stroke-related death associated with the diagnosis of no, 1, or \(>1\) microbleed. Subjects with \(>1\) microbleed diagnosed had an increased risk of overall death compared to subjects without CMB after adjustment for age, sex, use of statins, and cardiovascular risk factors (HR, 2.67; 95\% CI, 1.23–5.81; \(P=0.01\); Table 2). Strikingly, subjects with \(>1\) microbleed diagnosed had \(≈6\)-fold risk of stroke-related death compared to subjects without microbleeds after adjustment for age, sex, use of statins, and cardiovascular risk factors (HR, 5.97; 95\% CI, 1.60–22.26; \(P=0.01\)). Figure 1 shows the corresponding Kaplan-Meier survival curves for overall (Figure 1A), cardiovascular (Figure 1B), and stroke-related mortality (Figure 1C).

Subjects with nonlobar microbleeds diagnosed had \(>2\)-fold risk of cardiovascular death compared to subjects without CMB after adjustment for age, sex, use of statins, and cardiovascular risk factors (HR, 2.67; 95\% CI, 1.23–5.81; \(P=0.01\); Table 3). This association remained unchanged after additional adjustment for other cerebral changes on MRI (cerebral and hippocampal atrophy, WML, cortical and lacunar infarctions; HR, 3.03; 95\% CI, 1.34–6.85; \(P=0.01\)). The corresponding Kaplan-Meier survival curves are shown in Figure 2A. Approximately 65\% of these subjects had CMB located in the basal ganglia diagnosed, 52\% had cerebellar CMB diagnosed, 32\% had lobar CMB diagnosed, 13\% had CMB located in the brain stem diagnosed, and 45\% had CMB in at least 2

### Table 2. Risk of Overall, Cardiovascular-Related Mortality, and Stroke-Related Mortality Associated With Cerebral Microbleeds

<table>
<thead>
<tr>
<th>Microbleeds</th>
<th>d/n</th>
<th>Model 1 HR (95% CI)</th>
<th>(P)</th>
<th>d/n</th>
<th>Model 2 HR (95% CI)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mortality</td>
<td>(n=435)</td>
<td>1.00 (reference)</td>
<td>(P=0.005)</td>
<td>(n=418)</td>
<td>1.00 (reference)</td>
<td>(P=0.005)</td>
</tr>
<tr>
<td>0</td>
<td>115/331</td>
<td>1.00 (reference)</td>
<td>(P=0.16)</td>
<td>109/320</td>
<td>1.00 (reference)</td>
<td>(P=0.12)</td>
</tr>
<tr>
<td>1</td>
<td>15/52</td>
<td>0.76 (0.45–1.31)</td>
<td>(0.33)</td>
<td>12/47</td>
<td>0.70 (0.38–1.28)</td>
<td>(0.24)</td>
</tr>
<tr>
<td>(&gt;1)</td>
<td>22/52</td>
<td>1.23 (0.78–1.95)</td>
<td>(0.38)</td>
<td>22/51</td>
<td>1.41 (0.87–2.27)</td>
<td>(0.16)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>(n=434)</td>
<td>1.00 (reference)</td>
<td>(P=0.16)</td>
<td>(n=417)</td>
<td>1.00 (reference)</td>
<td>(P=0.16)</td>
</tr>
<tr>
<td>0</td>
<td>40/330</td>
<td>1.00 (reference)</td>
<td>(P=0.82)</td>
<td>39/319</td>
<td>1.00 (reference)</td>
<td>(P=0.82)</td>
</tr>
<tr>
<td>1</td>
<td>7/52</td>
<td>1.05 (0.47–2.34)</td>
<td>(0.91)</td>
<td>4/47</td>
<td>0.60 (0.21–1.71)</td>
<td>(0.34)</td>
</tr>
<tr>
<td>(&gt;1)</td>
<td>10/52</td>
<td>1.61 (0.80–3.24)</td>
<td>(0.18)</td>
<td>10/51</td>
<td>1.78 (0.86–3.70)</td>
<td>(0.12)</td>
</tr>
<tr>
<td>Stroke-related mortality</td>
<td>(n=434)</td>
<td>1.00 (reference)</td>
<td>(P=0.16)</td>
<td>(n=417)</td>
<td>1.00 (reference)</td>
<td>(P=0.16)</td>
</tr>
<tr>
<td>0</td>
<td>9/330</td>
<td>1.00 (reference)</td>
<td>(P=0.82)</td>
<td>8/319</td>
<td>1.00 (reference)</td>
<td>(P=0.82)</td>
</tr>
<tr>
<td>1</td>
<td>0/52</td>
<td>No cases</td>
<td>(P=0.82)</td>
<td>0/47</td>
<td>No cases</td>
<td>(P=0.82)</td>
</tr>
<tr>
<td>(&gt;1)</td>
<td>5/52</td>
<td>3.41 (1.13–10.31)</td>
<td>(0.03)</td>
<td>5/51</td>
<td>5.97 (1.60–22.26)</td>
<td>(0.01)</td>
</tr>
</tbody>
</table>

\(d\) indicates deceased; HR, hazard ratio; \(n\), total number of subjects.

Values are HR adjusted for age, sex, and use of statins (model 1) and additionally for cardiovascular risk factors (model 2), respectively, with 95\% CI.
of the mentioned locations diagnosed. The HR for cardiovascular mortality were, respectively, 3.06, (95% CI, 1.12–8.34; \(P=0.03\); deceased/total number of subjects = 6/19, basal ganglia), 4.18 (95% CI, 1.57–11.11; \(P=0.004\); deceased/total number of subjects = 6/15, cerebellum), 2.51 (95% CI, 0.68–9.23; \(P=0.17\); deceased/total number of subjects = 3/10, lobar), and 1.62 (95% CI, 0.19–14.12; \(P=0.66\); deceased/total number of subjects = 1/4 brain stem).

Subjects with probable CAA-type microbleeds diagnosed were exposed to >7-fold risk of stroke-related death compared to subjects without CMB after adjustment for age, sex, use of statins, and cardiovascular risk factors.

Table 3. Risk of Overall and Cardiovascular Mortality Associated With Cerebral Microbleeds Scored Using the Boston Criteria

<table>
<thead>
<tr>
<th>Boston Criteria</th>
<th>d/n</th>
<th>Model 1 HR (95% CI)</th>
<th>(P)</th>
<th>d/n</th>
<th>Model 2 HR (95% CI)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No microbleeds</td>
<td>115/331</td>
<td>1.00 (reference)</td>
<td>0.40</td>
<td>109/320</td>
<td>1.00 (reference)</td>
<td>0.18</td>
</tr>
<tr>
<td>Probable CAA</td>
<td>14/32</td>
<td>1.27 (0.73–2.22)</td>
<td>1.31</td>
<td>5/32</td>
<td>1.31 (0.51–3.33)</td>
<td>0.58</td>
</tr>
<tr>
<td>Possible CAA</td>
<td>9/40</td>
<td>0.59 (0.30–1.16)</td>
<td>0.39</td>
<td>2/40</td>
<td>0.39 (0.09–1.60)</td>
<td>0.19</td>
</tr>
<tr>
<td>Nonlobar microbleeds</td>
<td>14/32</td>
<td>1.25 (0.71–2.18)</td>
<td>0.39</td>
<td>10/32</td>
<td>2.62 (1.30–5.29)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No microbleeds</td>
<td>40/330</td>
<td>1.00 (reference)</td>
<td>0.40</td>
<td>39/319</td>
<td>1.00 (reference)</td>
<td>0.32</td>
</tr>
<tr>
<td>Probable CAA</td>
<td>5/32</td>
<td>1.31 (0.51–3.33)</td>
<td>0.58</td>
<td>5/31</td>
<td>1.67 (0.63–4.46)</td>
<td>0.01</td>
</tr>
<tr>
<td>Possible CAA</td>
<td>2/40</td>
<td>0.39 (0.09–1.60)</td>
<td>0.39</td>
<td>0/36</td>
<td>No cases</td>
<td></td>
</tr>
<tr>
<td>Nonlobar microbleeds</td>
<td>10/32</td>
<td>2.62 (1.30–5.29)</td>
<td>0.01</td>
<td>9/31</td>
<td>2.67 (1.23–5.81)</td>
<td>0.01</td>
</tr>
<tr>
<td>Stroke-related mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No microbleeds</td>
<td>9/330</td>
<td>1.00 (reference)</td>
<td>0.40</td>
<td>8/319</td>
<td>1.00 (reference)</td>
<td>0.32</td>
</tr>
<tr>
<td>Probable CAA</td>
<td>3/32</td>
<td>3.27 (0.86–12.37)</td>
<td>0.08</td>
<td>3/31</td>
<td>7.20 (1.44–36.10)</td>
<td>0.24</td>
</tr>
<tr>
<td>Possible CAA</td>
<td>0/40</td>
<td>No cases</td>
<td>0.01</td>
<td>0/36</td>
<td>No cases</td>
<td></td>
</tr>
<tr>
<td>Nonlobar microbleeds</td>
<td>2/32</td>
<td>2.18 (0.46–10.23)</td>
<td>0.32</td>
<td>2/31</td>
<td>2.85 (0.49–16.46)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

CAA indicates cerebral amyloid angiopathy; d, deceased; HR, hazard ratio; n, total number of subjects.

Values are HR adjusted for age, sex, and use of statins (model 1) and additionally for cardiovascular risk factors (model 2), respectively, with 95% CI.
(HR, 7.20; 95% CI, 1.44–36.10; P=0.02). The corresponding Kaplan-Meier survival curves are shown in Figure 2B. Neither probable CAA-type CMB nor possible CAA-type CMB were associated with an increased risk of overall or cardiovascular death. Combining probable and possible CAA patients in 1 group did not change these results.

Discussion
The most important findings of this population-based study in elderly individuals are that nonlobar microbleeds are significantly and independently associated with cardiovascular mortality and that probable CAA-type microbleeds are significantly associated with stroke-related mortality.

Nonlobar CMB seem to represent a sensitive marker of increased cardiovascular risk beyond traditional cardiovascular risk factors. Presence of nonlobar CMB was significantly associated with an increased risk of cardiovascular-related but not stroke-related death, independent of cardiovascular risk factors and other cerebral changes on MRI, such as cortical and hippocampal atrophy, WML, and cortical and lacunar infarctions, which have been partly shown to be associated with mortality as well.12,21–23 CMB have been shown to be associated with primary and recurrent intracerebral hemorrhage,24–31 and especially nonlobar microbleeds are strongly associated with hypertension and elevated systolic blood pressure, the traditional risk factors for hemorrhagic and ischemic stroke.5,32,33 Against this background our results are striking, indicating that nonlobar CMB can be regarded as an additional marker of an unfavorable cardiovascular risk profile beyond traditional cardiovascular risk factors, such as hypertension or smoking, and other imaging markers of hypertension, such as left ventricular hypertrophy, which has been established as a predictor of excess cardiovascular mortality.34 Further studies will be needed to compare the predictive strength of nonlobar CMB against already-established imaging markers of cardiovascular mortality such as left ventricular hypertrophy. However, the value of this finding is limited by the small proportion of subjects with nonlobar CMB diagnosed who died from cardiovascular disease or stroke during follow-up.

CAA-type CMB seem to be markers of an increased risk of stroke-related death, independent of cardiovascular risk factors. However, the number of subjects who died from stroke was small. Furthermore, we could not differentiate between hemorrhagic and ischemic stroke as primary outcome and therefore are not able to further comment about possible associations between CAA-type microbleeds and hemorrhagic or ischemic stroke. Further studies are needed to assess the validity and possible underlying mechanisms of the association between probable CAA-type microbleeds and stroke-related mortality.

The association of CMB with mortality depends on the number of CMB diagnosed in subjects. We could show that subjects with 1 microbleed in general or possible CAA-type microbleeds diagnosed had no increased risk of mortality, whereas subjects with >1 microbleed in general or probable CAA-type microbleeds diagnosed were exposed to an increased risk of death. Within the group of subjects with nonlobar microbleeds, presence of ≥1 CMB was associated with an increased risk of mortality. Until now, there was only 1 study investigating the association between CMB and overall mortality in a memory clinic population.12 In this study, the diagnosis of ≥3 microbleeds was associated with an increased risk of overall death. However, because the conspicuity and therefore the accuracy of detection of CMB are strongly affected by the used MRI technique, available MRI field strength, and image post-processing,2 it remains difficult to compare these studies.

A strength of our study is the population-based setting in elderly individuals with or at high risk for vascular disease developing. Although our results might not be generalizable to the general elderly population, we were able to assess the predictive value of CMB in a population in which CMB are most likely to be clinically relevant. Furthermore, the large sample size and high prevalence of CMB in this specific population allowed us to assess the association between CMB and different outcome parameters, such as overall, cardiovascular-related, and stroke-related death, and to analyze these associations for different classifications of CMB and CMB in separate anatomic regions. However, there are also several limitations of this study. First, the adjudication of the primary outcome from the national registry instead of formal follow-up limited...
the possibility to reliably assess the association between CMB and different outcome parameters. One example is the missing differentiation between hemorrhagic and ischemic strokes. Second, the number of events during follow-up was relatively small, so the association between 1 microbleed in general or possible CAA and stroke-related mortality could not be assessed. Because we did not include other established neuroimaging markers of, for instance, cardiovascular mortality, such as left ventricular hypertrophy, in our study design we were not able to compare the predictive strength of CMB against these markers. Further studies will be needed to address this issue. Furthermore, our results are limited to a small group of elderly individuals enriched for or at high risk for cardiovascular disease and therefore were neither generalizable to the whole study cohort nor to the general elderly population.

**Conclusion**

In conclusion, this is the first study to our knowledge investigating the association between CMB and risk of overall, cardiovascular-related, and stroke-related mortality in an elderly population enriched for or at high risk for cardiovascular disease. Our findings indicate that the diagnosis of CMB is potentially of clinical relevance. Elderly people with CMB and additional cardiovascular risk factors could benefit from special cardiovascular monitoring to prevent death from cardiovascular complications. Larger studies are needed to expand our observations and to address potential clinical implications and cost-benefits of such a policy.

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**Disclosure**

None.

**References**


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배경과 목적
대뇌 미세출혈반(cerebral microbleed, CMB)이 심혈관계, 뇌졸중 관련 사망 및 전반적 사망과 관련된 예측력을 조사하고, CMB의 대뇌 아밀로이드혈관병증(cerebral amyloid angiopathy, CAA) 유형 및 비엽성(nonlobar) 분포에 기반한 차이점을 연구하기 위함이다.

방법
PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) 연구의 소집단 MRI 연구에 참여한 환자 435명을 대상으로 하였다. 전반적 CMB 혹은 CAA의 존재를 시사하는 엽성 분포의 CMB로 나누어 심혈관계, 뇌졸중 관련 사망 및 전반적 사망에 대한 위험을 추정하기 위하여 Cox 비례위험 모형이 적용되었고, 해당되는 Kaplan–Meier 생존 곡선이 측정되었다.

결과
1개보다 많은 CMB를 가진 환자들은 CMB가 없는 환자들에 비해 뇌졸중 관련 사망 위험의 증가가 6배 증가하였으며(위험도, 5.97: 95% CI, 1.60~22.26, P=0.01), 비엽성 CMB로 진단받은 경우 CMB가 없는 환자군에 비해 심혈관계 사망 위험이 2배 남게 증가하는 것으로 나타났다(위험도[hazard ratio], 2.67: 95% CI, 1.23~5.81, P=0.01). probable CAA 유형의 CMB를 가진 환자는 그렇지 않은 환자들에 비해 뇌졸중 관련 사망이 7배 남게 증가하는 것으로 조사되었다(위험도, 7.20: 95% CI, 1.44~36.10, P=0.02).

결론
본 연구는 고령에서 CMB와 전반적 혹은 심혈관계 관련, 뇌졸중 관련 사망과의 관계를 연구한 최초의 연구이다. 위 결과는 잠재적으로 CMB의 진단이 임상적 중요성이 있다는 것을 덜받침한다. 저작자의 관찰 연구 결과를 확장하기 위해 또한 잠재적인 임상적 중요성을 발견하고 이러한 제도의 비용 효과에 해당을 얻기 위해 보다 큰 연구들이 요구된다.
<table>
<thead>
<tr>
<th>Microbleeds</th>
<th>d/n</th>
<th>Model 1</th>
<th>d/n</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td></td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>n=435</td>
<td></td>
<td>n=418</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>115/331</td>
<td>1.00 (reference)</td>
<td></td>
<td>109/320</td>
</tr>
<tr>
<td>1</td>
<td>15/52</td>
<td>0.76 (0.45–1.31)</td>
<td>0.33</td>
<td>12/47</td>
</tr>
<tr>
<td>&gt;1</td>
<td>22/52</td>
<td>1.23 (0.78–1.95)</td>
<td>0.38</td>
<td>22/51</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>n=434</td>
<td></td>
<td>n=417</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>40/330</td>
<td>1.00 (reference)</td>
<td></td>
<td>39/319</td>
</tr>
<tr>
<td>1</td>
<td>7/52</td>
<td>1.65 (0.47–2.34)</td>
<td>0.91</td>
<td>4/47</td>
</tr>
<tr>
<td>&gt;1</td>
<td>10/52</td>
<td>1.61 (0.80–3.24)</td>
<td>0.18</td>
<td>10/51</td>
</tr>
<tr>
<td>Stroke-related mortality</td>
<td>n=434</td>
<td></td>
<td>n=417</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>9/330</td>
<td>1.00 (reference)</td>
<td></td>
<td>8/319</td>
</tr>
<tr>
<td>1</td>
<td>0/52</td>
<td>No cases</td>
<td>0/47</td>
<td>No cases</td>
</tr>
<tr>
<td>&gt;1</td>
<td>5/52</td>
<td>3.41 (1.13–10.31)</td>
<td>0.03</td>
<td>5/51</td>
</tr>
</tbody>
</table>

* d indicates deceased; HR, hazard ratio; n, total number of subjects.
* Values are HR adjusted for age, sex, and use of statins (model 1) and additionally for cardiovascular risk factors (model 2), respectively, with 95% CI.