Cerebral amyloid angiopathy (CAA) represents amyloid β-peptide deposition in small- and medium-sized blood vessels in the brain, leading to hemorrhagic and ischemic injury.\(^1\)-\(^5\) Classically, CAA patients are diagnosed when they develop lobar intracerebral hemorrhage (ICH), a severe type of stroke resulting in high rates of mortality and disability.\(^6\),\(^7\) Lobar microbleeds on T2*-weighted MRI have also been identified as a marker of CAA severity and constitute an important component of the Boston criteria, a validated set of clinical-radiological features that showed high accuracy in CAA diagnosis.\(^8\)-\(^10\) The Boston criteria were originally validated in patients presenting with lobar ICH. With growing use of T2*-weighted MRI and increasing awareness of this condition, however, the diagnosis of CAA is now often considered in the setting of isolated lobar microbleeds in patients with neurological symptoms not related to ICH.\(^11\)-\(^13\) Detection of lobar microbleeds in large proportions of stroke-free, community-dwelling older individuals\(^14\)-\(^15\) also raises the question of whether many or most of them have advanced CAA or are at risk of future ICH. This issue is particularly important for individuals needing long-term anticoagulation, as there are few data about the risk of ICH in the setting of isolated lobar microbleeds.

We explored these questions in a prospective observational cohort of patients diagnosed with CAA in the absence or the presence of prior ICH. We hypothesized that patients without symptomatic lobar ICH but otherwise meeting Boston criteria for CAA (aged >55 years with strictly lobar microbleeds and no other cause of hemorrhage)\(^8\),\(^16\),\(^17\) would demonstrate similar vascular risk factors and genetic/radiological characteristics as lobar ICH patients diagnosed with definite/probable CAA and an appreciable risk of future ICH.

**Methods**

**Study Population**

We have analyzed prospectively collected baseline and follow-up data from consecutive patients presenting to Massachusetts General Hospital. 

**Results**

Microbleed-only patients shared similar demographic, apolipoprotein E, and vascular risk profiles with lobar ICH patients, but had more lobar microbleeds (median, 10 versus 2; \(P<0.001\)) and higher leukoaraiosis volumes (median, 31 versus 23 mL; \(P=0.02\)). Microbleed-only patients had a nontrivial incidence rate of ICH, not different from patients presenting with ICH (5 versus 8.9 per 100 person-years; adjusted hazard ratio, 0.58; 95% confidence interval, 0.31-1.06; \(P=0.08\)). Microbleed-only patients had a higher mortality rate (hazard ratio, 1.67; 95% confidence interval, 1.1-2.6) compared with ICH survivors. Warfarin use and increasing age were independent predictors of future ICH among microbleed-only patients after correction for other covariates.

**Conclusions**

Patients presenting with isolated lobar microbleeds on MRI have a genetic, neuroimaging, and hemorrhagic risk profile suggestive of severe CAA pathology. They have a substantial risk of incident ICH, potentially affecting decisions regarding anticoagulation in clinical situations. (*Stroke*. 2014;45:2280-2285.)

**Key Words:** cerebral amyloid angiopathy ■ cerebral hemorrhage ■ cerebral microbleeds ■ magnetic resonance imaging
Hospital with neurological symptoms and enrolled in a longitudinal cohort study of the natural history of CAA. Patients were enrolled with definite or probable CAA according to the previously validated Boston criteria, by which individuals aged ≥55 years with multiple hemorrhagic lesions restricted to lobar, cortical, or cortico-subcortical regions (cerebellar hemorrhage allowed) and no other definite cause (trauma, ischemic stroke, tumor, vascular malformation, vasculitis, coagulopathy, anticoagulation with international normalized ratio >3.0) are diagnosed as probable CAA. For the current analysis, we grouped the patients into 2 categories: those presenting with (1) ≥2 lobar microbleeds in the absence of lobar ICH (microbleed-only patients) or (2) those presenting with a lobar ICH with ≥1 lobar microbleed (ICH patients). Patients with a diagnosis of inflammatory CAA or autosomal dominant hereditary CAA were not included into this analysis. A full history was obtained, a neurological examination was performed, and head computed tomography, brain MRI, and computed tomography angiography or magnetic resonance angiography of the brain were performed to exclude an underlying vascular abnormality or other structural causes of hemorrhage. Microbleed-only patients underwent neurological and cognitive testing including mini mental state examination as part of the research protocol on which they scored ≥27. For the survival analysis, day zero for the ICH group was taken as the date of ICH. For the microbleed-only subjects who entered the prospective study without a prior ICH, day zero for survival analyses was taken as the date of study enrollment.

Data Collection
Subject enrollment, baseline data collection, and MRI acquisition and analysis were performed as described previously. Baseline characteristics were compared between ICH patients and microbleed-only patients among all patients enrolled. Individuals who consented to longitudinal follow-up and ICH patients who survived the first 90 days after their index event were studied for incident lobar ICH or death as described. Forty-six patients who died within the first 3 months after their index ICH were not included into the longitudinal analyses. Thirty-three patients who did not consent for the longitudinal study were older (P=0.003), but other baseline characteristics (sex, vascular risk factors, and leukoaraiosis volume) did not differ from the longitudinal cohort. A full history was obtained, a neurological examination was performed, and head computed tomography, brain MRI, and computed tomography angiography or magnetic resonance angiography of the brain were performed to exclude an underlying vascular abnormality or other structural causes of hemorrhage. Microbleed-only patients underwent neurological and cognitive testing including mini mental state examination as part of the research protocol on which they scored ≥27. For the survival analysis, day zero for the ICH group was taken as the date of ICH. For the microbleed-only subjects who entered the prospective study without a prior ICH, day zero for survival analyses was taken as the date of study enrollment.

Clinical and Laboratory Data
Data on demographics (age, sex), vascular risk factors (hypertension, diabetes mellitus, and hypercholesterolemia), and APOE genotype was determined in a large subset of patients who provided research blood samples. APOE genotype was determined in a large subset of patients who provided research blood samples. MRI Acquisition and Analysis
Images were obtained using a 1.5-T magnetic resonance scanner (GE Signa), Whole-brain axial gradient-echo images (repetition time/echo time, 750/50 ms; 5 mm slice thickness; 1 mm interslice gap) and fluid-attenuated inversion recovery images (repetition time/echo time, 10000/140 ms; inversion time, 2200 ms; number of excitations, 1; 5 mm slice thickness; 1 mm interslice gap) were performed.

Lobar microbleeds were classified as punctate, hypointense foci (<5 mm in diameter) selectively involving the cortex and underlying white matter on gradient-echo images, distinct from vascular flow voids and leptomeningeal hemorrhosis. White matter hyperintensity (WMH or leukoaraiosis) volume was quantified as previously validated using a computer-assisted algorithm that identifies MIRcron, a freely available tool. All MRI analyses were performed and recorded by investigators blinded to clinical and genetic data.

Statistical Analysis
Univariate analyses were used to compare clinical characteristics, frequencies of the APOE ε2 and ε4 alleles, and radiological markers between the 2 groups. Subsequently, multivariate analyses were performed to look for independent associations between these predictors and diagnostic categories. For multivariate models, APOE genotype was analyzed as a categorical variable according to the presence or absence of the ε2 and ε4 alleles. As blood samples for genotyping were not available in 28% of subjects, multivariate models were built with and without APOE; addition of this variable did not change the associations observed among other variables. In the follow-up cohort, the mean follow-up time was calculated and the incidence rates of ICH and death were determined using the incidence per 100 person-years of follow-up. We used multivariable Cox regression analyses to calculate the crude and adjusted hazard ratios for occurrence of ICH and death. For the adjusted Cox regression model, patient group (with ICH as the control group), age, sex, hypertension, WMH volume, and lobar microbleed counts were entered in the model. In the microbleed-only patients, a multivariable Cox regression model was built to test the association between anti-coagulant use and incident ICH after adjustment for demographics, hypertension, WMH, and microbleeds. All analyses were performed with SPSS 22.0 (released 2012, IBM SPSS Statistics for Windows, version 22.0, IBM Corp, Armonk, NY). All tests of significance were 2 tailed.

Results
We analyzed a total of 379 patients who were enrolled between January 1993 and January 2012, of whom 63 patients presented with lobar microbleeds only and 316 with lobar ICH. Of the 63 microbleed-only patients, 26 patients underwent their index MRI for evaluation of symptoms suggestive of an ischemic event, 27 because of mild cognitive symptoms, 4 because of a gait disorder, and 6 because of transient sensory spells. None of the microbleed-only patients was found to have ischemic stroke, dementia, mass lesion, or other neurodegenerative conditions after complete evaluation.

Demographics (age, sex), vascular risk factors, and APOE genotype did not differ significantly between microbleed-only and ICH groups (Table 1). The lobar microbleed count was significantly higher in microbleed-only patients (median, 10; interquartile range, 4–30) compared with the ICH patients (median, 2; interquartile range, 1–9; P<0.001). This difference remained significant after adjusting for demographics and vascular risk factors (P<0.001). Within the lobar microbleed-only group, no significant correlation was found between microbleed counts and other factors such as demographics, vascular risk factors, or APOE. Microbleed-only patients had a larger median WMH volume compared with the patients with ICH (31 versus 23 mL; P=0.02; Table 1). Higher WMH volume remained independently associated with the microbleed-only category (P=0.04) after correction for age, sex, and vascular risk factors.
Three hundred patients (240 ICH who survived the first 90 days after their index ICH and 60 microbleed-only) were followed longitudinally for 5.3±3.8 years after their index event. Twelve microbleed-only patients (20% of the microbleed-only group, 5 per 100 person-years) developed a lobar ICH during follow-up versus 86 patients (36%) presenting with ICH (8.9 per 100 person-years). Details of the incident event rates, hazard ratios, and confidence intervals are presented in Table 2. Cox regression analysis showed a mildly lower risk of incident ICH for the microbleed-only versus the lobar ICH patients, but this difference did not reach statistical significance (Figure 1A; hazard ratio, 0.58; 95% confidence interval, 0.31–1.06; P=0.08). The ICH rate observed in either group of CAA patients was orders of magnitude greater than that of the general elderly population (estimated at 0.015–0.05 incident ICHs per 100 people per year).16,17 Figure 2 shows the baseline and follow-up imaging of an microbleed-only patient who later developed a symptomatic ICH.

We analyzed the predictors of incident ICH in the microbleed-only group. Warfarin use (P=0.02) and older age (P=0.04) were independently associated with time to incident ICH in a multivariable Cox regression model that also

### Table 1. Clinical and Radiological Characteristics of the 2 Patient Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients Presenting With</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lobar Microbleed-Only (n=63)</td>
</tr>
<tr>
<td>Definite/probable CAA</td>
<td>All</td>
</tr>
<tr>
<td>Clinical variables</td>
<td></td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>40 (63)</td>
</tr>
<tr>
<td>Age, y</td>
<td>73.6±8.3</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>34 (54)</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>26 (41)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>9 (14)</td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
</tr>
<tr>
<td>APOE ε2 frequency</td>
<td>15.6%</td>
</tr>
<tr>
<td>APOE ε4 frequency</td>
<td>25%</td>
</tr>
<tr>
<td>Radiological markers</td>
<td></td>
</tr>
<tr>
<td>Lobar microbleed count</td>
<td>10 (4–30)</td>
</tr>
<tr>
<td>WMH volume, mL</td>
<td>31 (18–46)</td>
</tr>
</tbody>
</table>

Values are displayed as mean±SD, median (25th–75th quartile), or n (%). APOE genotypes were available in 48 subjects with microbleed-only and 224 with ICH. APOE indicates apolipoprotein E; CAA, cerebral amyloid angiopathy; ICH, intracerebral hemorrhage; and WMH, white matter hyperintensity.

Three hundred patients (240 ICH who survived the first 90 days after their index ICH and 60 microbleed-only) were followed longitudinally for 5.3±3.8 years after their index event. Twelve microbleed-only patients (20% of the microbleed-only group, 5 per 100 person-years) developed a lobar ICH during follow-up versus 86 patients (36%) presenting with ICH (8.9 per 100 person-years). Details of the incident event rates, hazard ratios, and confidence intervals are presented in Table 2.

### Table 2. Incidence Rates and Hazard Ratios for the Occurrence of ICH and Death in Both Groups During Follow-Up

| Event Rate                                                      | No. of Patients Presenting With |
|                                                               | Lobar Microbleed-Only (n=60) | Lobar ICH (n=240) | P Value |
| Event: occurrence of lobar ICH                                 |                                 |                  |         |
| Observed person-years                                         | 241                             | 968              | …       |
| No. of occurrence (%)                                         | 12 (20)                         | 86 (36)          | …       |
| Incidence of ICH per 100 person-years (95% CI)                | 5 (2.6–8.7)                     | 8.9 (7.1–11)     | …       |
| Crude hazard ratio (95% CI)                                   | 0.57 (0.3–1.04)                 | Ref              | 0.07    |
| Adjusted hazard ratio* (95% CI)                               | 0.58 (0.31–1.06)                | Ref              | 0.08    |

| Event: occurrence of death                                    |                                 |                  |         |
| Observed person-years                                         | 261                             | 1316             | …       |
| No. of occurrence (%)                                         | 31 (52)                         | 105 (44)         | …       |
| Incidence of death per 100 person-years (95% CI)              | 11.9 (8.16–18)                  | 8 (6.5–9.7)      | …       |
| Crude hazard ratio (95% CI)                                   | 1.8 (1.2–2.8)                   | Ref              | 0.005   |
| Adjusted hazard ratio* (95% CI)                               | 1.67 (1.1–2.6)                  | Ref              | 0.02    |

CI indicates confidence interval; ICH, intracerebral hemorrhage; and ref, reference for hazard ratios.

*Adjusted for age, sex, hypertension, microbleed count, and white matter hyperintensity volume.

Figure 1. Survival curves of the 2 groups for occurrence of intracerebral hemorrhage (ICH; A) and death (B). MB indicates microbleed.
CAA patients presenting with ICH. The ongoing question in the field has been the diagnostic and prognostic importance of finding multiple lobar microbleeds on MRI of an older adult without any symptomatic ICH and without other causes for microbleeds. The results of our baseline comparisons that show similar demographic, genetic, and vascular risk profiles between the groups support the view that the lobar microbleed-only pattern can reliably be considered as probable CAA. The finding of a more severe marker of CAA-related cerebral damage (high WMH volume) also suggests vascular amyloid-related small vessel dysfunction as the principal pathological mechanism in these cases.

The current data bear on the important question of which patients should receive anticoagulant therapy. Individuals with isolated lobar microbleeds are being increasingly detected by more frequent use of sensitive MRI techniques, with prevalences in the range of 11% to 24% of the community-dwelling elderly. As the risk of ICH in these patients is largely unknown, however, there has been insufficient evidence to conclude that the presence of lobar microbleeds alone should preclude anticoagulant therapy. A neuropathologic study also suggested that CAA patients with multiple microbleeds might have different vessel pathology (with thicker amyloid-positive vessel walls) compared with CAA patients with fewer lobar microbleeds, suggesting that the ICH risk might be different across these groups. For these reasons, it has not been possible to extrapolate ICH risk estimates in a population with isolated lobar microbleeds based on prior studies of patients with past ICH. The current study suggests that microbleed-only CAA patients, though at mildly lower risk for future ICH than those with past ICH, are nonetheless at substantial risk.

Despite our relatively small sample size, we have also found that coumadin use was independently associated with the risk of incident symptomatic lobar ICH. An important area for future research will therefore be to determine, either by observational analysis or by randomized clinical trial, whether this risk of future ICH is sufficient to tip the risk versus benefit calculation away from anticoagulant treatment in specific clinical situations. Such a study will need to be powered to analyze the contribution of multiple ICH risk factors. A previous decision analysis suggested that the particularly high risk of future ICH among CAA patients with past ICH weighed strongly against anticoagulation, even in patients with nonvalvular atrial fibrillation.

In light of the substantial risk for future ICH observed among the microbleed-only subjects, it is reasonable to consider this condition as a potential precursor or early form of CAA-related ICH. In other respects, however, the microbleed-only patients in the current study demonstrate markers of CAA equal to or greater than those in the ICH group. Among these markers were increased microbleed counts (possibly a reflection of referral preferences as noted above), higher WMH burden, and earlier mortality. We were unable to determine the potential causes of increased mortality in patients with microbleed-only CAA, but this finding is in line with...
recent studies that show higher mortality in older adults with microbleeds.\textsuperscript{33,34} Although clearly requiring further analysis, the current data suggest that microbleed-only CAA may represent an alternative pathway by which this pathology can cause progressive neurological damage, even in the absence of major hemorrhagic stroke. Pathological confirmation of the CAA diagnosis in all 11 patients who underwent autopsy also supports the view that Boston criteria can accurately establish this diagnosis during life.

Our study has limitations. It is indeed likely that many of the microbleed-only patients were referred to our clinic because of finding relatively high number of lobar microbleeds, an issue that might be related to higher WMH load and mortality in this particular cohort. We do note, however, that the number of lobar microbleeds was not related to the risk of incident ICH in these subjects, suggesting that this possible referral bias did not account for the relatively high incidence of future hemorrhage in microbleed-only patients. The question of CAA diagnosis is typically raised when a brain MRI obtained for neurological complaints in an older adult shows lobar microbleeds. In that sense, our study population is similar to patients seen in clinical practice. None of our microbleed-only patients had dementia, stroke, or other neurodegenerative conditions at enrollment, limiting the contribution of potential confounders to the outcomes observed. A second limitation was our sample size, which limited our ability to assess the risk of antithrombotic use in better multivariate models. A larger study would be necessary to address the risk of ICH with or without antithrombotic use, in patients with isolated lobar microbleeds who are at high risk of ischemic events because of the presence of atrial fibrillation, deep venous thrombosis, or pulmonary embolism. Data from randomized clinical trials are unlikely to be forthcoming, however, as such trials to rule out harmful medication effects in high-risk subjects are difficult to justify and perform.

Conclusions

The vascular risk factors as well as genetic and radiological characteristics of patients with isolated lobar microbleeds are similar to patients with CAA diagnosed after a lobar ICH, therefore suggestive of substantial CAA pathology. In this sense, lobar microbleeds on MRI, a common finding in otherwise healthy elderly individuals with or without nonspecific symptoms, seem to be a promising diagnostic marker of advanced CAA. We also find that patients presenting with isolated lobar microbleeds are at considerable risk of future lobar ICH, a risk made worse by the use of warfarin. Given the high prevalence of isolated lobar microbleeds in the elderly, our findings support the importance of developing early detection markers for CAA in asymptomatic individuals, studying its impact in this population, and determining the feasibility of treating CAA before it becomes symptomatic.

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Disclosures

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脑叶微出血患者症状性脑出血的发生率

Incidence of Symptomatic Hemorrhage in Patients With Lobar Microbleeds

Ellis S. van Euten, MD; Eitan Auer, MD, MSc; Kelhen E. Haley, BA; Alison M. Ayres, BA; Anastasia Vashkivich, BA; Kristin M. Schwab, BA; Jonathan Rosand, MD, MSc; Ahmad Vinisuman, Viswanath, Ph.D.; Steven M. Greenberg, MD, PhD; M. Eldip Gurd, MD, MSc

背景和目的：脑叶微出血患者症状性脑出血的发生率(lobar microbleeds, LMB)是目前脑出血研究中的一个热点，但尚缺乏相关的研究，尤其是对脑叶微出血患者症状性脑出血的发生率的研究。本研究旨在评估脑叶微出血患者的症状性脑出血的发生率。

方法：本研究纳入了来自麻省总医院的连续性患者，所有患者均进行了详细的病史采集、神经影像学及基因学的检查。研究的主要终点是脑叶微出血患者的症状性脑出血的发生率。

结果：本研究共纳入了582例患者，其中454例患者为脑叶微出血患者。在随访期间，共有31例患者发生了症状性脑出血，其中26例为脑叶微出血患者。在脑叶微出血患者中，症状性脑出血的发生率为7.9%，而在非脑叶微出血患者中，此比例为4.4%。

结论：脑叶微出血患者症状性脑出血的发生率明显高于非脑叶微出血患者。这提示脑叶微出血可能是一个独立的风险因素，需要引起临床医生的重视。

关键词：脑叶微出血；症状性脑出血；危险因素

Hosseinpour ES et al. Postacute Cerebral Vasculopathy Disease 37

脑叶出血组(n=316) P值

致死致残率较高

本研究比较了单纯脑叶微出血患者和CAA相关的脑叶ICH患者的基线特征及随后ICH的风险。

P=0.08)。在校正相关变量后，华法林的应用和高龄是单纯脑微出血患者发生脑出血的独立危险因素。

出血灶更多(中位值,10:2; P < 0.001),脑白质疏松体积更大(中位值,31:23ml, P =0.02)且远期病死率较高(HR,1.67;95%CI,

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脑出血发生率之间的关系。所有分析均用 SPSS 20.0 软件完成。所有图 1. 两组患者发生脑内出血 (ICH; A) 和死亡 (B) 的生存曲线。结果

在单纯脑叶微出血和脑叶出血之间, 人口学资料、年龄、性别、白质高信号体积和微出血数量等因素后, 脑出血组的事件致死率高于单纯微出血组(表 2 和图 1B; 校正 HR 1.67; 95% CI 为 1.1-2.6;P=0.02)。将 APOE 引入多因素模型未对结果造成影响。2 例单纯微出血患者有相对较高的整体 ICH 发生率这一结果。对于因神经系统相关症状而接受治疗的患者, 他们可能潜在的 ICH 风险被忽略。这提示他们发生 ICH 的风险可能不同。30

本研究中, 我们证实仅在 MRI T2* 相发现脑叶微出血灶的患者与脑内出血患者相比存在等同甚至更强的 CAA 病变。这提示我们 ICH 风险增加可能最初由微出血病灶触发。这一研究结果支持了 APOE ε4 等位基因是 CAA 脑出血风险的独立预测因子。31

结论

研究证实脑出血患者与单纯脑叶 ICH 起病的 CAA 患者有相似的遗传学及影像学特征。两组患者发生症状性脑叶 ICH 的风险相似, 但是脑出血组为 105 例 (8/100 人 - 年)。校正年龄、性别、高血压、白质高信号体积和微出血数量等因素后, 脑出血组的事件致死率高于单纯微出血组(表 2 和图 1B; 校正 HR 1.67; 95% CI 为 1.1-2.6;P=0.02)。将 APOE 引入多因素模型未对结果造成影响。2 例单纯微出血患者有相对较高的整体 ICH 发生率这一结果。对于因神经系统相关症状而接受治疗的患者, 他们可能潜在的 ICH 风险被忽略。这提示他们发生 ICH 的风险可能不同。30

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在检测单纯脑叶微出血组的 ICH 发病率时, 要考虑患者可能存在其他出血相关因素。其中 63 例仅有脑叶微出血, 316 例有脑叶出血。在 63 例仅有脑叶微出血组的 MRI 上脑白质高信号更为明显, 提示 ICH 病变可能由其他原因导致。这提示我们 ICH 和脑叶微出血可能是 CAA 的标志。32

尽管需要进一步的研究分析, 但目前数据提示抗凝药物对 ICH 患者有益。33,34 然而, 本队列中的 ICH 患者表现出较高的死亡率。但是我们也注意到, 这些患者微出血病灶的数目与日后发生脑出血和死亡率高。33,34

针对这个问题, 需要进一步研究抗凝药物对 ICH 患者的疗效。目前的数据将影响抗凝治疗的抉择。随着 MRI 技术的广泛应用, CAA 的诊断标准也需更新。35、36

我们需要针对这部分患者开发出早期诊断标记物, 研究其对这部分人群的影响, 以及确定在出现症状前是否应该进行抗凝治疗。37

我们试图回答这样一个问题: 单纯脑叶微出血患者是否是 CAA 患者? 研究显示单纯脑叶微出血组的 ICH 发病风险高于单纯微出血组。29,31 但是, 我们对这些患者罹患 ICH 的风险所知甚少, 目前的研究结果也存在局限性。31

目前的数据显示单纯脑叶微出血患者可以作为 CAA 检测的筛选工具。38 由于 CAA 患者有较高的 ICH 风险, 我们认为单纯脑叶微出血是 CAA 的可能标志。39

前景

我们还需要进一步研究抗凝药物对 ICH 患者的疗效。目前的数据将影响抗凝治疗的抉择。33,34 然而, 本队列中的 ICH 患者表现出较高的死亡率。但是我们也注意到, 这些患者微出血病灶的数目与日后发生脑出血和死亡率高。33,34

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参考文献


