Apolipoprotein E Genotype Is Associated With CT Angiography Spot Sign in Lobar Intracerebral Hemorrhage

H. Bart Brouwers, MD; Alessandro Biffi, MD; Kristen A. McNamara, BA; Alison M. Ayres, BA; Valerie Valant, BA; Kristin Schwab, BA; Javier M. Romero, MD; Anand Viswanathan, MD, PhD; Steven M. Greenberg, MD, PhD; Jonathan Rosand, MD, MSc; Joshua N. Goldstein, MD, PhD

Background and Purpose—The CT angiography (CTA) spot sign predicts hematoma expansion and poor outcome in patients with primary intracerebral hemorrhage (ICH). The biological underpinnings of the spot sign remain poorly understood; it may be that the underlying vasculopathy influences its presence. Therefore, we conducted a study to identify genetic predictors of the spot sign.

Methods—In an ongoing prospective cohort study, we analyzed 371 patients with CTA and genetic data available. CTAs were reviewed for the spot sign by 2 experienced readers, blinded to clinical data, according to validated criteria. Analyses were stratified by ICH location.

Results—In multivariate analysis, patients on warfarin were more likely to have a spot sign regardless of ICH location (OR, 3.85; 95% CI, 1.33–11.13 in deep ICH and OR, 2.86; 95% CI, 1.33–6.13 in lobar ICH). Apolipoprotein E ε2, but not ε4, was associated with the presence of a spot sign in lobar ICH (OR, 2.09; 95% CI, 1.05–4.19). There was no effect for ε2 or ε4 in deep ICH.

Conclusions—Patients with ICH on warfarin are more likely to present with a spot sign regardless of ICH location. Among patients with lobar ICH, those who possess the apolipoprotein E ε2 allele are more likely to have a spot sign. Given the established relationship between apolipoprotein E ε2 and vasculopathic changes in cerebral amyloid angiopathy, our findings suggest that both hemostatic factors and vessel pathology influence spot sign presence. (Stroke. 2012;43:00-00.)

Key Words: APOE ■ CTA spot sign ■ genetics ■ hematoma expansion ■ intracerebral hemorrhage

Spontaneous intracerebral hemorrhage (ICH) accounts for 15% of all strokes and has a 30-day mortality rate of approximately 40%. The most potent determinant of poor outcome is baseline hematoma volume. Importantly, expansion of the initial hematoma occurs in 25% of hospitalized patients with ICH and forms another strong predictor of poor outcome. The attenuation of hematoma expansion gives clinical care providers an opportunity to decrease final ICH volume and is therefore a common target in ongoing clinical trials.

The extravasation of contrast into the hematoma after CT angiography (CTA), termed the “spot sign,” is frequently seen in patients with ICH and is an independent predictor of both hematoma expansion and poor outcome. The biological underpinnings of the CTA spot sign remain poorly understood, and there are no established risk factors for its presence besides early presentation.

A multicenter genetic association study led by the International Stroke Genetics Consortium showed that apolipoprotein E (APOE) ε2 and ε4 alleles increase risk of lobar intracerebral hemorrhage. In addition, the APOE ε2 allele has been associated with larger baseline ICH volumes, hematoma expansion, and poor outcome in lobar ICH. The role of the APOE alleles is probably related to their known effect in cerebral amyloid angiopathy (CAA), in which each allele is associated with characteristic pathological changes. The ε2 allele is predominantly associated with vasculopathic changes ultimately leading to rupture of the diseased vessels, whereas ε4 increases the severity of amyloid deposition within the vessel wall.

Given the unique role of APOE ε2 in lobar ICH, we hypothesized that the ε2 allele would also be associated with the presence of the CTA spot sign. To answer this question, we conducted a single-center prospective cohort study of patients with acute ICH.
Hematoma expansion was defined as an absolute increase in ICH volume \( \geq 6 \text{ mL} \) or an increase of \( \geq 33\% \) from baseline ICH volume.\(^{8,17,21}\) CTAAs were reviewed by 2 experienced readers, blinded to clinical data, for the presence of spot signs according to previously published and validated criteria.\(^{10,12}\) CTA reading differences were adjudicated by consensus. All study staff interpreting neuroimaging were blinded to clinical, genetic, and outcome data.

### Genotyping

DNA from whole blood samples was isolated, quantified, and normalized to a concentration of \( 10 \text{ ng/\mu L} \). Two single nucleotide polymorphisms of the APOE locus, rs7412 (APOE 158) and rs492358 (APOE 112), were independently genotyped using 2 separate assays. The allelic reads from each assay were translated to APOE genotypes (\( \varepsilon 3 \varepsilon 3, \varepsilon 3 \varepsilon 4, \varepsilon 4 \varepsilon 4, \varepsilon 3 \varepsilon 2, \varepsilon 2 \varepsilon 2, \) and \( \varepsilon 4 \varepsilon 4 \)). All ICH cases were in Hardy-Weinberg equilibrium for APOE genotypes. Genotyping personnel were blinded to clinical and neuroimaging data.

### CAA-Related ICH

Along with stratifying the analysis by ICH location, we separately analyzed patients meeting criteria for probable/definite CAA (according to the Boston criteria\(^{22}\)), because not all lobar hemorrhages are caused by CAA. Lobar ICH with confirmed CAA pathology or microbleeds restricted to the lobar brain region on MRI (on T2*, susceptibility, or gradient echo sequences) was defined as probable/definite CAA. In total, 140 of 196 (71%) patients with lobar ICH had MRI and/or pathology available. Of these patients, 69 (49%) met criteria for probable/definite CAA. Microbleed assessment was performed following previously validated methods.\(^{22,23}\)

### Statistical Analysis

Discrete variables are presented as count and percentage (%) and continuous variables are shown as mean and standard deviation or as median and interquartile range. We tested the potential role of the APOE \( \varepsilon 2 \) and \( \varepsilon 4 \) alleles as predictors of the CTA spot sign using univariate and multivariate logistic regression, stratified by ICH location (deep or lobar) and CAA-related ICH. This stratification was prespecified and used in previous studies.\(^{16,17}\) The CTA spot sign was analyzed as a dichotomized variable (present/absent). Multivariate models included age, sex, hypertension, use of warfarin, number of APOE \( \varepsilon 2 \) alleles (0, 1, or 2), and number of \( \varepsilon 4 \) alleles (0, 1, or 2). All analyses were repeated after adjustment for genetic population structure (principal components 1 and 2) based on genomewide data, which was available for a total of 268 patients (72%).\(^{15}\) These subset analyses returned identical results (data not shown). In a subset of patients with an available follow-up CT within 48 hours, we tested for association of the APOE alleles with hematoma volume \( > 6 \text{ mL} \) or an increase of \( > 33\% \) from baseline ICH volume.\(^{8,17,21}\)

---

**Figure.** Cohort flowchart. ICH indicates intracerebral hemorrhage; CTA, CT angiography; APOE, apolipoprotein E.
expansion, including the same covariates in the multivariate analysis with the addition of the CTA spot sign. The threshold of significance was set to $P < 0.05$. All statistical analyses were performed using Statistical Analysis Software Version 9.3 (SAS Institute Inc, Cary, NC).

**Results**

**Study Population**

After application of the previously described inclusion and exclusion criteria, 371 patients were available for analysis. Of these 371 patients, 151 had deep, 196 had lobar, and 24 had mixed ICH. The latter were excluded for the stratified analysis (Table 1).

**CT Imaging**

Radiographic characteristics are shown in Table 1 for the entire cohort and stratified by ICH location. Median baseline hematoma volumes were significantly different between deep and lobar ICH ($P < 0.001$). At least 1 spot sign was present in 97 patients (26%), and there was no difference between deep and lobar ICH ($P > 0.20$; Table 1).

**Predictors of the CTA Spot Sign**

**All ICH**

Univariate analysis was performed to assess association of the covariates with CTA spot sign presence in all patients with ICH. Both age ($P = 0.033$) and warfarin use at the time of hospital presentation ($P < 0.001$) showed an association with the spot sign (Table 2). In multivariate analysis, only warfarin use remained associated with spot sign presence ($P < 0.001$) after adjusting for age, sex, hypertension, warfarin use, APOE e2, APOE e4, and genetic population structure (Table 3).

**Deep ICH**

In deep ICH only warfarin showed an association with spot sign presence ($P = 0.007$) in univariate analysis (Table 2). In multivariate analysis, this association remained significant.
Table 2. Univariate Analysis of CTA Spot Sign

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n=371)</th>
<th>Deep ICH (n=151)</th>
<th>Lobar ICH (n=196)</th>
<th>Probable/Definite CAA (n=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>OR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Age</td>
<td>1.02</td>
<td>(1.00–1.04)</td>
<td>1.03</td>
<td>(0.99–1.06)</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>0.72</td>
<td>(0.28–1.91)</td>
<td>&gt;0.20</td>
<td>1.30 (0.61–2.77)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.77</td>
<td>(0.95–3.26)</td>
<td>0.97</td>
<td>(0.32–2.97)</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>3.49</td>
<td>(2.02–6.04)</td>
<td>&lt;0.001</td>
<td>3.67 (1.42–9.47)</td>
</tr>
<tr>
<td>APOE ε2</td>
<td>0.74</td>
<td>(0.40–1.33)</td>
<td>&gt;0.20</td>
<td>0.96 (0.34–2.70)</td>
</tr>
<tr>
<td>APOE ε4</td>
<td>0.79</td>
<td>(0.43–1.43)</td>
<td>&gt;0.20</td>
<td>0.60 (0.28–1.30)</td>
</tr>
</tbody>
</table>

CTA indicates CT angiography; ICH, intracerebral hemorrhage; CAA, cerebral amyloid angiopathy; APOE, apolipoprotein E.

(P=0.013). There was no association between either APOE ε2 or ε4 and spot sign presence (both P>0.20; Table 3).

**Lobar ICH**

In lobar ICH, the univariate analysis showed warfarin use (P=0.001) and APOE ε2 (P=0.025) to be associated with spot sign presence (Table 2). After adjusting for potential confounders, the effects for the use of warfarin (P=0.007) and APOE ε2 (P=0.036) remained significant. We found again no association between APOE ε4 and the CTA spot sign (P>0.20; Table 3).

**CAA-Related ICH**

In the subset of patients with lobar ICH meeting criteria for CAA-related ICH, warfarin use (P=0.011) and APOE ε2 (P=0.024) were associated with spot sign presence in the univariate analysis (Table 2). In multivariate analysis, the effect for APOE ε2 remained significant after adjusting for potential confounders (P=0.005). The effect for warfarin use in lobar ICH (OR, 2.86; 95% CI, 1.33–6.13) appeared heightened in patients meeting criteria for CAA-related ICH (OR, 6.65; 95% CI, 1.34–32.99).

**Predictors of Hematoma Expansion**

A follow-up CT within 48 hours was available in a subset of 228 patients (61%). Patients without follow-up imaging had lower Glasgow Coma Scale scores upon presentation, greater hematoma volumes, and higher mortality rates at discharge (all P<0.05).

Hematoma expansion was present in 42 of 228 patients (18%). In multivariate analysis, the spot sign was a strong independent predictor of hematoma expansion regardless of ICH location. Notably, warfarin use was no longer associated with hematoma expansion after introducing the CTA spot sign into the multivariate logistic regression model (all P>0.20). In lobar ICH, there was a trend toward significance for the association of APOE ε2 and hematoma expansion (OR, 2.48; 95% CI, 0.99–6.27; P=0.054; Table 4).

**Discussion**

Our findings demonstrate that patients with lobar ICH who possess the APOE ε2 allele are more likely to have a spot sign detected on CTA. APOE ε2 did not show an effect in deep ICH and the APOE ε4 allele was not associated with spot sign presence in either deep or lobar ICH. In addition, we show that patients on warfarin at the time of their presentation to the hospital are more likely to have a spot sign regardless of ICH location.

The isolated effect of APOE ε2 on presence of the CTA spot sign is consistent with the accumulating evidence of the unique effects of the APOE alleles in CAA and ICH. In CAA, the 2 APOE Variants appear to act through different histopathologic mechanisms. At autopsy or biopsy, the cerebral vessels of individuals with APOE ε2 demonstrate marked vasculopathic changes and vessel rupture, whereas possession of the ε4 allele increases the severity of amyloid deposition within the vessel wall with limited vasculopathic changes. In addition to these histopathologic findings in CAA, there is growing evidence on the isolated APOE ε2 effect in lobar ICH from prospective cohort studies. In these studies, APOE ε2 is associated with a greater severity of amyloid deposition within the vessel wall. The isolated APOE ε2 effect is consistent with the accumulating evidence of the unique effects of the APOE alleles in CAA and ICH. In CAA, the 2 APOE Variants appear to act through different histopathologic mechanisms. At autopsy or biopsy, the cerebral vessels of individuals with APOE ε2 demonstrate marked vasculopathic changes and vessel rupture, whereas possession of the ε4 allele increases the severity of amyloid deposition within the vessel wall with limited vasculopathic changes. In addition to these histopathologic findings in CAA, there is growing evidence on the isolated APOE ε2 effect in lobar ICH from prospective cohort studies. In these studies, APOE ε2 is associated with a greater severity of amyloid deposition within the vessel wall.

Table 3. Multivariate Analysis of CTA Spot Sign

<table>
<thead>
<tr>
<th>Variable*</th>
<th>All (n=371)</th>
<th>Deep ICH (n=151)</th>
<th>Lobar ICH (n=196)</th>
<th>Probable/Definite CAA (n=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.02</td>
<td>(1.00–1.04)</td>
<td>1.02</td>
<td>(0.99–1.06)</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>1.34</td>
<td>(0.70–2.58)</td>
<td>&gt;0.20</td>
<td>1.83 (0.81–4.16)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.28</td>
<td>(0.65–2.56)</td>
<td>&gt;0.20</td>
<td>0.81 (0.26–2.53)</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>3.46</td>
<td>(1.92–6.21)</td>
<td>&lt;0.001</td>
<td>3.85 (1.33–11.13)</td>
</tr>
<tr>
<td>APOE ε2</td>
<td>1.55</td>
<td>(0.81–2.96)</td>
<td>0.19</td>
<td>0.53 (0.16–1.70)</td>
</tr>
<tr>
<td>APOE ε4</td>
<td>0.64</td>
<td>(0.33–1.25)</td>
<td>&gt;0.20</td>
<td>0.70 (0.32–1.55)</td>
</tr>
</tbody>
</table>

CTA indicates CT angiography; ICH, intracerebral hemorrhage; CAA, cerebral amyloid angiopathy; APOE, apolipoprotein E.

*Analysis is also adjusted for principal components 1 and 2.


Table 4. Multivariate Analysis of Hematoma Expansion Among Patients With Follow-Up CT

<table>
<thead>
<tr>
<th>Variable*</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.01 (0.97–1.04)</td>
<td>&gt;0.20</td>
<td>1.01 (0.96–1.06)</td>
<td>&gt;0.20</td>
<td>0.98 (0.94–1.03)</td>
<td>&gt;0.20</td>
</tr>
<tr>
<td>Sex (male versus female)</td>
<td>1.70 (0.73–3.95)</td>
<td>&gt;0.20</td>
<td>1.60 (0.39–6.60)</td>
<td>&gt;0.20</td>
<td>1.32 (0.42–2.18)</td>
<td>&gt;0.20</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.57 (0.87–7.66)</td>
<td>0.089</td>
<td>2.33 (0.35–15.63)</td>
<td>&gt;0.20</td>
<td>2.47 (0.60–10.07)</td>
<td>&gt;0.20</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>1.66 (0.68–4.04)</td>
<td>&gt;0.20</td>
<td>0.53 (0.07–4.54)</td>
<td>&gt;0.20</td>
<td>1.30 (0.35–4.77)</td>
<td>&gt;0.20</td>
</tr>
<tr>
<td>CTA spot sign</td>
<td>7.78 (3.46–17.50)</td>
<td>&lt;0.001</td>
<td>9.40 (2.63–33.63)</td>
<td>0.001</td>
<td>7.55 (2.31–24.70)</td>
<td>0.001</td>
</tr>
<tr>
<td>APOE ε2</td>
<td>1.67 (0.76–3.65)</td>
<td>0.19</td>
<td>0.65 (0.07–6.48)</td>
<td>&gt;0.20</td>
<td>2.48 (0.99–6.27)</td>
<td>0.054</td>
</tr>
<tr>
<td>APOE ε4</td>
<td>0.59 (0.28–1.25)</td>
<td>&gt;0.20</td>
<td>0.79 (0.08–7.91)</td>
<td>&gt;0.20</td>
<td>0.94 (0.37–2.43)</td>
<td>&gt;0.20</td>
</tr>
</tbody>
</table>

ICH indicates intracerebral hemorrhage; CTA, CT angiography; APOE, apolipoprotein E.

*Analysis is also adjusted for principal components 1 and 2.

ε2 was associated with larger initial ICH volumes, hematoma expansion, and poor clinical outcome.16,17

The association between APOE ε2 and presence of the spot sign raises important hypotheses regarding the pathophysiology of this radiographic finding. If the spot sign reflects active extravasation of contrast into the hematoma, our findings fit within the proposed model of cascading small vessel injury after ICH.24 In this model, hematoma expansion occurs due to the additional rupture of small vessels adjacent to the initial hematoma. If this hypothesis holds true, the spot sign may be the visual representation of active hematoma expansion caused by the rupture of small (diseased) vessels surrounding the initial hematoma. This aligns with the isolated effect of APOE ε2 on lobar rather than deep ICH: given its unique role in CAA, it would predispose to additional vessel rupture and therefore hematoma expansion and spot sign presence. The previously published association between APOE ε2 and lobar hematoma expansion also fits within this model.17

Thus far, therapies aimed at arresting hematoma expansion have not improved clinical outcome in clinical trials, likely due to difficulty selecting the right patients for inclusion. The development of biomarkers for hematoma expansion will improve our ability to guide the most aggressive treatments to those with the greatest opportunity to benefit. APOE genotype may well be such a biomarker, because it is consistently associated with important measures in acute ICH including baseline hematoma volume, hematoma expansion, CTA spot sign, and clinical outcome.16,17 Bedside genotyping is on the verge of widespread availability, and potential uses may include risk stratification for hemostatic therapies and long-term anticoagulation use in those with ICH. Besides its potential role as a biomarker in acute ICH, at this point our findings on the APOE ε2 allele provide insight into the biological underpinnings of hematoma expansion and the epiphenomenon of the CTA spot sign.

Our study is limited by its lack of replication and the biased availability of follow-up CTs for the subgroup analysis. The latter is a recurring phenomenon, in which follow-up imaging is disproportionately not obtainable due to early death or care limitations in patients with the lowest Glasgow Coma Scale scores and largest hematomas. However, the baseline characteristics of patients with and without available CTA were not different in our study. Although our findings have not been replicated, the presented findings are in line with previous studies and generate interesting hypotheses regarding the pathophysiology of hematoma expansion. Further research on the role of APOE in ICH and replication of our results is necessary.

In conclusion, we show that the APOE ε2 allele is associated with the presence of the CTA spot sign in patients with lobar ICH. Patients on warfarin are also more likely to have a spot sign upon presentation regardless of ICH location. Given the established relationship between APOE ε2 and vasculopathic changes in CAA, our findings suggest that both hemostatic factors and vessel pathology influence the development of the spot sign and risk of prolonged bleeding in ICH.

Acknowledgments

We thank Tammy Gills, BSc, and Macey MacDonald, PhD, for technical assistance in genotyping APOE variants.

Sources of Funding

All funding entities had no involvement in study design, data collection, analysis, or interpretation, or writing of the article or in the decision to submit for publication. The project described was supported by National Institutes of Health—National Institute of Neurological Disorders and Stroke (NIH-NINDS) grants R01NS073344, R01NS059727, and 5K23NS059774 and the Edward and Maybeth Sonn Research Fund. Dr. Brouwers was supported by the NIH—NINDS Specialized Program of Translational Research in Acute Stroke (SPOTRIAS) fellowship grant P50NS051343. Dr. Biffi was supported in part by the American Heart Association/Bugher Foundation Centers for Stroke Prevention Research (0775010N). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the NINDS.

Disclosures

J.M.R. is on the Imaging Committee of the Desmoteplase in Acute Ischemic Stroke Trial (DIAS) trial and on the advisory board of Lundbeck Pharmaceuticals. S.M.G. received a research grant the National Institutes of Health; received honoraria from Medtronic and Pfizer; and is a consultant/on the advisory board of Hoffman-La Roche, Janssen Alzheimer Immunotheraphy, and Bristol-Myers Squibb Company. J.R. received research grants from the National Institutes of Health and the American Heart Association. J.N.G. received a research grant from the National Institute of Neurological Disorders and Stroke and is a consultant/on the advisory board of CSL Behring.
References


Apolipoprotein E Genotype Is Associated With CT Angiography Spot Sign in Lobar Intracerebral Hemorrhage

H. Bart Brouwers, Alessandro Biffi, Kristen A. McNamara, Alison M. Ayres, Valerie Valant, Kristin Schwab, Javier M. Romero, Anand Viswanathan, Steven M. Greenberg, Jonathan Rosand and Joshua N. Goldstein

Stroke. published online May 23, 2012;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://stroke.ahajournals.org/content/early/2012/05/22/STROKEAHA.112.659094

Data Supplement (unedited) at:

http://stroke.ahajournals.org/content/suppl/2013/10/02/STROKEAHA.112.659094.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:

http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:

http://stroke.ahajournals.org//subscriptions/
Abstract

Apolipoprotein E Genotype Is Associated With CT Angiography Spot Sign in Lobar Intracerebral Hemorrhage

H. Bart Brouwers, MD1,2,3,6; Alessandro Biffi, MD1,2,3,6; Kristen A. McNamara, BA2,3; Alison M. Ayres, BA2,3; Valerie Valant, BA2,3; Kristin Schwab, BA2,3; Javier M. Romero, MD4; Anand Viswanathan, MD, PhD2,3,6; Steven M. Greenberg, MD, PhD2,3; Jonathan Rosand, MD, MSc1,2,3,6; Joshua N. Goldstein, MD, PhD2,3,5,6

1 Center for Human Genetic Research, 2 Hemorrhagic Stroke Research Group, 3 J. Philip Kistler Stroke Research Center, 4 Neuroradiology Service, 5 Department of Radiology, Department of Emergency Medicine, and 6 Division of Neurocritical Care and Emergency Neurology, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA.

Stroke 2012; 43: 2120-2125

表3 CTA spot signの多変量解析

<table>
<thead>
<tr>
<th>変数*</th>
<th>全患者（n = 371） OR (95% CI) p値</th>
<th>深部ICH（n = 151） OR (95% CI) p値</th>
<th>高部ICH（n = 196） OR (95% CI) p値</th>
<th>ほぼ確実／確実なCAA（n = 68） OR (95% CI) p値</th>
</tr>
</thead>
<tbody>
<tr>
<td>年齢</td>
<td>1.02 (1.00 ~ 1.04) 0.05</td>
<td>1.02 (0.99 ~ 1.06) 0.14</td>
<td>1.02 (0.99 ~ 1.06) 0.17</td>
<td>1.08 (0.95 ~ 1.23) &gt;0.20</td>
</tr>
<tr>
<td>性別（男性対女性）</td>
<td>1.34 (0.70 ~ 2.58) &gt;0.20</td>
<td>1.83 (0.81 ~ 4.16) 0.15</td>
<td>1.91 (0.90 ~ 3.95) &gt;0.20</td>
<td>1.46 (0.37 ~ 5.77) &gt;0.20</td>
</tr>
<tr>
<td>高血压</td>
<td>1.28 (0.65 ~ 2.56) &gt;0.20</td>
<td>0.81 (0.26 ~ 2.53) &gt;0.20</td>
<td>0.53 (0.19 ~ 1.53) &gt;0.20</td>
<td>1.64 (0.37 ~ 7.61) &gt;0.20</td>
</tr>
<tr>
<td>ウルファリン使用</td>
<td>3.46 (1.92 ~ 6.21) &lt;0.001</td>
<td>3.85 (1.33 ~ 11.13) 0.013</td>
<td>2.86 (1.33 ~ 6.13) 0.007</td>
<td>6.65 (1.34 ~ 32.99) 0.020</td>
</tr>
<tr>
<td>APOE ε2</td>
<td>1.55 (0.81 ~ 2.96) 0.19</td>
<td>0.53 (0.16 ~ 1.70) &gt;0.20</td>
<td>2.09 (1.05 ~ 4.19) 0.036</td>
<td>2.07 (1.24 ~ 3.46) 0.005</td>
</tr>
<tr>
<td>APOE ε4</td>
<td>0.64 (0.33 ~ 1.25) &gt;0.20</td>
<td>0.70 (0.32 ~ 1.55) &gt;0.20</td>
<td>0.60 (0.26 ~ 1.36) &gt;0.20</td>
<td>0.77 (0.27 ~ 2.18) &gt;0.20</td>
</tr>
</tbody>
</table>

CTA: CT血管造影。ICH: 脳内出血。CAA: 脳アミロイド血管症。APOE: アポリポタック質E。*解析では主成分1および2についても検討している。