Published in final edited form as:
Stroke. 2012 August ; 43(8): 2120–2125. doi:10.1161/STROKEAHA.112.659094.

APOE Genotype Is Associated With CT Angiography Spot Sign In Lobar Intracerebral Hemorrhage

H. Bart Brouwers, M.D.[1,2,3,4], **Alessandro Biffi, M.D.**[1,2,3,4], **Kristen A. McNamara, B.A.**[3,4], **Alison M. Ayres, B.A.**[3,4], **Valerie Valant, B.A.**[1,3], **Kristin Schwab, B.A.**[3,4], **Javier M. Romero, M.D.**[5], **Anand Viswanathan, M.D., Ph.D.**[2,3,4], **Steven M. Greenberg, M.D., Ph.D.**[3,4], **Jonathan Rosand, M.D., M.Sc.**[1,2,3,4], and **Joshua N. Goldstein, M.D., Ph.D.**[2,3,4,6]

[1]Center for Human Genetic Research, Massachusetts General Hospital, Harvard Medical School, Boston

[2]Division of Neurocritical Care and Emergency Neurology, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston

[3]Hemorrhagic Stroke Research Group, Massachusetts General Hospital, Harvard Medical School, Boston

[4]J. Philip Kistler Stroke Research Center, Massachusetts General Hospital, Harvard Medical School, Boston

[5]Neuroradiology Service, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston

[6]Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston

Abstract

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 two 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

Correspondence H. Bart Brouwers, M.D. Center for Human Genetic Research – Rosand Lab Massachusetts General Hospital, Harvard Medical School 185 Cambridge Street; CPZN-6818 Boston, MA 02114 USA T: +1 (617) 643-3941 F: +1 (617) 643-3939 brouwers@chgr.mgh.harvard.edu.

Disclosures H.B. Brouwers: None; **A. Biffi:** None; **K.A. McNamara:** None; **A.M. Ayres:** None; **V. Valant:** None; **K. Schwab:** None; **J.M. Romero**, Imaging Committee DIAS trial / advisory board Lundbeck pharmaceuticals; **A. Viswanathan**, None; **S.M. Greenberg**, Research Grant NIH, Honoraria: Medtronic, Pfizer, Consultant / advisory board: Hoffman-La Roche, Janssen Alzheimer Immunotherapy, Bristol-Myers Squibb Company; **J. Rosand**, Research Grant NIH and AHA; **J.N. Goldstein**, Research Grant NINDS, Consultant / advisory board CSL Behring.

1.33 - 6.13) in lobar ICH. APOE ε2, but not ε4, was associated with 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—ICH patients on warfarin are more likely to present with a spot sign, regardless of ICH location. Among patients with lobar ICH, those who possess the APOE ε2 allele are more likely to have a spot sign. Given the established relationship between APOE ε2 and vasculopathic changes in cerebral amyloid angiopathy, our findings suggest that both hemostatic factors and vessel pathology influence spot sign presence.

Keywords

Intracerebral Hemorrhage; Genetics; APOE; CTA Spot Sign; Hematoma Expansion

INTRODUCTION

Spontaneous intracerebral hemorrhage (ICH) accounts for 15% of all strokes and has a 30-day mortality rate of approximately 40%.[1,2] The most potent determinant of poor outcome is baseline hematoma volume.[3] Importantly, expansion of the initial hematoma occurs in 25% of hospitalized ICH patients and forms another strong predictor of poor outcome.[4,5] 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.[6,7]

The extravasation of contrast into the hematoma following CT angiography (CTA), termed the ‘spot sign’, is frequently seen in ICH patients and is an independent predictor of both hematoma expansion[8-10] and poor outcome[11-13]. The biological underpinnings of the CTA spot sign remain poorly understood, and there are no established risk factors for its presence besides early presentation.[10,13,14]

A multi-center 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.[15] In addition, the APOE ε2 allele has been associated with larger baseline ICH volumes[16], hematoma expansion[17], and poor outcome[16] in lobar ICH. The role of the APOE alleles is probably related to their known effect in cerebral amyloid angiopathy (CAA)[18], where each allele is associated with characteristic pathologic 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.[19,20]

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.

METHODS

Study design

This study is a retrospective analysis of prospectively collected data from an ongoing cohort study at Massachusetts General Hospital (MGH), Boston, USA. All parts of the study were approved by the Institutional Review Board of MGH and informed consent was obtained from all participants or their families / surrogates.

Study subjects

Consecutive patients with acute primary ICH who presented between December 2000 and January 2011 to MGH and who met inclusion criteria were approached for enrollment in an

ongoing genetic ICH study. The inclusion criteria for this analysis were defined as: (1) diagnosis of non-traumatic ICH on CT; (2) availability of a baseline CTA; (3) self-reported European or European-American ancestry; and (4) APOE genotype data available. For a subgroup analysis, patients with an available follow-up CT scan within 48 hours of the baseline CT were included. Exclusion criteria were defined as: presence of a vascular malformation, aneurysmal subarachnoid hemorrhage, hemorrhagic transformation of acute infarction, traumatic ICH, brain neoplasm, or any other suspected cause of secondary ICH. Patients with ICH of the brainstem or primary intraventricular hemorrhage (IVH) were also excluded from the current analysis. (Figure 1)

Clinical data

Collected data included age, sex, and medical history including diabetes mellitus, hypertension, coronary artery disease, atrial fibrillation, hyperlipidemia, ischemic stroke, and previous ICH. Medications included the use of warfarin, antiplatelet therapy and statins. All data points were collected through interviews with the patient or their families / surrogates. Hospital charts were reviewed for Glasgow Coma Scale (GCS), time to initial imaging and interscan time for patients with a follow-up CT available.

CT analysis

ICH location was assigned by trained study staff based on the baseline CT. Deep ICH was defined as ICH exclusively involving thalamus or basal ganglia, whereas ICH originating at the cortical-subcortical junction was considered lobar ICH. For this analysis, hemorrhages involving both territories were labeled as mixed ICH.

The initial and follow-up volumes of both ICH and IVH were measured using Alice (PAREXEL International Corporation) and Analyze 9.0 (Mayo Clinic, Rochester, Minnesota) software following previously described methods.[10,12] Significant hematoma expansion was defined as an absolute increase in ICH volume greater than 6 mL or an increase of greater than 33% from baseline ICH volume.[8,17,21]

CTAs were reviewed by two 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 10ng/μl. Two single nucleotide polymorphisms of the APOE locus, rs7412 (APOE 158) and rs429358 (APOE 112), were independently genotyped using two separate assays. The allelic reads from each assay were translated to APOE genotypes (ε3ε3, ε3ε4, ε4ε4, ε3ε2, ε2ε2, and ε2ε4). All ICH cases were in Hardy-Weinberg equilibrium for APOE genotypes. Genotyping personnel were blinded to clinical and neuroimaging data.

Cerebral amyloid angiopathy-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]), since 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%) lobar ICH patients had MR imaging 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 (SD) or as median and Interquartile Range (IQR). We tested the potential role of the APOE ε2 and ε4 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 pre-specified 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 ε2 alleles (0, 1 or 2), and number of ε4 alleles (0, 1 or 2). All analyses were repeated after adjustment for genetic population structure (principal components 1 and 2) based on genome wide 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 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. 2011, 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 CTA spot sign presence

All ICH—Univariate analysis was performed to assess association of the covariates with CTA spot sign presence in all ICH patients. Both age ($p = 0.033$) and warfarin use at 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 ε2, APOE ε4, 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 ($p = 0.013$). 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 lobar ICH patients 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 GCS scores upon presentation, greater hematoma volumes, and higher mortality rates at discharge (all p < 0.05).

Hematoma expansion was present in 42 out 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 lobar ICH patients who posses 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 two APOE variants appear to act through different histopathological 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.[19,20] In addition to these histopathological 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 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 following 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, since 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 suffering from 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, where follow-up imaging is disproportionately not obtainable due to early death or care limitations in patients with the lowest GCS 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 suffering from 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 would like to thank Tammy Gills, B.Sc., and Marcy MacDonald, Ph.D., for technical assistance in genotyping APOE variants.

Sources of Funding All funding entities had no involvement in study design, data collection, analysis, and interpretation, writing of the manuscript and 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, 5K23NS059774, and the Edward and Maybeth Sonn Research Fund. Dr. Brouwers was supported by the NIH – NINDS SPOTRIAS fellowship grant P50NS051343. Dr. Biffi was supported in part by the American Heart Association (AHA) / 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.

REFERENCES

(1). Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneous intracerebral hemorrhage. N Engl J Med. 2001; 344:1450–1460. [PubMed: 11346811]

(2). van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. Lancet Neurol. 2010; 9:167–176. [PubMed: 20056489]

(3). Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G. Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. Stroke. 1993; 24:987–993. [PubMed: 8322400]

(4). Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, et al. Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. Neurology. 2006; 66:1175–1181. [PubMed: 16636233]

(5). Dowlatshahi D, Demchuk AM, Flaherty ML, Ali M, Lyden PL, Smith EE. VISTA Collaboration. Defining hematoma expansion in intracerebral hemorrhage: relationship with patient outcomes. Neurology. 2011; 76:1238–1244. [PubMed: 21346218]

(6). Delcourt C, Huang Y, Wang J, Heeley E, Lindley R, Stapf C, et al. INTERACT2 Investigators. The second (main) phase of an open, randomised, multicentre study to investigate the effectiveness of an intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT2). Int J Stroke. 2010; 5:110–116. [PubMed: 20446945]

(7). Qureshi AI, Palesch YY. Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) II: design, methods, and rationale. Neurocrit Care. 2011; 15:559–576. [PubMed: 21626077]

(8). Goldstein JN, Fazen LE, Snider R, Schwab K, Greenberg SM, Smith EE, et al. Contrast extravasation on CT angiography predicts hematoma expansion in intracerebral hemorrhage. Neurology. 2007; 68:889–894. [PubMed: 17372123]

(9). Wada R, Aviv RI, Fox AJ, Sahlas DJ, Gladstone DJ, Tomlinson G, et al. CT angiography "spot sign" predicts hematoma expansion in acute intracerebral hemorrhage. Stroke. 2007; 38:1257–1262. [PubMed: 17322083]

(10). Delgado Almandoz JE, Yoo AJ, Stone MJ, Schaefer PW, Goldstein JN, Rosand J, et al. Systematic characterization of the computed tomography angiography spot sign in primary intracerebral hemorrhage identifies patients at highest risk for hematoma expansion: the spot sign score. Stroke. 2009; 40:2994–3000. [PubMed: 19574553]

(11). Kim J, Smith A, Hemphill JC 3rd, Smith WS, Lu Y, Dillon WP, et al. Contrast extravasation on CT predicts mortality in primary intracerebral hemorrhage. AJNR Am J Neuroradiol. 2008; 29:520–525. [PubMed: 18065505]

(12). Delgado Almandoz JE, Yoo AJ, Stone MJ, Schaefer PW, Oleinik A, Brouwers HB, et al. The spot sign score in primary intracerebral hemorrhage identifies patients at highest risk of in hospital mortality and poor outcome among survivors. Stroke. 2010; 41:54–60. [PubMed: 19910545]

(13). Li N, Wang Y, Wang W, Ma L, Xue J, Weissenborn K, et al. Contrast extravasation on computed tomography angiography predicts clinical outcome in primary intracerebral hemorrhage: a prospective study of 139 cases. Stroke. 2011; 42:3441–3446. [PubMed: 21980207]

(14). Becker KJ, Baxter AB, Bybee HM, Tirschwell DL, Abouelsaad T, Cohen WA. Extravasation of radiographic contrast is an independent predictor of death in primary intracerebral hemorrhage. Stroke. 1999; 30:2025–2032. [PubMed: 10512902]

(15). Biffi A, Sonni A, Anderson CD, Kissela B, Jagiella JM, Schmidt H, et al. International Stroke Genetics Consortium. Variants at APOE influence risk of deep and lobar intracerebral hemorrhage. Ann Neurol. 2010; 68:934–943. [PubMed: 21061402]

(16). Biffi A, Anderson CD, Jagiella JM, Schmidt H, Kissela B, Hansen BM, et al. International Stroke Genetics Consortium. APOE genotype and extent of bleeding and outcome in lobar intracerebral haemorrhage: a genetic association study. Lancet Neurol. 2011; 10:702–709. [PubMed: 21741316]

(17). Brouwers HB, Biffi A, Ayres AM, Schwab K, Cortellini L, Romero JM, et al. APOE Genotype Predicts Hematoma Expansion in Lobar Intracerebral Hemorrhage. Stroke. 2012; 43:1490–1495. [PubMed: 22535266]

(18). Vinters HV. Cerebral amyloid angiopathy. A critical review. Stroke. 1987; 18:311–324. [PubMed: 3551211]

(19). Greenberg SM, Vonsattel JP, Segal AZ, Chiu RI, Clatworthy AE, Liao A, et al. Association of apolipoprotein E epsilon2 and vasculopathy in cerebral amyloid angiopathy. Neurology. 1998; 50:961–965. [PubMed: 9566379]

(20). Alonzo NC, Hyman BT, Rebeck GW, Greenberg SM. Progression of cerebral amyloid angiopathy: accumulation of amyloid-beta40 in affected vessels. J Neuropathol Exp Neurol. 1998; 57:353–359. [PubMed: 9600229]

(21). Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. Stroke. 1997; 28:1–5. [PubMed: 8996478]

(22). Knudsen KA, Rosand J, Karluk D, Greenberg SM. Clinical diagnosis of cerebral amyloid angiopathy: validation of the Boston criteria. Neurology. 2001; 56:537–539. [PubMed: 11222803]

(23). Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Al-Shahi Salman R, Warach S, et al. Microbleed Study Group. Cerebral microbleeds: a guide to detection and interpretation. Lancet Neurol. 2009; 8:165–174. [PubMed: 19161908]

(24). Fisher CM. Pathological observations in hypertensive cerebral hemorrhage. J Neuropathol Exp Neurol. 1971; 30:536–550. [PubMed: 4105427]

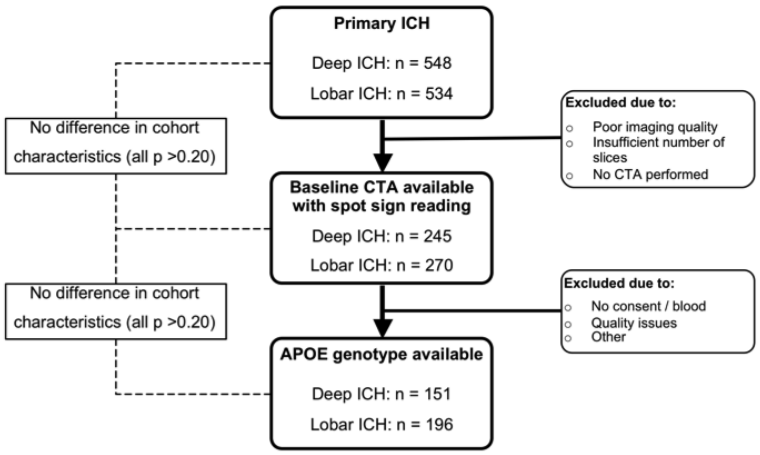

Figure 1.
Cohort flowchart

Table 1

Cohort characteristics

Variable	All (n, %)	Deep ICH (n, %)	Lobar ICH (n, %)
Number of subjects	371	151	196
Age (mean, SD)	72.6 (12.8)	68.6 (14.3)	75.9 (10.7)
Female sex	180 (48.5)	65 (43.0)	102 (52.0)
Diabetes mellitus	77 (20.8)	40 (26.5)	29 (14.8)
Hypertension	289 (77.9)	132 (87.4)	133 (67.9)
Coronary artery disease	69 (18.6)	31 (20.5)	33 (16.8)
Atrial fibrillation	78 (21.0)	23 (15.2)	50 (25.5)
Hyperlipidemia	150 (40.4)	59 (39.1)	85 (43.4)
Previous ICH	28 (7.5)	6 (4.0)	21 (10.7)
Pre-ICH ischemic stroke	41 (11.1)	14 (9.3)	21 (10.7)
Warfarin use	69 (18.6)	21 (13.9)	43 (21.9)
Antiplatelet therapy	22 (5.9)	11 (7.3)	11 (5.6)
Statin use	120 (32.3)	46 (30.5)	69 (35.2)
Probable / definite CAA	70 (18.9)	0 (0.0)	69 (35.2)
GCS (median, IQR)	14 (7-15)	12 (6-15)	14 (7-15)
Time to baseline imaging in hours (median, IQR)	6.0 (3.0-13.0)	5.0 (3.0-9.0)	6.0 (4.0-17.0)
Baseline ICH volume (median, IQR)	24.4 (8.0-59.0)	17.9 (5.4-44.6)	36.0 (16.3-71.6)
Follow-up ICH volume (median, IQR) *	19.0 (6.2-42.8)	12.8 (4.1-35.3)	27.1 (11.5-52.0)
Intraventricular extension	182 (49.1)	89 (58.9)	80 (40.8)
Baseline IVH volume (median, IQR) **	7.7 (2.2-24.0)	15.0 (3.2-35.0)	6.5 (2.3-17.8)
Follow-up IVH volume (median, IQR) *	6.5 (2.0-21.3)	11.0 (3.4-24.5)	4.0 (2.0-13.0)
Interscan time in hours (median, IQR) *	10.0 (6.0-17.0)	9.0 (6.0-14.5)	12.0 (6.3-18.0)
Spot sign presence	97 (26.1)	41 (27.2)	52 (26.5)
Hematoma expansion *	42 (18.4)	19 (20.2)	20 (16.7)
Death at 90 days	156 (42.0)	63 (41.7)	87 (44.4)
mRS at 90 days (0 – 2) ***	106 (31.0)	37 (26.4)	60 (32.8)
APOE ε2 (minor allele frequency)	0.09	0.08	0.11
APOE ε4 (minor allele frequency)	0.19	0.17	0.22

* Among patients who had a follow-up CT within 48 hours (61%)

** Data refers only to ICH cases with intraventricular extension

*** Among patients with available 3-month follow-up (92%)

ICH = intracerebral hemorrhage; CAA = cerebral amyloid angiopathy; GCS = Glasgow Coma Scale; IQR = interquartile range; IVH = intraventricular hemorrhage; mRS = modified Rankin Scale; APOE = Apolipoprotein E

Table 2

Univariate analysis of CTA spot sign

Variable	All (n = 371)		Deep ICH (n = 151)		Lobar ICH (n = 196)		Probable / definite CAA (n = 69)	
	OR (95% CI)	p – value	OR (95% CI)	p – value	OR (95% CI)	p – value	OR (95% CI)	p – value
Age	**1.02 (1.00-1.04)**	**0.033**	1.03 (0.99-1.06)	0.055	1.02 (0.99-1.06)	0.14	1.07 (0.96-1.19)	>0.20
Sex (male vs. female)	0.72 (0.28-1.91)	>0.20	1.30 (0.61-2.77)	>0.20	0.64 (0.29-1.42)	>0.20	1.46 (0.37-5.77)	>0.20
Hypertension	1.77 (0.95-3.26)	0.070	0.97 (0.32-2.97)	>0.20	0.76 (0.30-1.98)	>0.20	1.58 (0.13-19.21)	>0.20
Warfarin use	**3.49 (2.02-6.04)**	**<0.001**	**3.67 (1.42-9.47)**	**0.007**	**3.18 (1.56-6.46)**	**0.001**	**6.30 (1.52-26.22)**	**0.011**
APOE ε2	0.74 (0.40-1.33)	>0.20	0.96 (0.34-2.70)	>0.20	**1.70 (1.08-2.63)**	**0.025**	**2.10 (1.10-4.03)**	**0.024**
APOE ε4	0.79 (0.43-1.43)	>0.20	0.60 (0.28-1.30)	>0.20	0.66 (0.37-1.22)	>0.20	0.71 (0.24-2.11)	>0.20

ICH = intracerebral hemorrhage; CAA = cerebral amyloid angiopathy; APOE = Apolipoprotein E

Table 3

Multivariate analysis of CTA spot sign

Variable*	All (n = 371)		Deep ICH (n = 151)		Lobar ICH (n = 196)		Probable / definite CAA (n = 69)	
	OR (95% CI)	p – value	OR (95% CI)	p – value	OR (95% CI)	p – value	OR (95% CI)	p – value
Age	1.02 (1.00-1.04)	0.05	1.02 (0.99-1.06)	0.14	1.02 (0.99-1.06)	0.17	1.08 (0.95-1.23)	>0.20
Sex (male vs. female)	1.34 (0.70-2.58)	>0.20	1.83 (0.81-4.16)	0.15	1.91 (0.90-3.95)	>0.20	1.46 (0.37-5.77)	>0.20
Hypertension	1.28 (0.65-2.56)	>0.20	0.81 (0.26-2.53)	>0.20	0.53 (0.19-1.53)	>0.20	1.64 (0.37-7.61)	>0.20
Warfarin use	**3.46 (1.92-6.21)**	**<0.001**	**3.85 (1.33-11.13)**	**0.013**	**2.86 (1.33-6.13)**	**0.007**	**6.65 (1.34-32.99)**	**0.020**
APOE ε2	1.55 (0.81-2.96)	0.19	0.53 (0.16-1.70)	>0.20	**2.09 (1.05-4.19)**	**0.036**	**2.07 (1.24-3.46)**	**0.005**
APOE ε4	0.64 (0.33-1.25)	>0.20	0.70 (0.32-1.55)	>0.20	0.60 (0.26-1.36)	>0.20	0.77 (0.27-2.18)	>0.20

*Analysis is also adjusted for principal components 1 and 2

ICH = intracerebral hemorrhage; CAA = cerebral amyloid angiopathy; APOE = Apolipoprotein E

Table 4

Multivariate analysis of hematoma expansion among patients with follow-up CT

Variable*	All (n = 228)		Deep ICH (n = 94)		Lobar ICH (n = 120)	
	OR (95% CI)	p – value	OR (95% CI)	p – value	OR (95% CI)	p – value
Age	1.01 (0.97-1.04)	>0.20	1.01 (0.96-1.06)	>0.20	0.98 (0.94-1.03)	>0.20
Sex (male vs. female)	1.70 (0.73-3.95)	>0.20	1.60 (0.39-6.60)	>0.20	1.32 (0.42-2.18)	>0.20
Hypertension	2.57 (0.87-7.66)	0.089	2.33 (0.35-15.63)	>0.20	2.47 (0.60-10.07)	>0.20
Warfarin use	1.66 (0.68-4.04)	>0.20	0.53 (0.07-4.54)	>0.20	1.30 (0.35-4.77)	>0.20
CTA spot sign	**7.78 (3.46-17.50)**	**<0.001**	**9.40 (2.63-33.63)**	**0.001**	**7.55 (2.31-24.70)**	**0.001**
APOE ε2	1.67 (0.76-3.65)	0.19	0.65 (0.07-6.48)	>0.20	2.48 (0.99-6.27)	0.054
APOE ε4	0.59 (0.28-1.25)	>0.20	0.79 (0.08-7.91)	>0.20	0.94 (0.37-2.43)	>0.20

*Analysis is also adjusted for principal components 1 and 2

ICH = intracerebral hemorrhage; APOE = Apolipoprotein E