Increased Cerebral Small Vessel Disease Burden With Renal Dysfunction and Albuminuria in Patients Taking Antithrombotic Agents: The Bleeding With Antithrombotic Therapy 2

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BACKGROUND: The aim of this study was to determine the associations of cerebral small vessel disease (SVD) burden with renal dysfunction and albuminuria in patients taking oral antithrombotic agents.

METHODS AND RESULTS: Patients who newly started or continued taking oral antiplatelets or anticoagulants were enrolled in a prospective, multicenter, observational study. Obligatorily acquired multimodal magnetic resonance imaging at registration with prespecified imaging conditions was assessed for cerebral microbleeds, white matter hyperintensities, enlarged basal ganglia perivascular spaces, or lacunes, and an ordinal SVD score was calculated (range, 0–4). Multivariable adjusting covariates were age, sex, hypertension, diabetes, dyslipidemia, current smoking, drinking, and estimated glomerular filtration rate (eGFR). Of 5324 patients (1762 women; median age, 73 years), 4797 (90.1%) patients were taking oral antithrombotic agents for secondary stroke prevention. Cerebral microbleeds were present in 32.7%, confluent white matter hyperintensities in 51.8%, extensive basal ganglia perivascular spaces in 38.9%, and lacunes in 59.4%. Median SVD score was 2. Compared with eGFR category G1 (eGFR ≥90 mL/min per 1.73 m²), adjusted odds ratios for SVD score increment were 1.63 (95% CI, 1.11–2.39) at category G4 (eGFR 15–<30 mL/min per 1.73 m²) and 2.05 (95% CI, 1.33–3.16) at G5 (eGFR <15 mL/min per 1.73 m²). Corresponding odds ratios relative to urinary albumin-to-creatinine ratio (ACR) category A1 (ACR <30 mg/g) were 1.29 (95% CI, 1.12–1.49) for category A2 (ACR 30–<300 mg/g) and 1.37 (95% CI, 1.05–1.77) for A3 (ACR ≥300 mg/g). When combined eGFR and ACR categories were assessed, risks for SVD score increment generally increased as eGFR decreased and ACR increased.

CONCLUSIONS: Both reduced eGFR and albuminuria were independently associated with increased cerebral SVD burden in patients requiring oral antithrombotic medication mainly for secondary stroke prevention.

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Key Words: albuminuria □ anticoagulant □ antiplatelet agent □ cerebral small vessel disease □ chronic kidney disease

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Among the magnetic resonance imaging (MRI) biomarkers for cerebral small vessel disease (SVD), cerebral microbleeds (CMBs) are known predictors of intracranial hemorrhage especially in patients on antithrombotic therapy post stroke.1–4 Cerebral SVD is also associated with noncerebral problems as a marker of systemic SVD including chronic kidney disease (CKD), which also seems to increase risks for bleeding events.5,6 A total SVD score combining individual MRI features of SVD offers potential for more accurate stratification of the cerebral SVD burden than the use of individual features separately,7,8 and the association of total SVD score increment with reduced estimated glomerular filtration rate (eGFR) was reported in an analysis of 1080 patients with ischemic stroke or transient ischemic attack from the Oxford Vascular Study, with the associations attenuating at older ages.9 Albuminuria was related to the increased SVD score in 1037 hypertensives from the Investigating Silent Strokes in Hypertensives: a Magnetic Resonance Imaging Study, in which concurrently investigated eGFR showed no significant association with the SVD score.10

The importance of bleeding complications associated with antithrombotic therapy, including an increased bleeding risk with dual antithrombotic use and the association of high blood pressure levels in the outpatient clinic with later intracerebral hemorrhage occurrence, was clarified in a multicenter registry, the BAT (Bleeding with Antithrombotic Therapy) study.11,12 Responding to the subsequent prevalence of antithrombotic medication, such as development of direct oral anticoagulants and new P2Y12 receptor blockers and improvement of dual antiplatelet therapy for stroke,13–18 we newly organized the BAT2 study.19 BAT2 aims to provide a precise risk model for antithrombotic-associated bleeding, taking the cerebral SVD burden into account, and multimodal brain MRI was acquired at baseline for all patients under prespecified imaging conditions. BAT2 also collected data of eGFR as well as albuminuria. Given the association of bleeding risk with reduced eGFR and albuminuria,20 simultaneous analyses of the 2 CKD measures with total SVD score in patients on antithrombotic therapy are relevant.

The objective of this cross-sectional study was to determine the associations of cerebral SVD burden with renal dysfunction and albuminuria in patients who newly started or continued taking oral antithrombotic agents, using the baseline data from BAT2.

METHODS
Data supporting the findings of this study are available from the principal investigator of BAT2 (Toyoda) on reasonable request.

Study Design and Participants
The BAT2 study was an investigator-initiated, prospective, multicenter, observational study involving 52 hospital sites across Japan from the Network for Clinical Stroke Trials (Table S1).21 BAT2 was designed to determine the incidence and details of
bleeding complications in patients treated with oral antithrombotic agents. The study was registered with ClinicalTrials.gov (NCT02889653) and the University Hospital Medical Information Network clinical trial registry in Japan (UMIN 000023669). The overall protocol has been published elsewhere.19 All study procedures were reviewed and approved by the ethics committee of the participating sites. The investigators obtained written informed consent from patients or their family members before registration.

Patients with cerebrovascular or cardiovascular diseases (either symptomatic or asymptomatic) who newly started or continued taking oral antplatelets or anticoagulants were enrolled from October 2016 through April 2019. Brain MRI was mandatory for all patients at registration and contraindication to MRI was an exclusion criterion of this study.

Clinical Data Acquisition and Management
At registration, baseline clinical information and blood test and urinalysis results were collected. The Research Electronic Data Capture system was used for the collection and management of data from each participating site through a secured network connection with authentication. The eGFR (mL/min per 1.73 m²) was estimated based on serum creatinine level using the equation of Japanese Society of Nephrology.22 CKD severity was staged by the glomerular filtration rate categories according to the NKF-KDOQI (National Kidney Foundation-Kidney Disease Outcomes Quality Initiative) guideline.23 Albuminuria was assessed by urinary albumin-to-creatinine ratio (ACR, mg/g) using a spot urine sample and categorized also according to the NKF-KDOQI guideline.23

Acquisition and Management of Brain MRI Data
Brain MRI of magnetic field at 3 or 1.5 Tesla was obtained parallel to the anterior comissure-posterior commissure line or the orbitomeatal line. MRI was allowed to be performed from 90 days before to 14 days after registration. MRI sequences included T1-weighted, T2-weighted, fluid-attenuated inversion recovery, and T2*-weighted imaging. T1-weighted and T2-weighted images represent water content in low and high intensities, respectively. Fluid-attenuated inversion recovery images have similar characteristics to T2-weighted imaging, but the signal of cerebrospinal fluid is suppressed. T2*-weighted images can detect hemorrhagic changes with high sensitivity. Three-dimensional time-of-flight magnetic resonance angiography was performed.

All MRI examinations were interpreted by a central diagnostic radiology committee consisting of 13 members (Chair: Sasaki) for CMBs, cortical superficial siderosis, white matter hyperintensity (WMH), enlarged basal ganglia perivascular spaces (BG-PVS), lacunes, and other infarctions according to the criteria of Standards for Reporting Vascular Changes in Neuroimaging.24 All committee members were blinded to clinical information.

Details for acquisition and interpretation of MRI are described in Data S1 and Tables S2 and S3.25

Statistical Analysis
One point for each SVD feature of CMBs (≥1 for any CMBs), confluent WMH, extensive BG-PVS (≥11), and lacunes (≥1) on MRI was summed as an ordinal SVD score, from a minimum score of 0 to a maximum of 4. Confluent WMH was diagnosed as positive when periventricular hyperintensity grade was 3 or deep and subcortical WMH grade was 2 to 3.8

Data were summarized as median (25th percentile, 75th percentile) for continuous variables and as frequency and percentage for categorical variables. Correlations between MRI findings were evaluated with Spearman’s rank order correlation coefficients. We divided patients into 2 groups (lower and higher SVD score groups) using the median SVD score as a cutoff. Statistical differences between these 2 groups were assessed using the Mann-Whitney U test or the Pearson χ² test, as appropriate. Proportional odds ordinal logistic regression models were applied to explore risk factors for SVD score increment, using ordinal SVD score as a dependent variable.8–10 Brant test was used to examine whether the proportional odds assumption was upheld. Binary logistic regression models were also applied to assess risk factors for assignment to the higher SVD score group and the presence of each MRI feature for cerebral SVD. Two multivariable models were created to adjust confounding factors with these logistic models. Model 1 included age and sex. Adjusted covariates for Model 2 included hypertension, diabetes, dyslipidemia, current smoking, drinking, and eGFR categories, as well as age and sex.7,9,26,27 Each interaction among age, hypertension, eGFR categories, and ACR categories was tested as an addition to logistic models. Stratified analyses by age group (≤74 and >75 years), hypertension (presence and absence), eGFR (<30, 30–<60, and ≥60 mL/min per 1.73 m²), and ACR (<30 and ≥30 mg/g) were performed. The reason for including not only eGFR and ACR but also age and hypertension in the stratified analyses was that among the variables studied, age and hypertension have consistently shown strong associations with cerebral SVD.7,26,27 For sensitivity analyses, ordinal and binary logistic analyses were conducted for cerebral SVD burden using the same model as in the main analyses on the subgroup in which MRI data were obtained at or after the time of registration.
Missing values were handled using a pairwise deletion method. Statistical significance was set at \( P < 0.05 \) for all tests. In the present analyses, Stata/MP statistical package (version 16.1; Stata Corp LP, College Station, TX) was used. Correlations between MRI findings were calculated and visualized using Pandas, Numpy, Matplotlib, and Seaborn libraries of Python programming language (3.8.5).

**RESULTS**

Among the 5378 patients registered, 11 patients with contraindication to MRI, 17 patients without MRI data acquisition for the reasons other than contraindication, 24 patients with incomplete baseline clinical data, and 2 with duplicated registration proved to be ineligible. Thus, 5324 patients (1762 women; median age, 73 years; 5321 Asian) were eligible for the present analyses. Of these, 4797 (90.1%) patients had a history of ischemic stroke or transient ischemic attack at a median of 71 (15, 1428) days for 4371 patients with available data after symptom onset and were taking oral antithrombotic agents as secondary stroke prevention; the remaining 527 (9.9%) patients were receiving antithrombotic therapy as primary prevention of stroke or secondary prevention of cardiovascular diseases.

**MRI Findings**

Baseline MRI scans were performed at 1.5 T in 3087 (58.0%) cases and 3 T in 2237 (42.0%) cases. T1-weighted, T2-weighted, and fluid-attenuated inversion recovery images were acquired in 4529 (85.1%), 5072 (95.3%), and 4974 (93.4%) cases, respectively. T2*-weighted imaging was obtained in 4984 (93.6%) patients and susceptibility-weighted imaging in 125 (2.3%) patients. The median date of MRI performance from the date of registration was −5 (−15, 0) days. The number of patients in whom MRI were acquired at or after the time of registration was 1900 (35.7%). Interrater reliability values of MRI interpretation by the central diagnostic radiology committee expressed as median kappa coefficients were as follows: for deep CMBs, 0.87 (0.72, 0.97); for lobar CMBs, 0.86 (0.74, 0.96); for periventricular hyperintensity grade, 0.68 (0.57, 0.86); for deep and subcortical WMH grade, 0.75 (0.63, 0.81); for BG-PVS, 0.61 (0.52, 0.81); and for lacunes, 0.75 (0.65, 0.98). Regarding intrarater reliability for these findings, median kappa coefficients ranged from 0.66 to 0.94. Kappa coefficients and concordance rates for MRI findings are shown in detail in Data S1 and Table S4.

On MRI, CMBs were identified in 32.7% (1671/5116), confluent WMH in 51.8% (2681/5172), extensive BG-PVS in 38.9% (1998/5135), and lacunes in 59.4% (3118/5247). Overall (n=5324), median SVD score was 2 (1, 3) (Figure S1). Distributions of cerebral SVD scores were similar between patients in whom MRI was performed before registration (median 2 [1, 3]) and those with MRI data acquired at or after registration (median 2 [1, 3]), although the \( P \) value was 0.044 (Figure S2). SVD scores were also similar between 1.5-Tesla (median 2 [1, 3]) and 3-Tesla (median 2 [1, 3]) MRI scanners (\( P=0.51 \)). Detailed findings of each SVD marker and its combination are shown in Figures S3 and S4. Relatively strong correlation was seen between deep and lobar CMBs (Spearman’s rho=0.41) and between periventricular hyperintensity grade and deep and subcortical WMH grade (Spearman’s rho=0.78) (Figure S5).

Cortical superficial siderosis was observed in 2.1% and nonlacunar infarct in 33.1%. On magnetic resonance angiography, normal or mild stenosis of intracranial arterial stenosis was found in 72.0%, moderate in 10.9%, severe in 7.6%, and occlusion in 9.5%.

**Patient Characteristics by SVD Features**

Baseline patient characteristics are shown in Table 1. Patients with higher SVD scores (≥3, n=1617) were older, more frequently displayed hypertension and required support in daily life, and had lower eGFR and higher ACR than those with lower SVD scores (≤2, n=3707, \( P<0.001 \) each). As comorbidities, ischemic stroke or transient ischemic attack, intracerebral hemorrhage, acute coronary syndrome, and dementia were more frequent and atrial fibrillation was less frequent in the higher SVD score group than in the lower SVD score group (\( P<0.01 \) each). Patients with CMBs, with confluent WMH, with extensive BG-PVS, or with lacunes were older and more frequently had hypertension, lower eGFR, and higher ACR compared with those without each SVD feature. (Tables S5 and S6).

Figure 1 shows that proportions of advanced age and hypertension increased along with an increase in SVD score. The higher the SVD score, the greater the proportion of advanced eGFR categories. Likewise, the proportion of microalbuminuria as well as macroalbuminuria increased with the SVD score. Note that data for ACR were unavailable in 2182 patients (40.9%). Vascular risk factors were generally more frequent in patients with ACR data than in those without ACR data (Table S7). Patients with higher SVD score more frequently used antiplatelet agents and less frequently used anticoagulants than those with the lower score (Table S8).

**Risk Factors for Increased Cerebral SVD Score**

The ordinal logistic regression models consistently showed significant associations of SVD score-increment with advanced age, hypertension, lower eGFR, and higher ACR (Figure 2). SVD
### Table 1. Patient Characteristics and Cerebral SVD Score

| Age, y | Total (n=5324) | Total SVD score ≤2 (n=3707) | Total SVD score ≥3 (n=1617) | P value |
|--------|----------------|-------------------------------|-------------------------------|---------|
| 73.0 (66.0, 79.0) | 71.0 (63.0, 78.0) | 76.0 (69.0, 81.0) | <0.001 |
| Female sex | 1762 (33.1) | 1226 (33.1) | 536 (33.1) | 0.96 |
| Height, cm | 162.0 (155.0, 168.0) | 163.0 (155.0, 169.0) | 161.0 (153.0, 166.0) | <0.001 |
| Weight, kg | 61.0 (53.0, 69.0) | 62.0 (54.0, 70.0) | 60.0 (52.0, 67.0) | <0.001 |
| Body mass index, kg/m² | 23.2 (21.2, 25.5) | 23.3 (21.2, 25.6) | 23.1 (21.2, 25.3) | 0.096 |
| Systolic blood pressure, mm Hg | 134.0 (122.0, 148.0) | 133.0 (121.0, 147.0) | 135.0 (123.0, 149.0) | <0.001 |
| Diastolic blood pressure, mm Hg | 77.0 (68.0, 86.0) | 77.0 (69.0, 86.0) | 77.0 (68.0, 86.0) | 0.96 |
| Pulse rate, beats/min | 75.0 (66.0, 84.0) | 74.0 (65.0, 84.0) | 75.0 (66.0, 85.0) | 0.007 |

### Risk factors

| Hypertension | 4203 (79.0) | 2796 (75.4) | 1407 (87.1) | <0.001 |
| Diabetes | 1483 (27.9) | 1021 (27.5) | 462 (28.6) | 0.43 |
| Dyslipidemia | 3453 (64.9) | 2433 (65.7) | 1020 (63.1) | 0.075 |
| Current smoking | 781 (14.7) | 568 (15.3) | 213 (13.2) | 0.044 |
| Current drinking (≥8 units/wk) | 1615 (30.4) | 1179 (31.9) | 436 (27.1) | <0.001 |
| Habitual use of nonsteroidal anti-inflammatory drugs | 148 (2.8) | 105 (2.8) | 43 (2.7) | 0.73 |

### Comorbidities

| Ischemic stroke or transient ischemic attack | 4797 (90.1) | 3294 (88.9) | 1503 (92.9) | <0.001 |
| Intracerebral hemorrhage | 117 (2.2) | 43 (1.2) | 74 (4.6) | <0.001 |
| Subarachnoid hemorrhage | 27 (0.5) | 15 (0.4) | 12 (0.7) | 0.11 |
| Asymptomatic cerebrovascular disease | 390 (7.3) | 300 (8.1) | 90 (5.6) | 0.001 |
| Atrial fibrillation | 1070 (20.1) | 780 (21.0) | 290 (17.9) | 0.010 |
| Acute coronary syndrome | 377 (7.1) | 232 (8.3) | 145 (9.0) | <0.001 |
| Congestive heart failure | 208 (3.9) | 138 (3.7) | 70 (4.3) | 0.29 |
| Peripheral artery disease | 123 (2.3) | 79 (2.1) | 44 (2.7) | 0.19 |
| Deep venous thrombosis | 95 (1.8) | 65 (1.8) | 30 (1.9) | 0.80 |
| Active malignancy | 106 (2.0) | 82 (1.7) | 44 (2.7) | 0.012 |
| Liver disease | 54 (1.0) | 40 (1.1) | 14 (0.9) | 0.48 |
| Chronic obstructive pulmonary disease | 90 (1.7) | 58 (1.6) | 32 (2.0) | 0.28 |
| Dementia requiring support | 170 (3.2) | 80 (2.2) | 90 (5.6) | <0.001 |
| eGFR *, mL/min per 1.73 m² | 64.4 (53.3, 75.8) | 65.7 (55.0, 77.1) | 61.5 (50.6, 72.9) | <0.001 |

### eGFR categories, mL/min per 1.73 m²

| G1, <90 | 411 (7.8) | 316 (8.6) | 95 (5.9) |
| G2, 60–<90 | 2797 (53.0) | 2045 (55.7) | 752 (46.8) |
| G3a, 45–<60 | 1406 (26.6) | 908 (24.7) | 498 (31.0) |
| G3b, 30–<45 | 485 (9.2) | 307 (8.4) | 178 (11.1) |
| G4, 15–<30 | 113 (2.1) | 60 (1.6) | 53 (3.3) |
| G5, <15 | 88 (1.3) | 36 (1.0) | 32 (2.0) |

### ACR †, mg/g

| ACR categories, mg/g | 17.0 (7.0, 51.7) (n=3142) | 14.5 (8.1, 45.0) (n=2180) | 23.0 (9.9, 78.7) (n=962) | <0.001 |

### ACR categories, mg/g

| A1, <30 | 1985 (65.2) | 1454 (66.7) | 531 (55.2) |
| A2, 30–<300 | 926 (29.5) | 581 (26.7) | 345 (35.9) |
| A3, ≥300 | 231 (7.4) | 145 (6.7) | 86 (8.9) |

N (%) or median (25th percentile, 75th percentile).

ACR indicates urinary albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; and SVD, small vessel disease.

*eGFR is estimated as follows: eGFR=194×serum creatinine−1.094×age−0.287[×0.739 if female].

†Data for albuminuria are unavailable in 2182 patients.
Figure 1. Age (A), hypertension (B), estimated glomerular filtration rate (C), and albuminuria (D) by total SVD score.
ACR indicates urinary albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; and SVD, small vessel disease.
score significantly increased in patients with eGFR category G4 (adjusted odds ratio [OR], 1.63; 95% CI, 1.11–2.39; Model 2) and G5 (adjusted OR, 2.05; 95% CI, 1.33–3.16; Model 2) as compared with G1. Significant SVD score increment was also shown in patients with ACR category A2 (adjusted OR, 1.29; 95% CI, 1.12–1.49; Model 2) and A3 (adjusted OR, 1.37; 95% CI, 1.05–1.77; Model 2) as compared with A1. Associations between these CKD measures and SVD burden were relatively evident in patients ≤74 years old and in hypertensive patients (Figures S6 and S7). When combined eGFR and ACR were assessed, risks for SVD score increment generally increased as eGFR decreased and ACR increased (Table 2). The proportional odds assumption was not violated for each risk factor. Binary logistic regression models for SVD score ≥3 versus ≤2 showed associations similar to those seen in the ordinal logistic regression models (Figure 2).

**Risk Factors for Each SVD Marker**

Both advanced age and hypertension showed significant associations with the presence of any CMBs, confluent WMH, extensive BG-PVS, and lacunes (Figure 3). Lower eGFR and higher ACR also showed significantly or marginally significantly increased risks of these MRI SVD markers. Higher ACR showed a significant association with the presence of any CMBs.

**Sensitivity Analyses With Subgroup With MRI Data Acquired at or After Registration**

Because the sample size of this sensitivity analyses (n=1900) was considered to be statistically underpowered for the detailed eGFR and ACR categories as in the main analyses, eGFR was grouped into ≥60, 30 to <60, and <30 mL/min per 1.73 m², and ACR was grouped into <30 and ≥30 mg/g. The distribution of ORs calculated in the multivariable analyses showed

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**Figure 2.** Multivariable models of risk factors for cerebral SVD burden. Plots showing odds ratios (ORs) and 95% CIs from multivariable models. Adjusting covariates are age categories and sex for Model 1 and age categories, sex, hypertension, diabetes, dyslipidemia, current smoking, drinking, and eGFR categories for Model 2. ACR indicates urinary albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; and SVD, small vessel disease.
no relevant difference from that of the main analyses (Figure S8).

**DISCUSSION**

The BAT2 study retains data for cerebral SVD based on multimodal MRI under prespecified imaging conditions for 5324 patients who were taking oral antithrombotic agents mainly for secondary stroke prevention. In the present analysis using the baseline data from BAT2, both reduced eGFR and albuminuria were independently associated with increased SVD score.

Among the 2 CKD measures, albuminuria showed significant associations with the SVD score increment at microalbuminuria as well as macroalbuminuria categories, although the clear association between SVD score and eGFR was observed only at the eGFR categories G4 and G5, when eGFR was already severely decreased. Albuminuria not only reflects glomerular damage but also is a sensitive indicator of generalized endothelial dysfunction, and extensive studies have also been conducted on the role of endothelial dysfunction in the pathogenesis of cerebral SVD. Recently, risk scores for ischemic or hemorrhagic stroke using a component of SVD like CMBs have been given attention. Nonetheless, both albuminuria and reduced eGFR would also increase the risks for ischemic and hemorrhagic stroke. Our results suggest that, in determining the antithrombotic-associated bleeding risk in association with the cerebral SVD burden, these CKD measures should be included in the risk models.

Regarding each component of SVD score, lower eGFR was associated with increased white matter lesions and lacunar infarcts in both the present study and the Rotterdam Scan Study involving 484 participants ≥60 years old. In contrast, reduced eGFR was independently associated with the presence of CMBs in a hospital-based cross-sectional study involving 162 patients with predialysis CKD but not ours. A positive association of albuminuria with increased risk of any CMBs has been identified both in the present study and in a hospital-based study of 285 patients with hypertension.

The relationship between the total MRI burden of cerebral SVD and body mass index has not been established. In the present analysis of BAT2, body mass index was not included in adjusting covariates because body mass index was not significantly associated with the severity of cerebral SVD.

Key strengths of this study were, first, the much larger number of registered patients than similar cohort studies and, second, the unified imaging conditions of MRI for all the patients and central diagnosis by experts with sufficient intra- and interrater reliability. This study has some limitations. First, almost all participants were Asian, which might affect generalization of the present results to other ethnicities. A previous pooled meta-analysis suggested that there were some differences in predominant underlying SVD between East Asian and Western populations. Second, unavailable data on ACR in 40.9% of the overall patient cohort might have contributed to bias in the analysis. Third, the cross-sectional design of this study precludes investigation of

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**Table 2. Risks for SVD Score by Estimated Glomerular Filtration Rate and Albuminuria**

| Adjusted odds ratios of SVD score increment* | ACR (mg/g) | <30 | ≥30 |
|--------------------------------------------|------------|-----|-----|
| Estimated glomerular filtration rate (mL/min per 1.73 m²) | ≥60 | 1 (Reference) | Model 1<br>1.57 (1.31–1.88), P<0.001 | Model 2<br>1.43 (1.19–1.71), P<0.001 |
| | n=1333 | n=558 |
| 30–<60 | Model 1<br>1.22 (1.03–1.46), P=0.023 | Model 1<br>1.49 (1.23–1.79), P<0.001 | Model 2<br>1.32 (1.09–1.60), P=0.005 |
| | n=631 | n=520 |
| <30 | Model 1<br>1.49 (0.64–3.45), P=0.35 | Model 1<br>2.34 (1.56–3.49), P<0.001 | Model 2<br>1.96 (1.31–2.95), P=0.001 |
| | n=19 | n=77 |

Adjusted odds ratios (95% CI). ACR indicates urinary albumin-to-creatinine ratio; and SVD, small vessel disease.

*Ordinal logistic regression models. Adjusting covariates are age categories and sex for Model 1 and age categories, sex, hypertension, diabetes, dyslipidemia, current smoking, and drinking for Model 2. P for interaction=0.69 in Model 1; P for interaction=0.65 in Model 2.
Figure 3. Multivariable models of risk factors for SVD features.
Plots showing odds ratios (ORs) and 95% CIs from binary logistic regression models. Adjusting covariates are age categories and sex for Model 1 and age categories, sex, hypertension, diabetes, dyslipidemia, current smoking, drinking, and eGFR categories for Model 2. ACR indicates urinary albumin-to-creatinine ratio; BG-PVS, enlarged basal ganglia perivascular spaces; CMB, cerebral microbleed; eGFR, estimated glomerular filtration rate; SVD, small vessel disease; and WMH, white matter hyperintensity.
a causal relationship between CKD and cerebral SVD. Last, both the patients who newly started oral antithrombotic agents and those who had been on antithrombotic medication for a certain period of time were included, and there were no data on the duration of the medication for the latter patients.

CONCLUSIONS

In conclusion, albuminuria as well as reduced eGFR were independently associated with increased cerebral SVD burden in patients who newly started or continued taking oral antithrombotic agents mainly for secondary stroke prevention. BAT2 will provide novel risk-stratification models for antithrombotic-associated bleeding risk in association with cerebral SVD and other biomarkers, including the CKD measures.

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Disclosures

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Supplemental Material

Data S1
Tables S1–S8
Figures S1–S8

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Data S1. Supplemental Methods and Results

Supplemental Methods

Conditions for MRI are described in Table S2. The anonymized Digital Imaging and Communication in Medicine data of MRI were uploaded through a secure network Medical Imaging Cloud Communication and Knowledge System. The Medical Imaging Cloud Communication and Knowledge System platform provides a secure cloud environment for integrated diagnosis support utilizing the Extensible Neuroimaging Archive Toolkit and the Secure Sockets Layer/Transport Layer Security communication protocol with client and server certificates.

All MRI examinations were interpreted by a central diagnostic radiology committee consisting of 13 members (Chair: Sasaki) for cerebral microbleeds (CMBs), cortical superficial siderosis, white matter hyperintensity, enlarged basal ganglia perivascular spaces (BG-PVS), lacunes, and other infarctions according to the criteria of STandards for ReportIng Vascular changes in nEuroimaging. All committee members were blinded to clinical information.

First, 5 cases were randomly chosen from the registered patients by the coordinating investigators of the National Cerebral and Cardiovascular Center, and brain MRI findings from these cases were assessed by the radiology committee in order to build a consensus about how to evaluate and describe the MRI findings of cerebral small vessel disease (SVD) (Table S3).

Next, 20 cases other than the above 5 cases used for consensus building were randomly selected to evaluate the reliability of MRI interpretation. For this purpose, the number of CMBs was categorized as 0, 1, 2, 3, 4, or ≥5; the grade of periventricular hyperintensity (PVH) as 0, 1, 2, or 3; the grade of deep and subcortical white matter hyperintensity (DSWMH) as 0, 1, 2, or 3; the number of BG-PVS as 0, 1–10, or ≥11; and the number of lacunes as 0, 1, 2, 3, 4, or ≥5.

Twelve members of the radiology committee other than the committee chair assessed brain MRIs of these 20 cases twice, 2 months apart, to evaluate intra-rater reliability. Between the first and second MRI sessions, patient identifiers were rewritten to reduce the bias of the first assessment with respect to the second MRI assessment. The gold standard of MRI findings for the 20 cases was then finalized after discussions by the radiology committee. Inter-rater reliability of MRI interpretations was evaluated between the MRI findings of each rater and the gold standards, using the kappa coefficient for the dichotomized findings and the weighted kappa coefficient for the ordinal findings.

Findings of MRA were evaluated for intracranial arterial stenosis at every participating site according to a standardized method: percent stenosis = [(1 – (D_{stenosis}/D_{normal})) × 100], where D_{stenosis} represents the diameter of the artery at the site of most severe stenosis, and D_{normal} represents the diameter of the proximal normal artery. If diameter of the proximal normal artery could not be measured, a distal normal artery was measured instead. For D_{stenosis}, measurements were performed from at least two directions. After assessing the intracranial internal carotid
artery, M1 and M2 segments of the middle cerebral artery, A1 and A2 segments of the anterior cerebral artery, intracranial vertebral artery, basilar artery, and P1 and P2 segments of the posterior cerebral artery, only the one lesion showing the most severe stenosis was selected. Using the most severe percent stenosis, the severity of intracranial arterial stenosis was classified into 4 grades: 1) normal or mild (<50%); 2) moderate (≥50%, but not severe stenosis); 3) severe (absence of blood flow signal at the stenotic lesion and presence of signal distal to the stenosis); and 4) occluded (absence of blood flow signals at both the stenotic lesion and the distal portion). When MRA findings were attributed to hypoplasia or aplasia, the finding was not diagnosed as stenosis or occlusion. Inter- and intra-rater reliabilities of MRA assessment were not evaluated.

**Supplemental Results**

The inter- and intra-rater reliabilities for diagnosing deep and lobar cerebral microbleeds, periventricular hyperintensity, deep and subcortical white matter hyperintensity, and enlarged basal ganglia perivascular space (BG-PVS) were determined to be good, as median values of kappa coefficient generally exceeded a cut-point of 0.6. Regarding inter-rater reliability for BG-PVS, the median kappa coefficient at the 1st session was below 0.6, but it improved to exceed 0.6 in the 2nd session. Kappa coefficients for lacunes were below 0.6 at both the 1st and 2nd sessions. The 12 MRI interpreters therefore received feedback on the diagnosis of lacunes based on the gold standard, and also conducted a 3rd session of MRI assessment for lacunes using 20 cases other than the cases used for the 1st and 2nd sessions. The median kappa coefficient for inter-rater reliability of the 3rd session of lacunes assessment was 0.75. Kappa coefficients and concordance rates for MRI findings are shown in detail in Table S4.
## Table S1. The participating sites

| Participating site                                      | Principal investigator | Number of enrolled patients |
|---------------------------------------------------------|------------------------|----------------------------|
| National Cerebral and Cardiovascular Center             | Kazunori Toyoda        | 1015                       |
| Nakamura Memorial Hospital                             | Kenji Kamiyama         | 831                        |
| Kawasaki Medical School Hospital                       | Yoshiki Yagita         | 294                        |
| Kyoto Second Red Cross Hospital                        | Yoshinari Nagakane     | 222                        |
| Tokyo Saiseikai Central Hospital                       | Haruhiko Hoshino       | 205                        |
| Japanese Red Cross Kumamoto Hospital                    | Tadashi Terasaki       | 188                        |
| National Hospital Organization Kyushu Medical Center    | Yasushi Okada          | 186                        |
| Saga University Hospital                                | Yusuke Yaksushiji      | 156                        |
| St. Marianna University School of Medicine Hospital     | Yasuhiro Hasegawa      | 145                        |
| Keio University Hospital                                | Shinichi Takahashi     | 142                        |
| St. Marianna University School of Medicine Toyoko Hospital | Toshihiro Ueda        | 136                        |
| Yamagata Prefectural Central Hospital                   | Hikaru Nagasawa        | 125                        |
| Kyushu Rosai Hospital                                  | Shoji Arihiro          | 122                        |
| Tokyo Metropolitan Geriatric Medical Center             | Naoki Saji             | 117                        |
| Jichi Medical University Hospital                      | Shigeru Fujimoto       | 114                        |
| Research Institute for Brain and Blood Vessels Akita    | Tatsuya Ishikawa       | 106                        |
| The Hospital of Hyogo College of Medicine              | Shinichi Yoshimura     | 104                        |
| National Hospital Organization Kagoshima Medical Center | Hideki Matsuoka        | 98                         |
| Yamagata City Hospital Saiseikan                       | Rei Kondo              | 98                         |
| National Hospital Organization Nagoya Medical Center    | Satoshi Okuda          | 97                         |
| Mihara Memorial Hospital                               | Takao Kanzawa          | 84                         |
| Gifu University Hospital                               | Toru Iwama             | 82                         |
| Kitasato University Hospital                           | Kazutoshi Nishiyama    | 66                         |
| University Hospital, Kyoto Prefectural University of Medicine | Toshiki Mizuno  | 60                         |
| Hirosaki Stroke and Rehabilitation Center              | Norifumi Metoki        | 58                         |
| Iwate Medical University Hospital                      | Kuniaki Ogasawara      | 54                         |
| Obihiro Kosei General Hospital                         | Masafumi Otaki         | 52                         |
| Nagasaki University Hospital                           | Akira Tsujino          | 46                         |
| Kumamoto University Graduate School                     | Makoto Nakajima        | 41                         |
| Kyorin University Hospital                             | Teruyuki Hirano        | 36                         |
| Iwate Prefectural Central Hospital                     | Ryosuke Doijiri        | 35                         |
| Hospital                                                      | Name               | Number |
|---------------------------------------------------------------|--------------------|--------|
| Japanese Red Cross Nagoya Daini Hospital                      | Keizo Yasui        | 34     |
| The Jikei University Hospital                                 | Yasuyuki Iguchi    | 31     |
| Hiroshima University Hospital                                 | Hirofumi Maruyama  | 30     |
| Konan Hospital                                                | Yukako Yazawa      | 26     |
| Kobe City Medical Center General Hospital                     | Nobuyuki Sakai     | 21     |
| Saiseikai Fukuoka General Hospital                           | Takeshi Yamada     | 18     |
| TOYOTA Memorial Hospital                                     | Yasuhiro Ito       | 18     |
| National Hospital Organization Osaka National Hospital        | Hiroshi Yamagami   | 16     |
| Steel Memorial Yawata Hospital                               | Shuji Arakawa      | 16     |
| Toho University Omori Medical Center                          | Yasuo Iwasaki      | 12     |
| Toranomon Hospital                                            | Yoshikazu Uesaka   | 12     |
| Juntendo University Hospital                                 | Hiroyuki Daida     | 10     |
| Tokushima University Hospital                                | Yasushi Takagi     | 7      |
| Nippon Medical School Hospital                                | Kazumi Kimura      | 5      |
| Hyogo Brain and Heart Center                                  | Toshiyuki Uehara   | 4      |
| National Hospital Organization Osaka Minami Medical Center    | Daisuke Takahashi  | 2      |
| St Luke’s International Hospital                             | Yasunari Niimi     | 1      |
| Sequence               | FOV (mm) | Thickness (mm) | Gap (mm) | Matrix       | TR (ms) | TE (ms) | TI (ms) |
|------------------------|----------|----------------|----------|--------------|---------|---------|---------|
| T1-weighted imaging    | Spin echo| 240            | ≈5       | 0–1          | 256 × 256 | 500     | 15      |
| T2-weighted imaging    | Fast spin echo | 240       | ≈5       | 0–1          | 256 × 256 | ≥2000   | 80–120   |
| FLAIR (1.5-T)          | Fast spin echo | 240       | ≈5       | 0–1          | 256 × 256 | ≥8000   | 100–140  | ≈2300 |
| FLAIR (3.0-T)          | Fast spin echo | 240       | ≈5       | 0–1          | 256 × 256 | ≥10000  | 95–125  | ≈2600 |
| T2*-weighted imaging † | Gradient echo | 240       | ≈5       | 0–1          | 256 × 192 | 900     | 20–40   |

† Flip angle was set at 15°. Susceptibility-weighted imaging can be used as an alternative.

Abbreviations: FLAIR, fluid-attenuated inversion recovery; FOV, field of view; MRI, magnetic resonance imaging; TE, echo time; TI, inversion time; TR, repetition time.
| Table S3. Methods for assessing and reporting MRI findings of cerebral small vessel disease |
|------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------------------|
| **Cerebral microbleed** | Small (2–10 mm) signal voids seen on T2*-weighted imaging that are not seen on T1-weighted, T2-weighted, or FLAIR images. Susceptibility-weighted imaging can also be used. | **MRI assessment** | **Reporting format** |
| **Lobar** | In the cortex and subcortex. | | Number: 0, 1, 2, 3, 4, or ≥5 |
| **Deep** | In brain regions other than the cortex/subcortex. Infratentorial microbleeds are coded as deep. | | Number: 0, 1, 2, 3, 4, or ≥5 |
| **Cortical superficial siderosis** | Well-defined, homogeneous hypointense curvilinear signal intensity on T2*-weighted imaging. Susceptibility-weighted imaging can also be used. | | Presence or absence |
| **White matter hyperintensity** | Hyperintense on T2-weighted imaging and can appear as iso- or hypointense on T1-weighted imaging. | | **Periventricular hyperintensity** | Surrounding ventricles. | Grade: 0, 1, 2, or 3 |
| **Deep and subcortical white matter hyperintensity** | In subcortical and deep white matter. | | Grade: 0, 1, 2, or 3 |
| **Enlarged basal ganglia perivascular space** | Small (<3 mm) delineated round structures with high signal on T2-weighted images and low signal on T1-weighted and FLAIR images in the caudate nucleus, lentiform nucleus, internal capsule, external capsule, thalamus, and insular cortex. Numbers refer to perivascular spaces on one side of the brain; the higher number was used if asymmetry was present between sides and perivascular spaces were counted in the slice with the highest number. In the presence of cerebral lesions, perivascular spaces were counted in the contralateral hemisphere. | | Number: 0, 1–10, or ≥11 |
| **Lacune** | Round or ovoid, subcortical fluid-filled cavity of 3–15 mm in diameter. Generally have a central CSF-like hypointensity with a surrounding rim of hyperintensity on FLAIR images. The number was counted regardless of whether lacunes were above or below the tentorium cerebelli. | | Number: 0, 1, 2, 3, 4, or ≥5 |
| **Non-lacunar infarct** | Infarct of >15 mm in diameter was coded as non-lacunar infarct. | | Presence or absence |

Abbreviations: CSF, cerebrospinal fluid; FLAIR, fluid-attenuated inversion recovery; MRI: magnetic resonance imaging.
Table S4. Kappa coefficients and concordance rates for MRI findings by the 12 interpreters

|                | 1st session vs. Gold standard | 2nd session vs. Gold standard | 1st session vs. 2nd session | 3rd session vs. Gold standard |
|----------------|-----------------------------|-------------------------------|-----------------------------|-------------------------------|
|                | Kappa coefficient | Concordance rate, % | Kappa coefficient | Concordance rate, % | Kappa coefficient | Concordance rate, % | Kappa coefficient | Concordance rate, % |
| **CMB, deep** |                |                            |                            |                             |                            |                            |                            |                            |
| 0, 1, 2, 3, 4, ≥5 | 0.89 [0.73, 0.97]  | 98 [95, 99]               | 0.87 [0.72, 0.97]  | 97 [94, 99]              | 0.92 [0.80, 0.97]  | 98 [97, 99]               | --                       | --                       |
| 0, 1, 2–4, ≥5   | 0.91 [0.73, 0.96]  | 98 [95, 99]               | 0.85 [0.72, 0.97]  | 96 [94, 99]              | 0.93 [0.80, 0.97]  | 99 [96, 99]               | --                       | --                       |
| **CMB, lobar**  |                |                            |                            |                             |                            |                            |                            |                            |
| 0, 1, 2, 3, 4, ≥5 | 0.88 [0.84, 0.94]  | 97 [96, 99]               | 0.86 [0.74, 0.96]  | 97 [94, 99]              | 0.94 [0.82, 0.97]  | 98 [97, 99]               | --                       | --                       |
| 0, 1, 2–4, ≥5   | 0.89 [0.83, 0.94]  | 97 [96, 98]               | 0.87 [0.78, 0.96]  | 97 [95, 99]              | 0.93 [0.84, 0.98]  | 99 [96, 99]               | --                       | --                       |
| **cSS**         |                |                            |                            |                             |                            |                            |                            |                            |
| +/-             | --              | 100 [93, 100]             | --                          | 100 [95, 100]             | --                          | 100 [95, 100]             | --                       | --                       |
| **PVH grade**   |                |                            |                            |                             |                            |                            |                            |                            |
| 0, 1, 2, 3      | 0.73 [0.64, 0.82]  | 93 [90, 96]               | 0.68 [0.57, 0.86]  | 93 [88, 97]              | 0.72 [0.66, 0.83]  | 96 [93, 97]               | --                       | --                       |
| **DSWMH grade** |                |                            |                            |                             |                            |                            |                            |                            |
| 0, 1, 2, 3      | 0.72 [0.67, 0.82]  | 94 [91, 95]               | 0.75 [0.63, 0.81]  | 91 [89, 96]              | 0.70 [0.62, 0.84]  | 93 [91, 96]               | --                       | --                       |
| **BG-PVS**      |                |                            |                            |                             |                            |                            |                            |                            |
| 0, 1–10, ≥11    | 0.57 [0.39, 0.77]  | 86 [83, 93]               | 0.61 [0.52, 0.81]  | 89 [80, 94]              | 0.65 [0.26, 0.77]  | 91 [81, 96]               | --                       | --                       |
| **Lacune**      |                |                            |                            |                             |                            |                            |                            |                            |
| 0, 1, 2, 3, 4, ≥5 | 0.43 [0.32, 0.51]  | 86 [85, 88]               | 0.39 [0.26, 0.49]  | 86 [83, 89]              | 0.66 [0.47, 0.79]  | 96 [89, 97]               | 0.75 [0.65, 0.98]  | 95 [91, 99]              |
| +/-             | 0.29 [0.20, 0.43]  | 68 [63, 75]               | 0.30 [0.13, 0.39]  | 65 [55, 68]              | 0.47 [0.24, 0.55]  | 75 [65, 80]               | 0.54 [0.28, 0.80]  | 85 [75, 93]              |
| **Non-lacunar infarct** |            |                            |                            |                             |                            |                            |                            |                            |
| +/-             | --              | --                        | --                          | --                          | --                          | --                          | 0.55 [0.43, 0.63]  | 83 [80, 85]              |

Median [25th percentile, 75th percentile].

Abbreviations: BG-PVS, enlarged basal ganglia perivascular space; CMB, cerebral microbleed; cSS, cortical superficial siderosis; DSWMH, deep and subcortical white matter hyperintensity; MRI, magnetic resonance imaging; PVH, periventricular hyperintensity.
|                          | CMBs (-) (n=3445) | CMBs (+) (n=1671) | P value | Confluent WMH (-) (n=2491) | Confluent WMH (+) (n=2681) | P value |
|--------------------------|-------------------|-------------------|---------|-----------------------------|-----------------------------|---------|
| Age, years               | 72.0 [64.0, 78.0] | 74.0 [67.0, 80.0] | <0.001  | 69.0 [60.0, 76.0]           | 76.0 [69.0, 81.0]           | <0.001  |
| Female                   | 1137 (33.0%)      | 544 (32.6%)       | 0.75    | 728 (29.2%)                 | 978 (36.5%)                 | <0.001  |
| Height, cm               | 163.0 [155.0, 168.0] | 161.0 [154.0, 167.0] | <0.001  | 164.0 [157.0, 169.0]        | 160.0 [153.0, 167.0]        | <0.001  |
| Weight, kg               | 61.0 [54.0, 69.0] | 60.0 [53.0, 68.0] | <0.001  | 63.0 [55.0, 70.0]           | 59.0 [52.0, 66.0]           | <0.001  |
| Body mass index, kg/m²   | 23.3 [21.2, 25.6] | 23.1 [21.2, 25.4] | 0.18    | 23.4 [21.4, 25.8]           | 23.1 [21.0, 25.3]           | <0.001  |
| Systolic blood pressure, mmHg | 134.0 [122.0, 148.0] | 135.0 [122.0, 149.0] | 0.087   | 133.0 [120.0, 146.0]        | 135.0 [123.0, 150.0]        | <0.001  |
| Diastolic blood pressure, mmHg | 77.0 [69.0, 86.0] | 78.0 [68.0, 86.0] | 1.00    | 78.0 [69.0, 86.0]           | 77.0 [68.0, 86.0]           | 0.093   |
| Pulse rate, beats/min    | 75.0 [66.0, 84.0] | 75.0 [66.0, 84.0] | 0.83    | 74.0 [65.0, 83.0]           | 75.0 [66.0, 85.0]           | 0.002   |
| Modified Rankin Scale score of 0–2 | 3098 (90.4%) | 1399 (84.0%)       | <0.001  | 2300 (92.7%)                | 2225 (83.4%)                | <0.001  |
| **Risk factors**         |                   |                   |         |                             |                             |         |
| Hypertension             | 2635 (76.5%)      | 1414 (84.7%)      | <0.001  | 1810 (72.7%)                | 2281 (85.1%)                | <0.001  |
| Diabetes mellitus        | 971 (28.2%)       | 462 (27.7%)       | 0.71    | 686 (27.5%)                 | 757 (28.3%)                 | 0.57    |
| Dyslipidemia             | 2260 (65.6%)      | 1046 (62.6%)      | 0.036   | 1628 (65.4%)                | 1724 (64.3%)                | 0.43    |
| Current smoking          | 520 (15.1%)       | 236 (14.1%)       | 0.35    | 424 (17.0%)                 | 338 (12.6%)                 | <0.001  |
| Current drinking (≥8 units/week) | 1063 (31.0%) | 495 (29.7%)       | 0.35    | 870 (35.0%)                 | 707 (26.5%)                 | <0.001  |
| Habitual use of NSAIDs   | 97 (2.8%)         | 40 (2.4%)         | 0.38    | 69 (2.8%)                   | 70 (2.6%)                   | 0.73    |
| **Comorbidities**        |                   |                   |         |                             |                             |         |
| Ischemic stroke or TIA   | 3077 (89.3%)      | 1521 (91.0%)      | 0.058   | 2205 (88.5%)                | 2442 (91.1%)                | 0.002   |
| Intracerebral hemorrhage | 41 (1.2%)         | 73 (4.4%)         | <0.001  | 27 (1.1%)                   | 87 (3.2%)                   | <0.001  |
| Subarachnoid hemorrhage  | 11 (0.3%)         | 13 (0.8%)         | 0.024   | 7 (0.3%)                    | 20 (0.7%)                   | 0.020   |
| Asymptomatic cerebrovascular disease | 289 (8.4%) | 89 (5.3%)         | <0.001  | 190 (7.6%)                  | 196 (7.3%)                  | 0.66    |
| Atrial fibrillation      | 681 (19.8%)       | 366 (21.9%)       | 0.074   | 497 (20.0%)                 | 547 (20.4%)                 | 0.68    |
| Acute coronary syndrome  | 229 (6.6%)        | 137 (8.2%)        | 0.043   | 137 (5.5%)                  | 238 (8.9%)                  | <0.001  |
| Congestive heart failure | 122 (3.5%)        | 85 (5.1%)         | 0.008   | 72 (2.9%)                   | 132 (4.9%)                  | <0.001  |
| Condition                              | N (%) or median [25th percentile, 75th percentile] | p-value | N (%) or median [25th percentile, 75th percentile] | p-value |
|----------------------------------------|--------------------------------------------------|---------|--------------------------------------------------|---------|
| Peripheral artery disease              | 75 (2.2%) [46 (2.8%)]                            | 0.020   | 50 (2.0%) [71 (2.6%)]                            | 0.13    |
| Deep venous thrombosis                 | 57 (1.7%) [35 (2.1%)]                            | 0.27    | 41 (1.6%) [53 (2.0%)]                            | 0.37    |
| Active malignancy                      | 76 (2.2%) [28 (1.7%)]                            | 0.21    | 38 (1.5%) [65 (2.4%)]                            | 0.021   |
| Liver disease                          | 40 (1.2%) [11 (0.7%)]                            | 0.090   | 24 (1.0%) [30 (1.1%)]                            | 0.58    |
| Chronic obstructive pulmonary disease  | 55 (1.6%) [33 (2.0%)]                            | 0.33    | 37 (1.5%) [52 (1.9%)]                            | 0.21    |
| Dementia requiring support             | 77 (2.2%) [82 (4.9%)]                            | <0.001  | 37 (1.5%) [130 (4.9%)]                           | <0.001  |
| eGFR *, mL/min/1.73 m^2                | 65.3 [54.6, 76.9] 62.4 [51.5, 73.5]             | <0.001  | 66.8 [56.2, 78.0] 62.2 [50.6, 73.5]              | <0.001  |
| eGFR categories, mL/min/1.73 m^2       | <0.001                                           |         | <0.001                                           |         |
| G1, ≥90                                | 291 (8.5%) [97 (5.9%)]                           |         | 235 (9.5%) [166 (6.2%)]                          |         |
| G2, 60--<90                            | 1872 (54.7%) [819 (49.4%)]                      |         | 1417 (57.3%) [1292 (48.5%)]                      |         |
| G3a, 45--<60                           | 861 (25.2%) [487 (29.4%)]                       |         | 597 (24.2%) [775 (29.1%)]                        |         |
| G3b, 30--<45                           | 291 (8.5%) [185 (11.2%)]                        |         | 179 (7.2%) [296 (11.1%)]                         |         |
| G4, 15--<30                            | 66 (1.9%) [45 (2.7%)]                           |         | 28 (1.1%) [83 (3.1%)]                           |         |
| G5, <15                                | 40 (1.2%) [25 (1.5%)]                           |         | 16 (0.6%) [52 (2.0%)]                           |         |
| ACR †, mg/g                            | 15.6 [6.4, 46.3] (n=2122)                        | <0.001  | 12.1 [5.8, 36.7] (n=1500)                        | <0.001  |
| ACR categories, mg/g                   | <0.001                                           |         | <0.001                                           |         |
| A1, <30                                | 1396 (65.8%) [551 (56.7%)]                      |         | 1060 (70.7%) [908 (56.2%)]                       |         |
| A2, 30--<300                           | 588 (27.7%) [328 (33.8%)]                       |         | 349 (23.3%) [569 (35.2%)]                        |         |
| A3, ≥300                               | 138 (6.5%) [92 (9.5%)]                           |         | 91 (6.1%) [138 (8.5%)]                           |         |

N (%) or median [25th percentile, 75th percentile].

*eGFR is estimated as follows: eGFR = 194 × serum creatinine^{-1.094} × age^{-0.287} [× 0.739 if female].
† Data for albuminuria are unavailable in 2182 patients.

Abbreviations: ACR, urinary albumin-to-creatinine ratio; CMBs, cerebral microbleeds; eGFR, estimated glomerular filtration rate; NSAIDS, non-steroidal anti-inflammatory drugs; TIA, transient ischemic attack; WMH, white matter hyperintensity.
Table S6. Patient characteristics, extensive basal ganglia perivascular spaces, and lacunes

|                        | Extensive BG-PVS (-) (n=3137) | Extensive BG-PVS (+) (n=1998) | P value | Lacune (-) (n=2129) | Lacune (+) (n=3118) | P value |
|------------------------|-------------------------------|--------------------------------|---------|----------------------|----------------------|---------|
| Age, years             | 70.0 [62.0, 77.0]             | 76.0 [69.0, 81.0]               | <0.001  | 71.0 [63.0, 78.0]    | 73.0 [66.0, 80.0]    | <0.001  |
| Female                 | 1061 (33.8%)                  | 627 (31.4%)                    | 0.069   | 749 (35.2%)          | 977 (31.3%)          | 0.004   |
| Height, cm             | 163.0 [155.0, 169.0]          | 162.0 [154.0, 167.0]           | <0.001  | 163.0 [155.0, 169.0] | 162.0 [155.0, 167.0] | 0.005   |
| Weight, kg             | 62.0 [54.0, 70.0]             | 60.0 [53.0, 68.0]              | <0.001  | 62.0 [53.0, 69.0]    | 61.0 [53.0, 68.0]    | 0.14    |
| Body mass index, kg/m² | 23.3 [21.2, 25.7]             | 23.2 [21.3, 25.4]              | 0.17    | 23.2 [21.3, 25.5]    | 23.2 [21.2, 25.5]    | 0.90    |
| Systolic blood pressure, mmHg | 133.0 [121.0, 147.0] | 135.0 [123.0, 149.0] | <0.001  | 133.0 [120.0, 147.0] | 134.5 [123.0, 148.0] | <0.001  |
| Diastolic blood pressure, mmHg | 77.0 [68.0, 86.0] | 77.0 [69.0, 86.0]              | 0.50    | 77.0 [68.0, 86.0]    | 77.0 [69.0, 86.0]    | 0.64    |
| Pulse rate, beats/min  | 75.0 [66.0, 84.0]             | 75.0 [66.0, 84.0]              | 0.23    | 74.0 [65.0, 84.0]    | 75.0 [66.0, 84.0]    | 0.005   |
| Modified Rankin Scale score of 0–2 | 2812 (90.0%) | 1701 (85.5%)                  | <0.001  | 1909 (89.9%)         | 2695 (86.9%)         | 0.001   |

**Risk factors**

|                        |                  |                  |         |                     |                     |         |
|------------------------|------------------|------------------|---------|---------------------|---------------------|---------|
| Hypertension           | 2369 (75.6%)     | 1690 (84.6%)     | <0.001  | 1551 (72.9%)        | 2596 (83.3%)        | <0.001  |
| Diabetes mellitus      | 869 (27.7%)      | 567 (28.4%)      | 0.61    | 515 (24.2%)         | 951 (30.5%)         | <0.001  |
| Dyslipidemia           | 2057 (65.6%)     | 1284 (64.3%)     | 0.32    | 1362 (64.0%)        | 2046 (65.6%)        | 0.22    |
| Current smoking        | 497 (15.9%)      | 245 (12.3%)      | <0.001  | 277 (13.0%)         | 498 (16.0%)         | 0.003   |
| Current drinking (≥8 units/week) | 993 (31.7%) | 570 (28.6%)      | 0.019   | 656 (30.9%)         | 942 (30.3%)         | 0.67    |
| Habitual use of NSAIDs | 83 (2.6%)        | 60 (3.0%)        | 0.45    | 50 (2.3%)           | 95 (3.0%)           | 0.13    |

**Comorbidities**

|                        |                  |                  |         |                     |                     |         |
|------------------------|------------------|------------------|---------|---------------------|---------------------|---------|
| Ischemic stroke or TIA | 2798 (89.2%)     | 1822 (91.2%)     | 0.020   | 1812 (85.1%)        | 2910 (93.3%)        | <0.001  |
| Intracerebral hemorrhage | 41 (1.3%)      | 72 (3.6%)        | <0.001  | 31 (1.5%)           | 82 (2.6%)           | 0.004   |
| Subarachnoid hemorrhage | 14 (0.4%)       | 10 (0.5%)        | 0.78    | 7 (0.3%)            | 20 (0.6%)           | 0.12    |
| Asymptomatic cerebrovascular disease | 264 (8.4%) | 117 (5.9%)       | <0.001  | 202 (9.5%)          | 185 (5.9%)          | <0.001  |
| Atrial fibrillation    | 635 (20.2%)     | 392 (19.6%)      | 0.58    | 527 (24.8%)         | 525 (16.8%)         | <0.001  |
| Acute coronary syndrome | 210 (6.7%)      | 157 (7.9%)       | 0.11    | 135 (6.3%)          | 241 (7.7%)          | 0.056   |
| Congestive heart failure | 123 (3.9%)     | 77 (3.9%)        | 0.90    | 98 (4.6%)           | 106 (3.4%)          | 0.027   |
| Condition                                      | Group 1 | Group 2 | p-value | Group 3 | Group 4 | p-value |
|-----------------------------------------------|---------|---------|---------|---------|---------|---------|
| Peripheral artery disease                     | 73 (2.3%) | 48 (2.4%) | 0.86 | 41 (1.9%) | 81 (2.6%) | 0.11 |
| Deep venous thrombosis                        | 55 (1.8%) | 34 (1.7%) | 0.89 | 47 (2.2%) | 48 (1.5%) | 0.074 |
| Active malignancy                              | 56 (1.8%) | 48 (2.4%) | 0.13 | 35 (1.6%) | 70 (2.2%) | 0.13 |
| Liver disease                                  | 32 (1.0%) | 21 (1.1%) | 0.92 | 21 (1.0%) | 32 (1.0%) | 0.89 |
| Chronic obstructive pulmonary disease          | 55 (1.8%) | 34 (1.7%) | 0.89 | 30 (1.4%) | 59 (1.9%) | 0.18 |
| Dementia requiring support                    | 67 (2.1%) | 88 (4.4%) | <0.001 | 52 (2.4%) | 111 (3.6%) | 0.022 |
| eGFR *, mL/min/1.73 m²                         | 65.9 [54.7, 77.2] | 62.5 [51.5, 73.7] | <0.001 | 65.4 [55.2, 76.8] | 63.6 [52.1, 75.1] | <0.001 |
| eGFR categories, mL/min/1.73 m²               |         |         | <0.001 |         |         | <0.001 |
| G1, ≥90                                       | 281 (9.0%) | 111 (5.6%) |         | 171 (8.1%) | 233 (7.5%) |         |
| G2, 60–<90                                    | 1712 (55.0%) | 985 (49.7%) |         | 1185 (56.2%) | 1570 (50.7%) |         |
| G3a, 45–<60                                   | 772 (24.8%) | 591 (29.8%) |         | 536 (25.4%) | 855 (27.6%) |         |
| G3b, 30–<45                                   | 264 (8.5%) | 202 (10.2%) |         | 172 (8.2%) | 308 (9.9%) |         |
| G4, 15–<30                                    | 52 (1.7%) | 58 (2.9%) |         | 32 (1.5%) | 80 (2.6%) |         |
| G5, <15                                       | 32 (1.0%) | 33 (1.7%) |         | 13 (0.6%) | 52 (1.7%) |         |
| ACR †, mg/g                                   | 14.4 [6.1, 46.0] (n=1908) | 21.2 [8.6, 65.6] (n=1178) | <0.001 | 15.0 [6.1, 44.0] (n=1273) | 18.8 [7.7, 57.8] (n=1849) | <0.001 |
| ACR categories, mg/g                          |         |         | <0.001 |         |         | 0.019 |
| A1, <30                                       | 1264 (66.2%) | 690 (58.6%) |         | 837 (65.8%) | 1134 (61.3%) |         |
| A2, 30–<300                                   | 514 (26.9%) | 392 (33.3%) |         | 357 (28.0%) | 563 (30.4%) |         |
| A3, ≥300                                      | 130 (6.8%) | 96 (8.1%) |         | 79 (6.2%) | 152 (8.2%) |         |

N (%) or median [25th percentile, 75th percentile].

* eGFR is estimated as follows: eGFR = 194 × serum creatinine^{-1.094} × age^{-0.287} × [× 0.739 if female].

† Data for albuminuria are unavailable in 2182 patients.

Abbreviations: ACR, urinary albumin-to-creatinine ratio; BG-PVS, basal ganglia perivascular spaces; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NSAIDS, non-steroidal anti-inflammatory drugs; TIA, transient ischemic attack.
Table S7. Characteristics in patients with and without data for urinary albumin-to-creatinine ratio

|                         | ACR data (–) (n=2182) | ACR data (+) (n=3142) | P value |
|-------------------------|------------------------|------------------------|---------|
| Age, years              | 72.0 [65.0, 79.0]      | 73.0 [66.0, 79.0]      | 0.037   |
| Female                  | 735 (33.7%)            | 1027 (32.7%)           | 0.45    |
| Height, cm              | 162.0 [155.0, 168.0]   | 162.0 [155.0, 168.0]   | 0.51    |
| Weight, kg              | 61.0 [53.0, 69.0]      | 61.0 [53.0, 69.0]      | 0.69    |
| Body mass index, kg/m²  | 23.2 [21.1, 25.4]      | 23.2 [21.2, 25.6]      | 0.25    |
| Systolic blood pressure, mmHg | 134.0 [122.0, 148.0] | 134.0 [122.0, 148.0] | 0.25 |
| Diastolic blood pressure, mmHg | 77.0 [69.0, 86.0] | 77.0 [68.0, 86.0] | 0.084 |
| Pulse rate, beats/min   | 74.0 [66.0, 84.0]      | 75.0 [66.0, 84.0]      | 0.41    |
| Modified Rankin Scale score of 0–2 | 1896 (87.1%) | 2770 (88.6%) | 0.096 |

**Risk factors**

- Hypertension: 1674 (76.8%) vs. 2529 (80.5%), <0.001
- Diabetes mellitus: 555 (25.4%) vs. 928 (29.5%), 0.001
- Dyslipidemia: 1406 (64.5%) vs. 2047 (65.2%), 0.60
- Current smoking: 329 (15.1%) vs. 452 (14.4%), 0.50
- Current drinking (≥8 units/week): 686 (31.5%) vs. 929 (29.7%), 0.15

**Comorbidities**

- Ischemic stroke or TIA: 2031 (93.1%) vs. 2766 (88.0%), <0.001
- Intracerebral hemorrhage: 41 (1.9%) vs. 76 (2.4%), 0.19
- Subarachnoid hemorrhage: 15 (0.7%) vs. 12 (0.4%), 0.12
- Asymptomatic cerebrovascular disease: 137 (6.3%) vs. 253 (8.1%), 0.015
- Atrial fibrillation: 365 (16.7%) vs. 705 (22.4%), <0.001
- Acute coronary syndrome: 135 (6.2%) vs. 242 (7.7%), 0.034
- Congestive heart failure: 80 (3.7%) vs. 128 (4.1%), 0.45
- Peripheral artery disease: 49 (2.2%) vs. 74 (2.4%), 0.79
- Deep venous thrombosis: 35 (1.6%) vs. 60 (1.9%), 0.41
- Active malignancy: 46 (2.1%) vs. 60 (1.9%), 0.61
- Liver disease: 12 (0.6%) vs. 42 (1.3%), 0.005
- Chronic obstructive pulmonary disease: 32 (1.5%) vs. 58 (1.8%), 0.29
- Dementia requiring support: 78 (3.6%) vs. 92 (2.9%), 0.18
- eGFR *, mL/min/1.73 m² | 64.8 [54.4, 75.8] | 64.1 [52.9, 75.6] | 0.14 |
| eGFR categories, mL/min/1.73 m² |                      |                     | <0.001 |
| G1, ≥90                  | 179 (8.4%)            | 232 (7.4%)           |         |
N (%) or median [25th percentile, 75th percentile].

* eGFR is estimated as follows: $eGFR = 194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ if female.\(^{22}\)

Abbreviations: ACR, urinary albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; IQR, interquartile range; TIA, transient ischemic attack.
Table S8. Oral antithrombotic medication at baseline

| Combination                        | Total SVD score ≤2 (n=3707) | Total SVD score ≥3 (n=1617) | P value |
|-----------------------------------|-----------------------------|-----------------------------|---------|
| Antiplatelet agents alone         | 2561 (69.1%)                | 1178 (72.9%)                | 0.006   |
| Dual antiplatelet agents          | 381 (10.3%)                 | 200 (12.4%)                 | 0.024   |
| Anticoagulants alone              | 970 (26.2%)                 | 347 (21.5%)                 | <0.001  |
| Both antiplatelet agents and anticoagulants | 176 (4.7%)             | 91 (5.6%)                   | 0.18    |
| Dual antiplatelet agents plus anticoagulants | 14 (0.4%)              | 6 (0.4%)                    | 0.97    |
| Major antiplatelet agents         |                            |                             |         |
| Aspirin                           | 1190 (32.1%)                | 507 (31.4%)                 | 0.59    |
| Clopidogrel                       | 1383 (37.3%)                | 642 (39.7%)                 | 0.098   |
| Cilostazol                        | 495 (13.4%)                 | 292 (18.1%)                 | <0.001  |
| Anticoagulant agents              |                            |                             |         |
| Warfarin                          | 400 (10.8%)                 | 156 (9.6%)                  | 0.21    |
| Dabigatran                        | 115 (3.1%)                  | 32 (2.0%)                   | 0.024   |
| Rivaroxaban                       | 148 (4.0%)                  | 48 (3.0%)                   | 0.021   |
| Apixaban                          | 312 (8.4%)                  | 127 (7.9%)                  | 0.068   |
| Edoxaban                          | 172 (4.6%)                  | 77 (4.8%)                   | 0.49    |

Abbreviations: SVD, small vessel disease.
Confluent WMH is diagnosed as present when PVH grade is 3 or DSWMH grade is 2–3. Extensive BG-PVS is defined as number of BG-PVS ≥11. For patients in whom one SVD feature is missing, 0 point is awarded for that SVD feature.

Abbreviations: BG-PVS, enlarged basal ganglia perivascular spaces; CMBs, cerebral microbleeds; DSWMH, deep and subcortical white matter hyperintensity; PVH: periventricular hyperintensity; SVD, small vessel disease; WMH, white matter hyperintensity.
Figure S2. Distribution of SVD score by timing of MRI acquisition

Abbreviations: MRI, magnetic resonance imaging; SVD, small vessel disease
Figure S3. MRI markers for cerebral small vessel disease

Abbreviations: BG-PVS, enlarged basal ganglia perivascular spaces; CMB, cerebral microbleed; MRI, magnetic resonance imaging; PVH, periventricular hyperintensity; DSWMH, deep and subcortical white matter hyperintensity.
Figure S4. Composition of small vessel disease markers in the different small vessel disease scores

Data from patients with SVD score 0 and SVD score 4 are not shown because none and all SVD markers, respectively, were present in all patients with these scores.

Abbreviations: BG-PVS, enlarged basal ganglia perivascular spaces; CMBs, cerebral microbleeds; SVD, small vessel disease; WMH, white matter hyperintensity.
Spearman’s correlation coefficients between MRI findings are shown. Intracranial arterial stenosis is handled as categorical data of normal/mild, moderate, severe, and occluded. Only a weak correlation is seen between MRI SVD markers (Spearman’s rho, 0.17–0.35), except for the relatively strong correlation between deep and lobar CMBs (Spearman’s rho=0.41), and between PVH grade and DSWMH grade (Spearman’s rho=0.78). Non-lacunar infarcts and degrees of intracranial arterial stenosis do not show any correlations with other MRI findings.

Abbreviations: BG-PVS, enlarged basal ganglia perivascular spaces; CMB, cerebral microbleed; cSS, cortical superficial siderosis; DSWMH, deep and subcortical white matter hyperintensity; MRI, magnetic resonance imaging; PVH, periventricular hyperintensity.
Figure S6. Chronic kidney disease measures and small vessel disease score increment stratified by age

A. eGFR (mL/min/1.73m²) by age for SVD score increment (OR, 95% CI)

| Age ≤74 years (n=3015) | Age ≥75 years (n=2265) |
|------------------------|------------------------|
| (Reference) G1, ≥90    | 1                      |
| G2, 60–90              | 1.04                   |
| G3a, 45–60             | 1.25                   |
| G3b, 30–<45            | 1.54                   |
| G4, 15–<30             | 2.33                   |
| G5, <15                | 2.75                   |

P for interaction between age and eGFR was 0.62 in Model 1 and 0.77 in Model 2.

B. ACR (mg/g) by age for SVD score increment (OR, 95% CI)

| Age ≤74 years (n=1765) | Age ≥75 years (n=1377) |
|------------------------|------------------------|
| (Reference) A1, <30    | 1                      |
| A2, 30–<300            | 1.43                   |
| A3, ≥300               | 1.87                   |

P for interaction between age and ACR was 0.45 in Model 1 and 0.40 in Model 2.

Abbreviations: ACR, urinary albumin-to-creatinine ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; SVD, small vessel disease.
Figure S7. Chronic kidney disease measures and small vessel disease score increment stratified by hypertension

Ordinal logistic regression models. Adjusting covariates are age categories and sex for Model 1 (blue rectangles) and age categories, sex, hypertension, diabetes mellitus, dyslipidemia, current smoking, drinking and eGFR categories for Model 2 (red rectangles). $P$ for interaction between hypertension and eGFR was 0.46 in Model 1 and 0.46 in Model 2. $P$ for interaction between hypertension and ACR was 0.13 in Model 1 and 0.11 in Model 2.

Abbreviations: ACR, urinary albumin-to-creatinine ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; SVD, small vessel disease.
Figure S8. Multivariable models for cerebral SVD burden within subgroup with MRI acquired at or after registration

Adjusting covariates are age categories and sex for Model 1 (blue rectangles) and age categories, sex, hypertension, diabetes mellitus, dyslipidemia, current smoking, drinking and eGFR categories for Model 2 (red rectangles).

Abbreviations: ACR, urinary albumin-to-creatinine ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; MRI, magnetic resonance imaging; OR, odds ratio; SVD, small vessel disease.