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ORIGINAL RESEARCH

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 m^2), 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 m^2) and 2.05 (95% CI, 1.33–3.16) at G5 (eGFR <15 mL/min per 1.73 m^2). 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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CLINICAL PERSPECTIVE

What Is New?

- The BAT (Bleeding with Antithrombotic Therapy) 2 study aims to provide a precise risk model for antithrombotic-associated bleeding, taking the cerebral small vessel disease burden into account, and multimodal brain magnetic resonance imaging was acquired at baseline for all patients under prespecified imaging conditions.
- BAT2 also collected data of estimated glomerular filtration rate as well as albuminuria.
- The objective of this study was to determine the associations of cerebral small vessel disease burden with renal dysfunction and albuminuria in patients who newly started or continued taking oral antithrombotic agents, using the baseline data from BAT2.

What Are the Clinical Implications?

- Albuminuria and reduced estimated glomerular filtration rate were independently associated with increased cerebral small vessel disease 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 small vessel disease and other biomarkers, including the chronic kidney disease measures.

Nonstandard Abbreviations and Acronyms

ACR	urinary albumin-to-creatinine ratio
BAT2	Bleeding with Antithrombotic Therapy
BG-PVS	enlarged basal ganglia perivascular spaces
CMB	cerebral microbleed
SVD	small vessel disease
WMH	white matter hyperintensity

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, and in particular the stronger association with 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 antiplatelets 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 m^2) 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 commissure-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 χ^2 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 m^2), 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

	Total (n=5324)	Total SVD score ≤2 (n=3707)	Total SVD score ≥3 (n=1617)	*P* value
Age, y	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/m^2	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
Modified Rankin Scale score of 0–2	4666 (88.0)	3340 (90.5)	1326 (82.4)	<0.001
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 (6.3)	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)	62 (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 m^2	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 m^2				<0.001
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	68 (1.3)	36 (1.0)	32 (2.0)	
ACR †, mg/g	17.0 (7.0, 51.7) (n=3142)	14.5 (6.1, 45.0) (n=2180)	23.0 (9.9, 78.7) (n=962)	<0.001
ACR categories, mg/g				<0.001
A1, <30	1985 (63.2)	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].[23]
†Data for albuminuria are unavailable in 2182 patients.

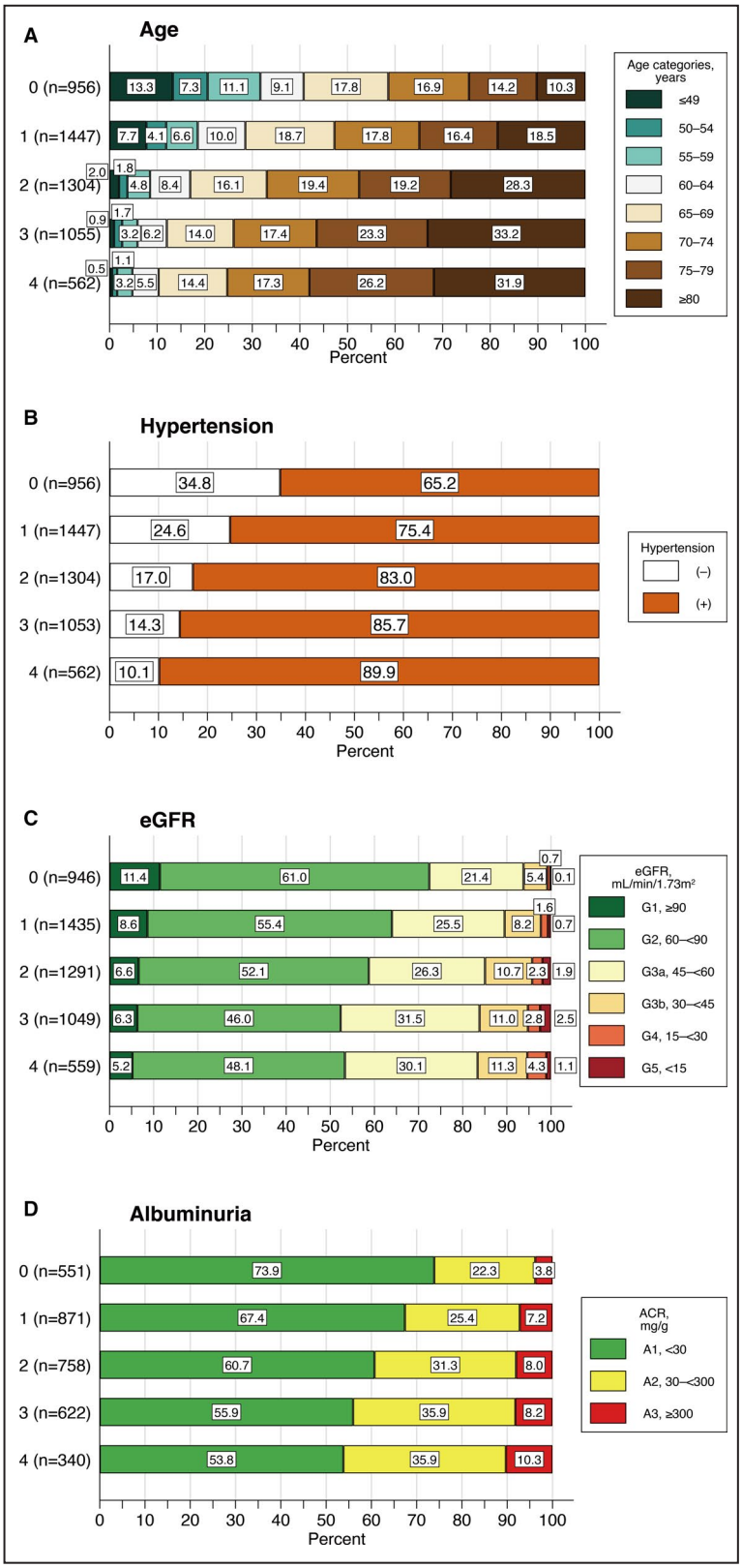

Figure 1. Age (A), hypertension (B), estimated glomerular filtration rate (C), and albuminuria (D) by total SVD score.
ACR indicates urinary albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; and SVD, small vessel disease.

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 m^2, and ACR was grouped into <30 and ≥30 mg/g. The distribution of ORs calculated in the multivariable analyses showed

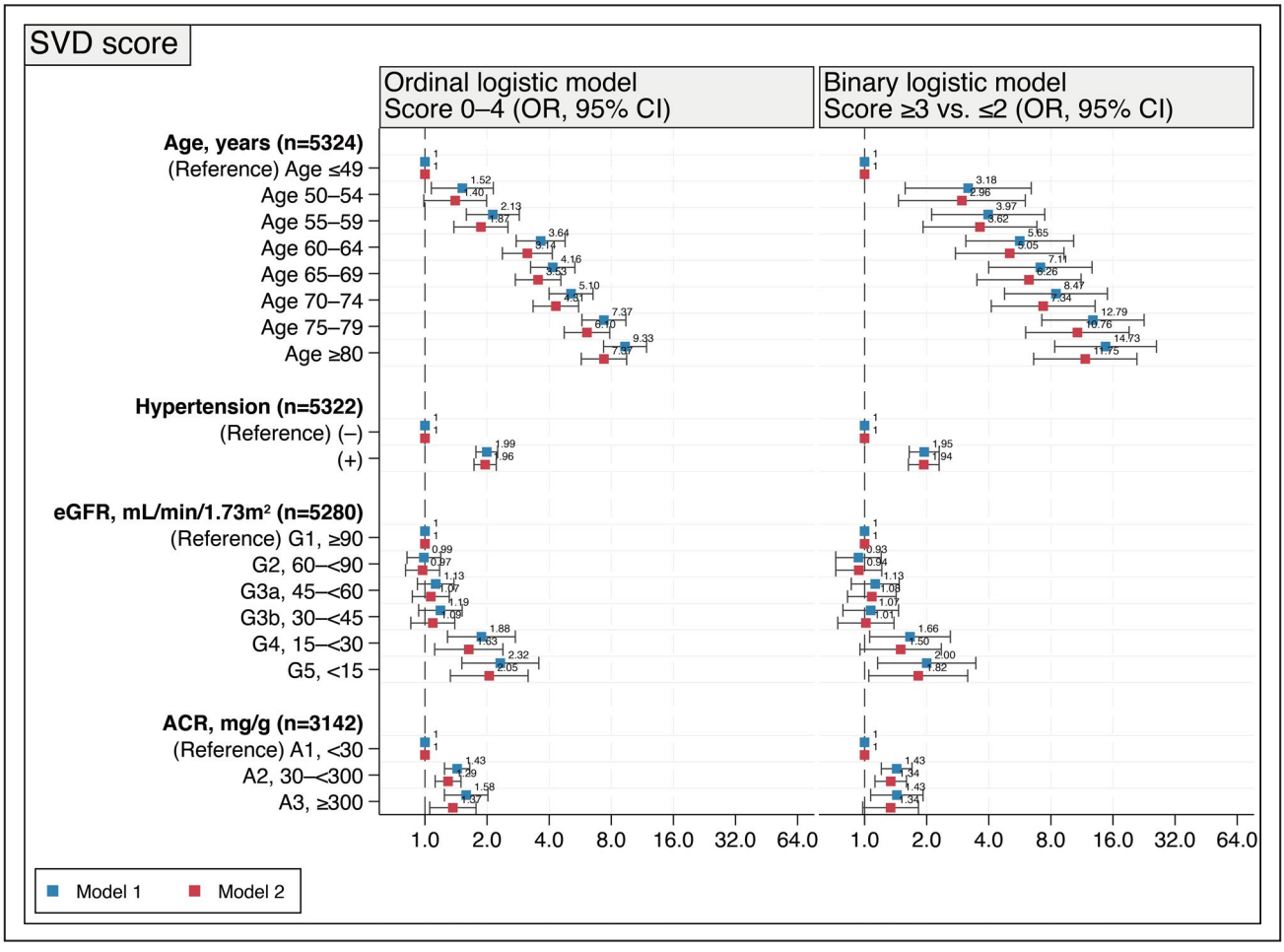

Figure 2. Multivariable models of risk factors for cerebral SVD burden.
Plots showing odds ratios (ORs) and 95% CIs from multivariable models. Adjusting covariates are age categories and sex for Model 1 and age categories, sex, hypertension, diabetes, dyslipidemia, current smoking, drinking, and eGFR categories for Model 2. ACR indicates urinary albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; and SVD, small vessel disease.

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 m^2)	≥60	1 (Reference)	Model 1 1.57 (1.31–1.88), *P*<0.001
			Model 2 1.43 (1.19–1.71), *P*<0.001
		n=1333	n=558
	30–<60	Model 1 1.22 (1.03–1.46), *P*=0.023	Model 1 1.49 (1.23–1.79), *P*<0.001
		Model 2 1.16 (0.97–1.38), *P*=0.108	Model 2 1.32 (1.09–1.60), *P*=0.005
		n=631	n=520
	<30	Model 1 1.49 (0.64–3.45), *P*=0.35	Model 1 2.34 (1.56–3.49), *P*<0.001
		Model 2 1.54 (0.66–3.62), *P*=0.31	Model 2 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.

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,[5,28] and extensive studies have also been conducted on the role of endothelial dysfunction in the pathogenesis of cerebral SVD.[29] Recently, risk scores for ischemic or hemorrhagic stroke using a component of SVD like CMBs have been given attention.[4] Nonetheless, both albuminuria and reduced eGFR would also increase the risks for ischemic and hemorrhagic stroke.[30,31] 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.[32] 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.[33] 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.[34]

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.[35] 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

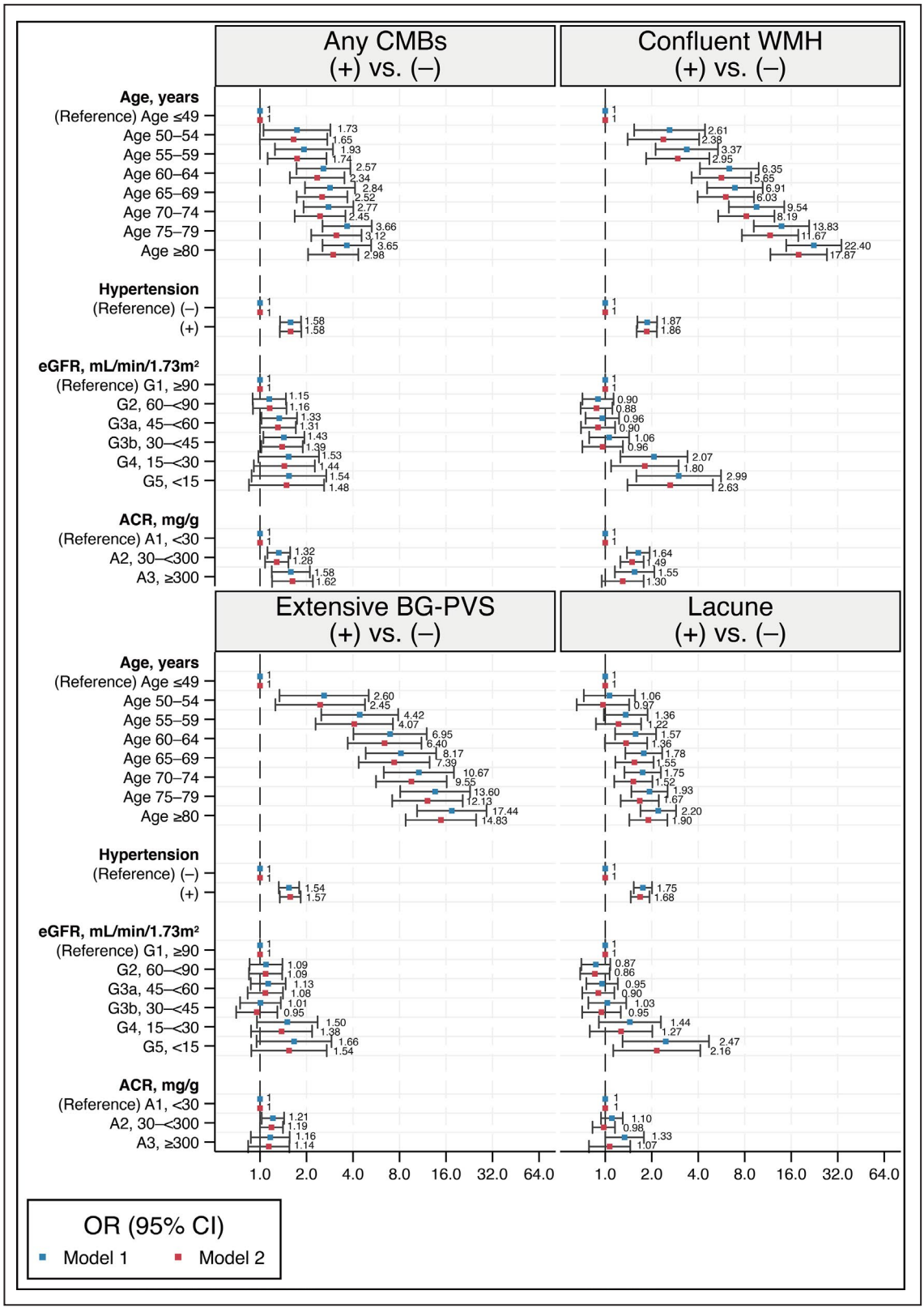

Figure 3. Multivariable models of risk factors for SVD features.
Plots showing odds ratios (ORs) and 95% CIs from binary logistic regression models. Adjusting covariates are age categories and sex for Model 1 and age categories, sex, hypertension, diabetes, dyslipidemia, current smoking, drinking, and 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.

ARTICLE INFORMATION

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Disclosures

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Supplemental Material

Data S1
Tables S1–S8
Figures S1–S8

REFERENCES

1. Wilson D, Ambler G, Shakeshaft C, Brown MM, Charidimou A, Al-Shahi Salman R, Lip GYH, Cohen H, Banerjee G, Houlden H, et al. Cerebral microbleeds and intracranial haemorrhage risk in patients anticoagulated for atrial fibrillation after acute ischaemic stroke or transient ischaemic attack (CROMIS-2): a multicentre observational cohort study. *Lancet Neurol*. 2018;17:539–547. doi: 10.1016/S1474-4422(18)30145-5
2. Wilson D, Ambler G, Lee K-J, Lim J-S, Shiozawa M, Koga M, Li L, Lovelock C, Chabriat H, Hennerici M, et al. Cerebral microbleeds and stroke risk after ischaemic stroke or transient ischaemic attack: a pooled analysis of individual patient data from cohort studies. *Lancet Neurol*. 2019;18:653–665. doi: 10.1016/S1474-4422(19)30197-8
3. Al-Shahi Salman R, Minks DP, Mitra D, Rodrigues MA, Bhatnagar P, du Plessis JC, Joshi Y, Dennis MS, Murray GD, Newby DE, et al. Effects of antiplatelet therapy on stroke risk by brain imaging features of intracerebral haemorrhage and cerebral small vessel diseases: subgroup analyses of the RESTART randomised, open-label trial. *Lancet Neurol*. 2019;18:643–652. doi: 10.1016/S1474-4422(19)30184-X
4. Best JG, Ambler G, Wilson D, Lee K-J, Lim J-S, Shiozawa M, Koga M, Li L, Lovelock C, Chabriat H, et al. Development of imaging-based risk scores for prediction of intracranial haemorrhage and ischaemic stroke in patients taking antithrombotic therapy after ischaemic stroke or transient ischaemic attack: a pooled analysis of individual patient data from cohort studies. *Lancet Neurol*. 2021;20:294–303. doi: 10.1016/S1474-4422(21)00024-7
5. Ito S, Nagasawa T, Abe M, Mori T. Strain vessel hypothesis: a viewpoint for linkage of albuminuria and cerebro-cardiovascular risk. *Hypertens Res*. 2009;32:115–121. doi: 10.1038/hr.2008.27
6. Toyoda K, Ninomiya T. Stroke and cerebrovascular diseases in patients with chronic kidney disease. *Lancet Neurol*. 2014;13:823–833. doi: 10.1016/S1474-4422(14)70026-2
7. Klarenbeek P, van Oostenbrugge RJ, Rouhl RP, Knottnerus IL, Staals J. Ambulatory blood pressure in patients with lacunar stroke: association with total MRI burden of cerebral small vessel disease. *Stroke*. 2013;44:2995–2999. doi: 10.1161/STROKEAHA.113.002545
8. Staals J, Makin SD, Doubal FN, Dennis MS, Wardlaw JM. Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. *Neurology*. 2014;83:1228–1234. doi: 10.1212/WNL.0000000000000837
9. Liu B, Lau KK, Li L, Lovelock C, Liu M, Kuker W, Rothwell PM. Age-specific associations of renal impairment with magnetic resonance imaging markers of cerebral small vessel disease in transient ischemic attack and stroke. *Stroke*. 2018;49:899–904. doi: 10.1161/STROKEAHA.117.019650
10. Vilar-Bergua A, Riba-Llena I, Ramos N, Mundet X, Espinel E, López-Rueda A, Ostos E, Seron D, Montaner J, Delgado P. Microalbuminuria and the combination of MRI markers of cerebral small vessel disease. *Cerebrovasc Dis*. 2016;42:66–72. doi: 10.1159/000445168
11. Toyoda K, Yasaka M, Iwade K, Nagata K, Koretsune Y, Sakamoto T, Uchiyama S, Gotoh J, Nagao T, Yamamoto M, et al. Dual antithrombotic therapy increases severe bleeding events in patients with stroke and cardiovascular disease: a prospective, multicenter, observational study. *Stroke*. 2008;39:1740–1745. doi: 10.1161/STROKEAHA.107.504993
12. Toyoda K, Yasaka M, Uchiyama S, Nagao T, Gotoh J, Nagata K, Koretsune Y, Sakamoto T, Iwade K, Yamamoto M, et al. Blood pressure levels and bleeding events during antithrombotic therapy: the bleeding with antithrombotic therapy (BAT) study. *Stroke*. 2010;41:1440–1444. doi: 10.1161/STROKEAHA.110.580506
13. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383:955–962. doi: 10.1016/S0140-6736(13)62343-0
14. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann F-J, Ardissino D, De Servi S, Murphy SA, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001–2015. doi: 10.1056/NEJMoa0706482
15. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045–1057. doi: 10.1056/NEJMoa0904327
16. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, Wang C, Li H, Meng X, Cui L, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med*. 2013;369:11–19. doi: 10.1056/NEJMoa1215340

17. Johnston SC, Easton JD, Farrant M, Barsan W, Conwit RA, Elm JJ, Kim AS, Lindblad AS, Palesch YY. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. *N Engl J Med*. 2018;379:215–225. doi: 10.1056/NEJMoa1800410
18. Toyoda K, Uchiyama S, Yamaguchi T, Easton JD, Kimura K, Hoshino H, Sakai N, Okada Y, Tanaka K, Origasa H, et al. Dual antiplatelet therapy using cilostazol for secondary prevention in patients with high-risk ischaemic stroke in Japan: a multicentre, open-label, randomised controlled trial. *Lancet Neurol*. 2019;18:539–548. doi: 10.1016/S1474-4422(19)30148-6
19. Takagi M, Tanaka K, Miwa K, Sasaki M, Koga M, Hirano T, Kamiyama K, Yagita Y, Nagakane Y, Hoshino H, et al. The bleeding with antithrombotic therapy study 2: rationale, design, and baseline characteristics of the participants. *Eur Stroke J*. 2020;5:423–431. doi: 10.1177/2396987320960618
20. Molnar AO, Bota SE, Garg AX, Harel Z, Lam N, McArthur E, Nesrallah G, Perl J, Sood MM. The risk of major hemorrhage with CKD. *J Am Soc Nephrol*. 2016;27:2825–2832. doi: 10.1681/ASN.2015050535
21. Toyoda K, Yamamoto H, Koga M. Network for clinical stroke trials (NECST) for the next stroke researchers in Japan. *Stroke*. 2016;47:304–305. doi: 10.1161/STROKEAHA.115.011841
22. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis*. 2009;53:982–992. doi: 10.1053/j.ajkd.2008.12.034
23. KDIGO CKD Work Group. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int*. 2013;3:1–150.
24. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley RI, O'Brien JT, Barkhof F, Benavente OR, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12:822–838. doi: 10.1016/S1474-4422(13)70124-8
25. Uchiyama S, Sakai N, Toi S, Ezura M, Okada Y, Takagi M, Nagai Y, Matsubara Y, Minematsu K, Suzuki N, et al. Final results of cilostazol-aspirin therapy against recurrent stroke with intracranial artery stenosis (CATHARSIS). *Cerebrovasc Dis Extra*. 2015;5:1–13. doi: 10.1159/000369610
26. Hilal S, Mok V, Youn YC, Wong A, Ikram MK, Chen CL. Prevalence, risk factors and consequences of cerebral small vessel disease: data from three Asian countries. *J Neurol Neurosurg Psychiatry*. 2017;88:669–674. doi: 10.1136/jnnp-2016-315324
27. Khan U, Porteous L, Hassan A, Markus HS. Risk factor profile of cerebral small vessel disease and its subtypes. *J Neurol Neurosurg Psychiatry*. 2007;78:702–706. doi: 10.1136/jnnp.2006.103549
28. Nagasawa T, Mori T, Ohsaki Y, Yoneki Y, Guo Q, Sato E, Oba I, Ito S. Albuminuria indicates the pressure-associated injury of juxtamedullary nephrons and cerebral strain vessels in spontaneously hypertensive stroke-prone rats. *Hypertens Res*. 2012;35:1024–1031. doi: 10.1038/hr.2012.112
29. Quick S, Moss J, Rajani RM, Williams A. A vessel for change: endothelial dysfunction in cerebral small vessel disease. *Trends Neurosci*. 2021;44:289–305. doi: 10.1016/j.tins.2020.11.003
30. Mahmoodi BK, Yatsuya H, Matsushita K, Sang Y, Gottesman RF, Astor BC, Woodward M, Longstreth WT, Psaty BM, Shlipak MG, et al. Association of kidney disease measures with ischemic versus hemorrhagic strokes: pooled analyses of 4 prospective community-based cohorts. *Stroke*. 2014;45:1925–1931. doi: 10.1161/STROKEAHA.114.004900
31. Bos MJ, Koudstaal PJ, Hofman A, Breteler MM. Decreased glomerular filtration rate is a risk factor for hemorrhagic but not for ischemic stroke: the Rotterdam Study. *Stroke*. 2007;38:3127–3132. doi: 10.1161/STROKEAHA.107.489807
32. Ikram MA, Vernooij MW, Hofman A, Niessen WJ, van der Lugt A, Breteler MM. Kidney function is related to cerebral small vessel disease. *Stroke*. 2008;39:55–61. doi: 10.1161/STROKEAHA.107.493494
33. Shima H, Ishimura E, Naganuma T, Yamazaki T, Kobayashi I, Shidara K, Mori K, Takemoto Y, Shoji T, Inaba M, et al. Cerebral microbleeds in predialysis patients with chronic kidney disease. *Nephrol Dial Transplant*. 2010;25:1554–1559. doi: 10.1093/ndt/gfp694
34. Umemura T, Kawamura T, Sakakibara T, Mashita S, Hotta N, Sobue G. Microalbuminuria is independently associated with deep or infratentorial brain microbleeds in hypertensive adults. *Am J Hypertens*. 2012;25:430–436. doi: 10.1038/ajh.2011.254
35. Yakushiji Y, Wilson D, Ambler G, Charidimou A, Beiser A, van Buchem MA, DeCarli C, Ding D, Gudnason V, Hara H, et al. Distribution of cerebral microbleeds in the East and West: individual participant meta-analysis. *Neurology*. 2019;92:e1086–e1097. doi: 10.1212/WNL.0000000000007039

Supplemental Material

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.[24] 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 = $[(1 - (D_{stenosis}/D_{normal})) \times 100]$, 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.[25] 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

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

Table S2. Conditions for brain MRI acquisition

	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

	MRI assessment	Reporting format
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.	
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.

Table S5. Patient characteristics, cerebral microbleeds, and confluent white matter 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/m^2	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

Peripheral artery disease	75 (2.2%)	46 (2.8%)	0.20	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)	21.0 [8.4, 73.0] (n=971)	<0.001	12.1 [5.8, 36.7] (n=1500)	22.3 [9.1, 70.8] (n=1615)	<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].[22]

[†] 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/m^2	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

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 m^2	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 m^2			<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].[22]

[†] 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/m^2	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%)	2529 (80.5%)	<0.001
Diabetes mellitus	555 (25.4%)	928 (29.5%)	0.001
Dyslipidemia	1406 (64.5%)	2047 (65.2%)	0.60
Current smoking	329 (15.1%)	452 (14.4%)	0.50
Current drinking (≥8 units/week)	686 (31.5%)	929 (29.7%)	0.15
Habitual use of non-steroidal anti-inflammatory drugs	71 (3.3%)	77 (2.5%)	0.079
Comorbidities			
Ischemic stroke or TIA	2031 (93.1%)	2766 (88.0%)	<0.001
Intracerebral hemorrhage	41 (1.9%)	76 (2.4%)	0.19
Subarachnoid hemorrhage	15 (0.7%)	12 (0.4%)	0.12
Asymptomatic cerebrovascular disease	137 (6.3%)	253 (8.1%)	0.015
Atrial fibrillation	365 (16.7%)	705 (22.4%)	<0.001
Acute coronary syndrome	135 (6.2%)	242 (7.7%)	0.034
Congestive heart failure	80 (3.7%)	128 (4.1%)	0.45
Peripheral artery disease	49 (2.2%)	74 (2.4%)	0.79
Deep venous thrombosis	35 (1.6%)	60 (1.9%)	0.41
Active malignancy	46 (2.1%)	60 (1.9%)	0.61
Liver disease	12 (0.6%)	42 (1.3%)	0.005
Chronic obstructive pulmonary disease	32 (1.5%)	58 (1.8%)	0.29
Dementia requiring support	78 (3.6%)	92 (2.9%)	0.18
eGFR [*], mL/min/1.73 m^2	64.8 [54.4, 75.8]	64.1 [52.9, 75.6]	0.14
eGFR categories, mL/min/1.73 m^2			<0.001
G1, ≥90	179 (8.4%)	232 (7.4%)	

G2, 60–<90	1138 (53.1%)	1659 (52.9%)	
G3a, 45–<60	558 (26.1%)	848 (27.0%)	
G3b, 30–<45	182 (8.5%)	303 (9.7%)	
G4, 15–<30	37 (1.7%)	76 (2.4%)	
G5, <15	48 (2.2%)	20 (0.6%)	

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].[22]

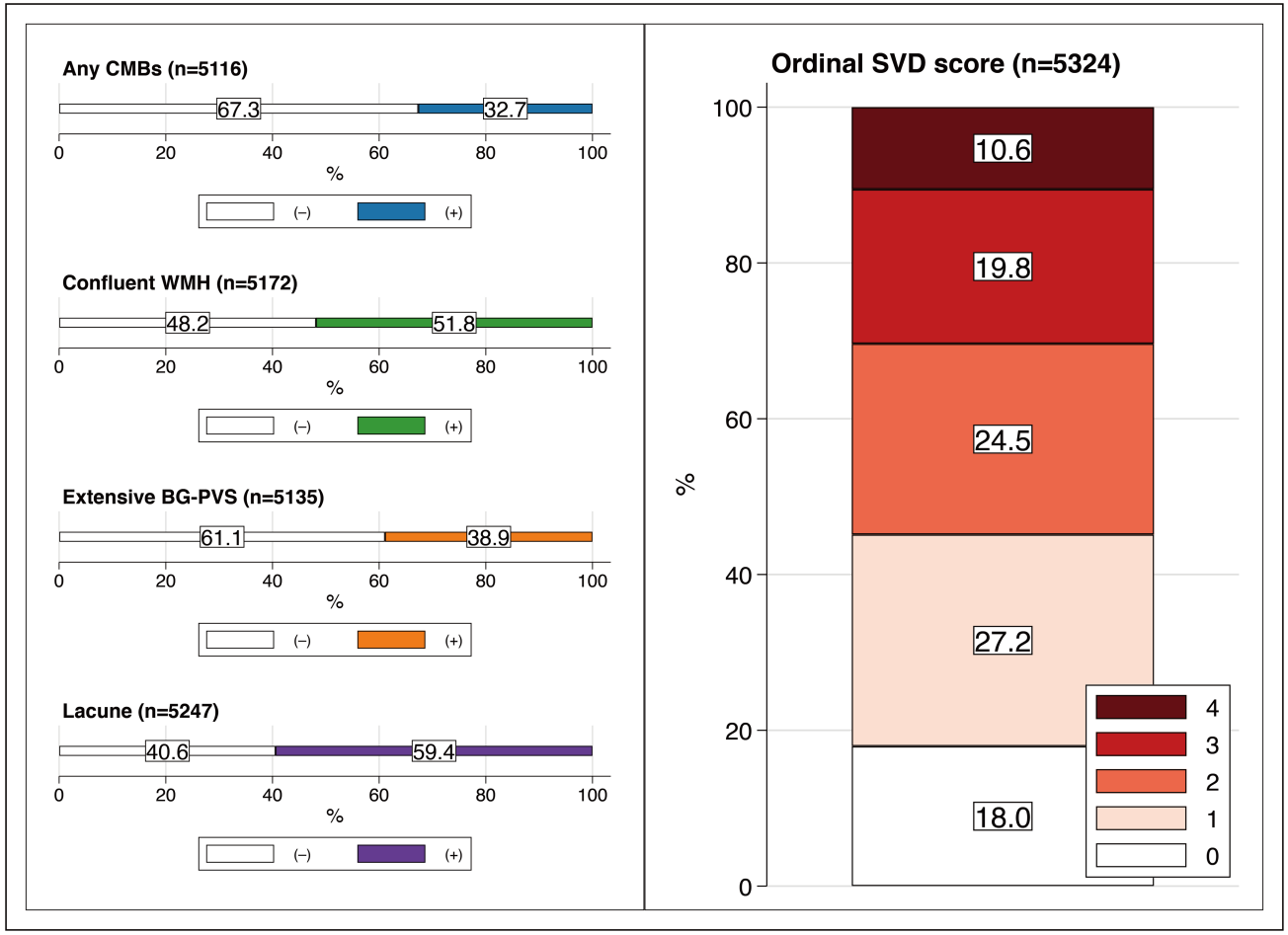
Abbreviations: ACR, urinary albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; IQR, interquartile range; TIA, transient ischemic attack.

Table S8. Oral antithrombotic medication at baseline

	Total SVD score ≤2 (n=3707)	Total SVD score ≥3 (n=1617)	P value
Combination			
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.

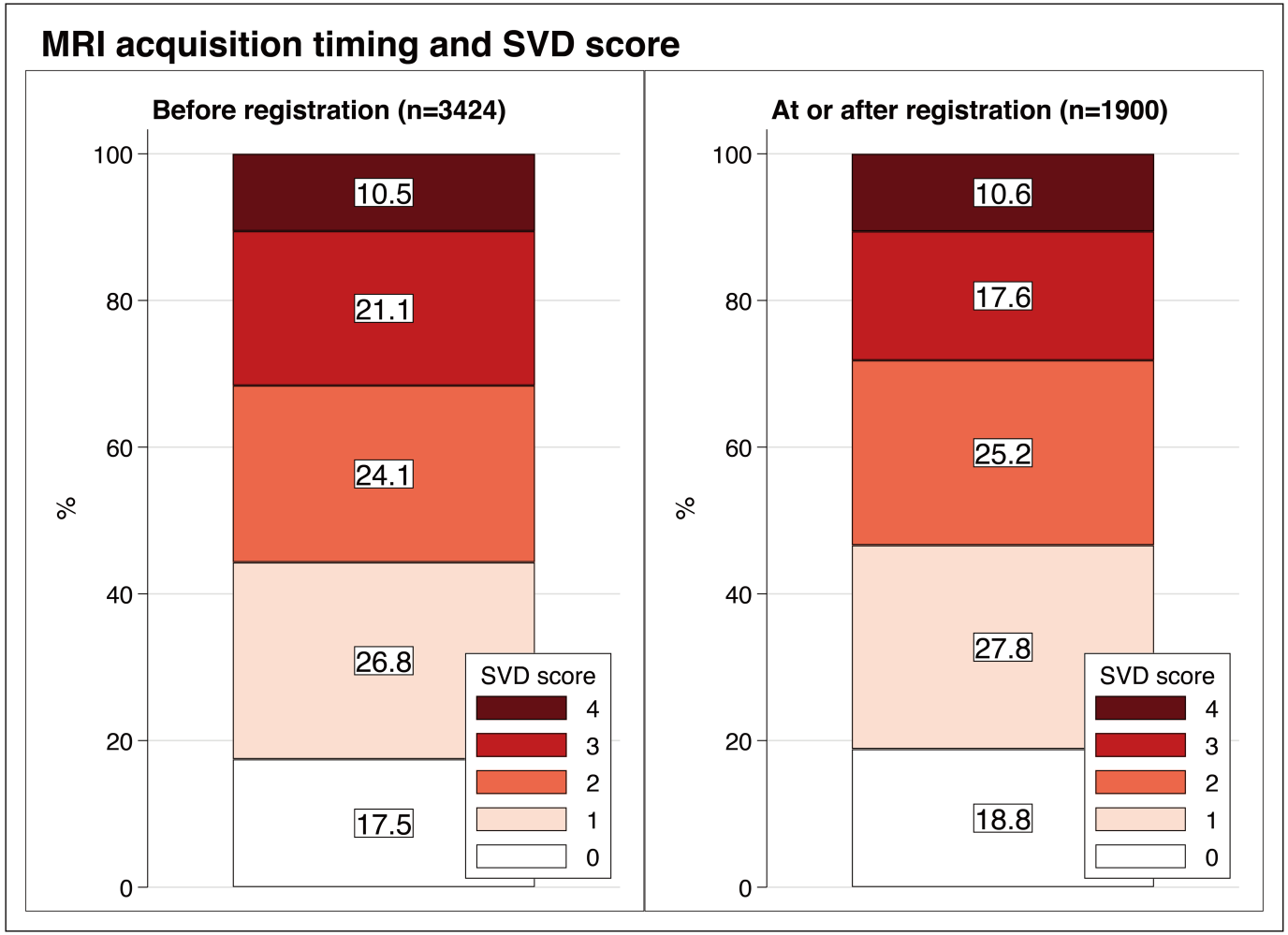
Figure S1. SVD markers and ordinal SVD score



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.

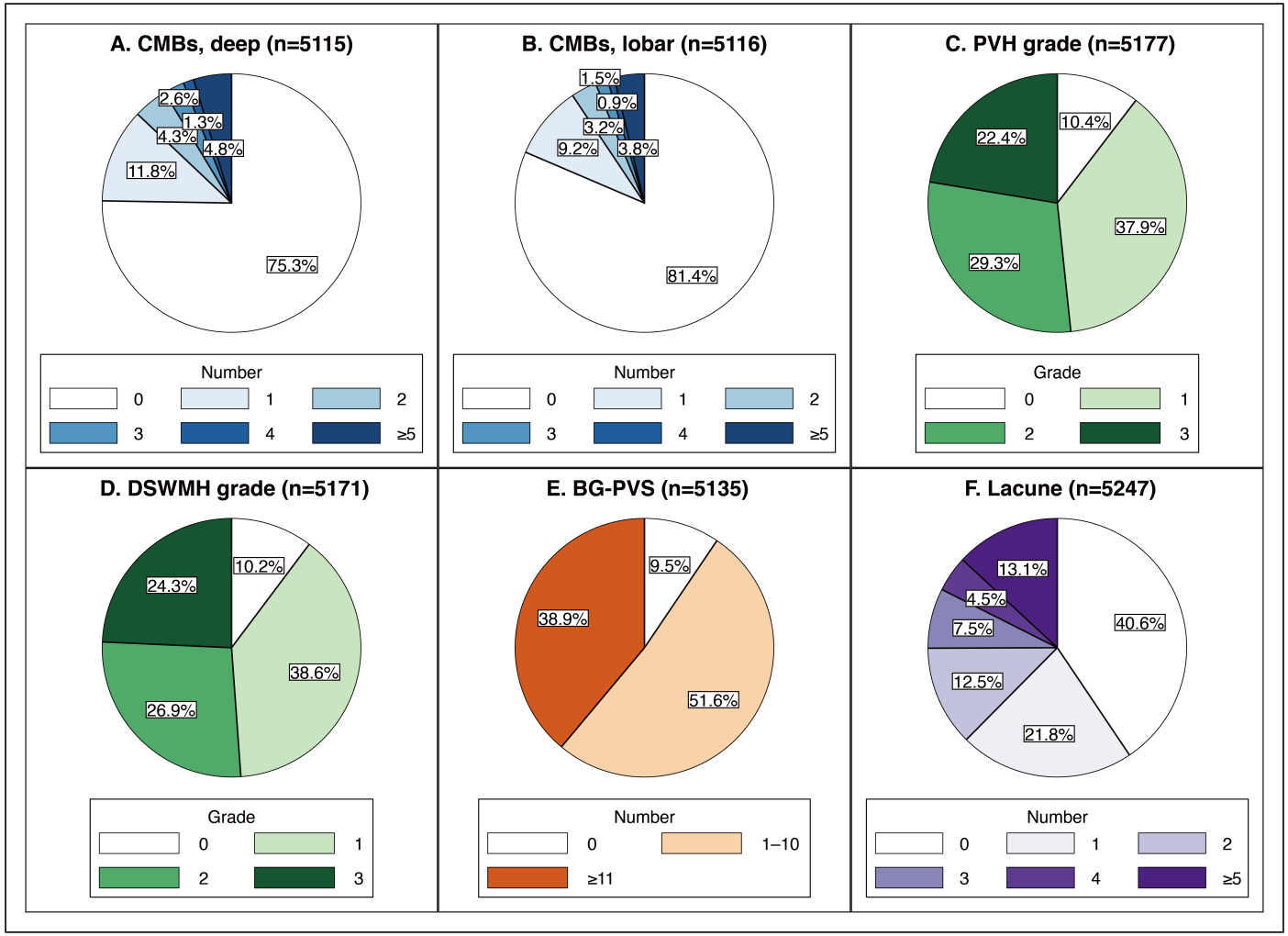
Abbreviations: BG-PVS, enlarged basal ganglia perivascular spaces; CMBs, cerebral microbleeds; DSWMH, deep and subcortical white matter hyperintensity; PVH: periventricular hyperintensity; SVD, small vessel disease; WMH, white matter hyperintensity.

Figure S2. Distribution of SVD score by timing of MRI acquisition



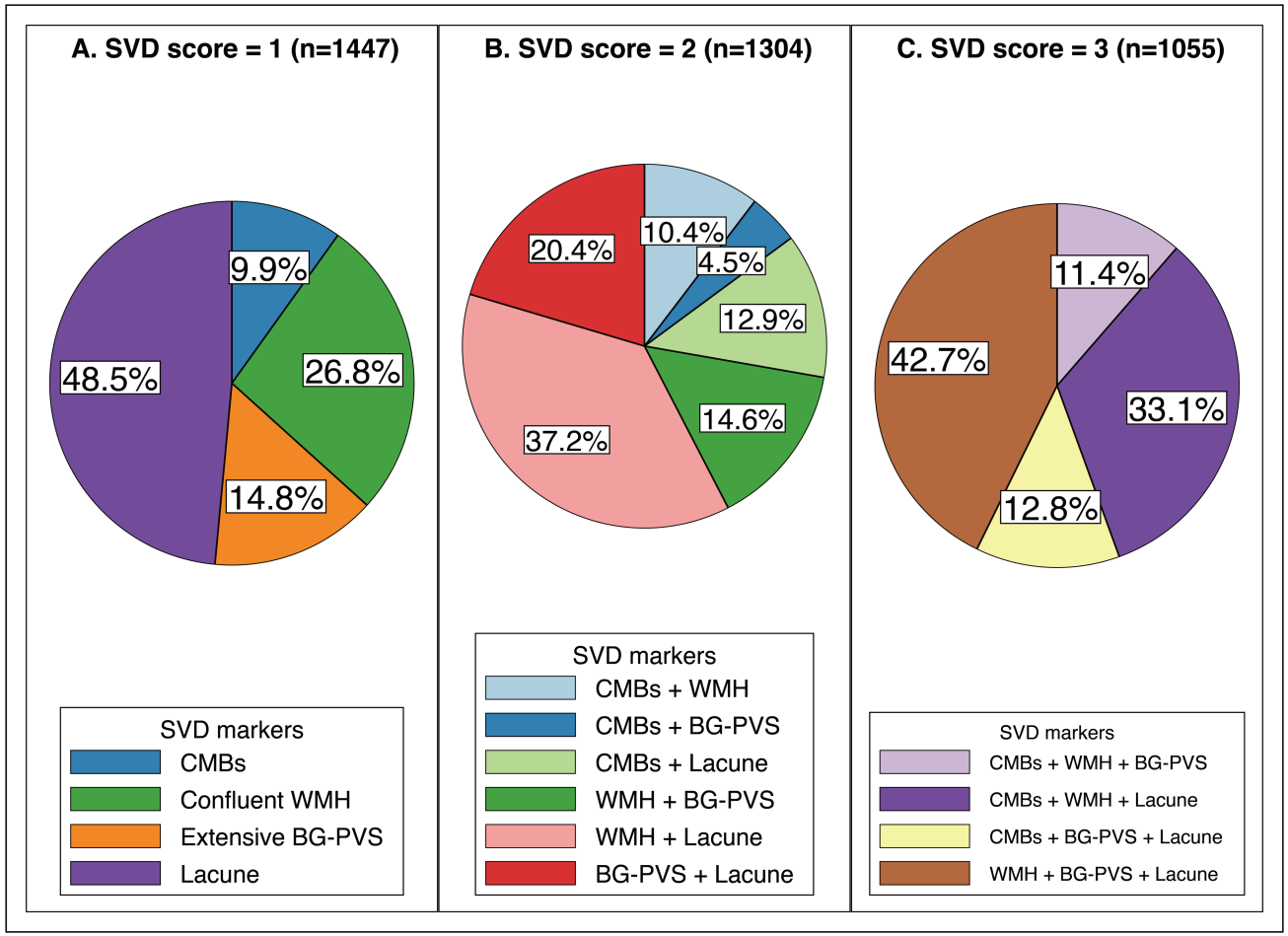
Abbreviations: MRI, magnetic resonance imaging; SVD, small vessel disease

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.

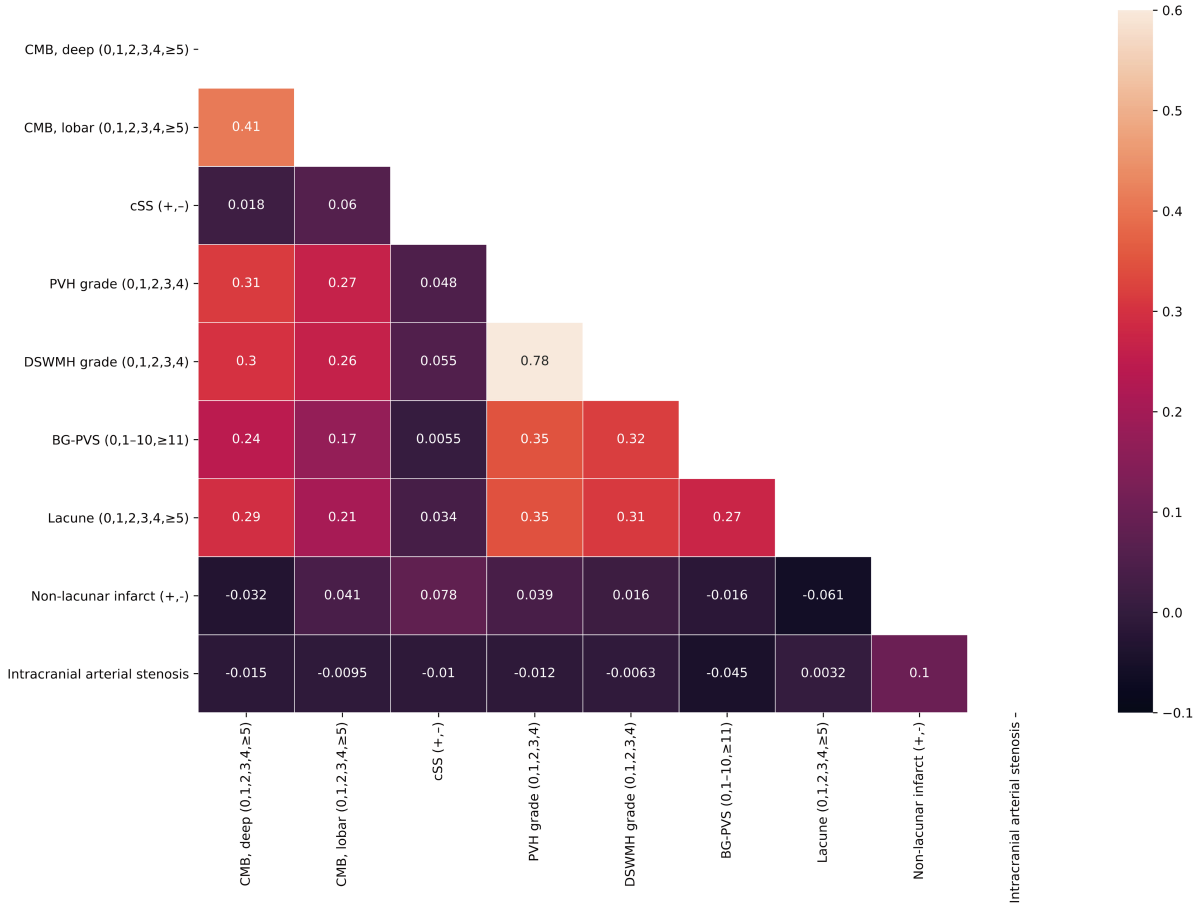
Figure S4. Composition of small vessel disease markers in the different small vessel disease scores



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.

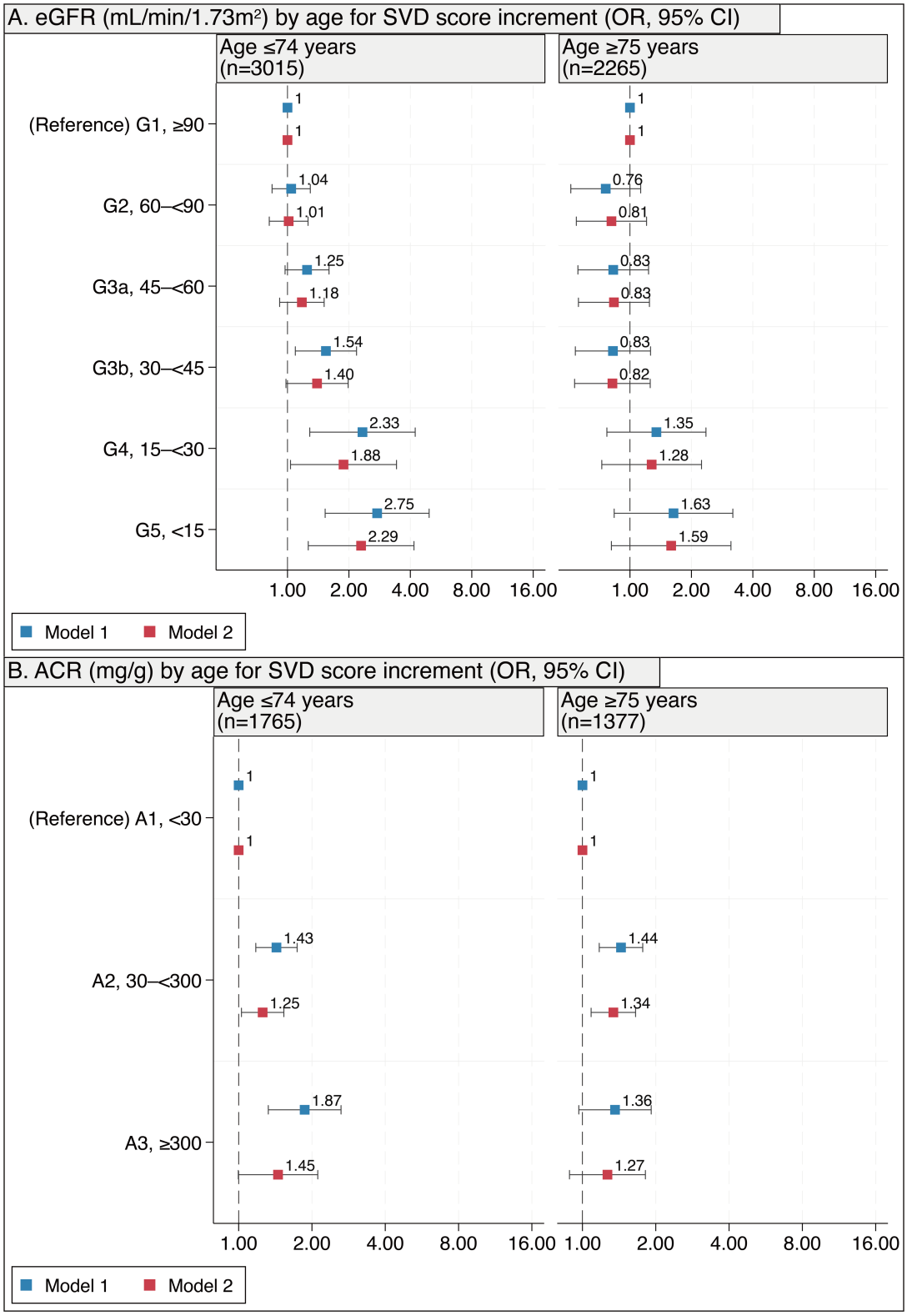
Abbreviations: BG-PVS, enlarged basal ganglia perivascular spaces; CMBs, cerebral microbleeds; SVD, small vessel disease; WMH, white matter hyperintensity.

Figure S5. Pairwise correlation mapping between MRI findings



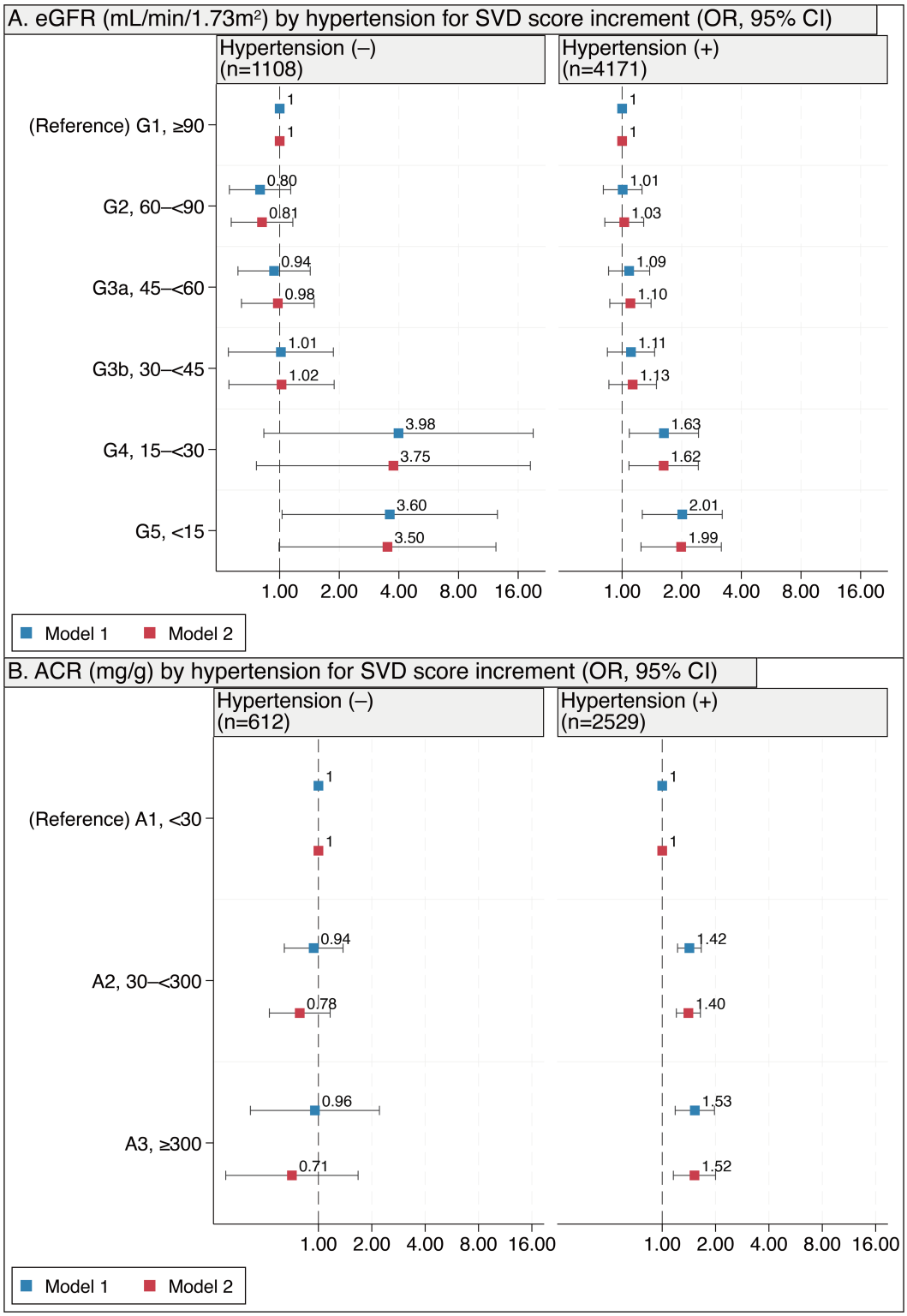
Spearman's correlation coefficients between MRI findings are shown. Intracranial arterial stenosis is handled as categorical data of normal/mild, moderate, severe, and occluded. Only a weak correlation is seen between MRI SVD markers (Spearman's rho, 0.17–0.35), except for the relatively strong correlation 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



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 age and eGFR was 0.62 in Model 1 and 0.77 in Model 2. *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.

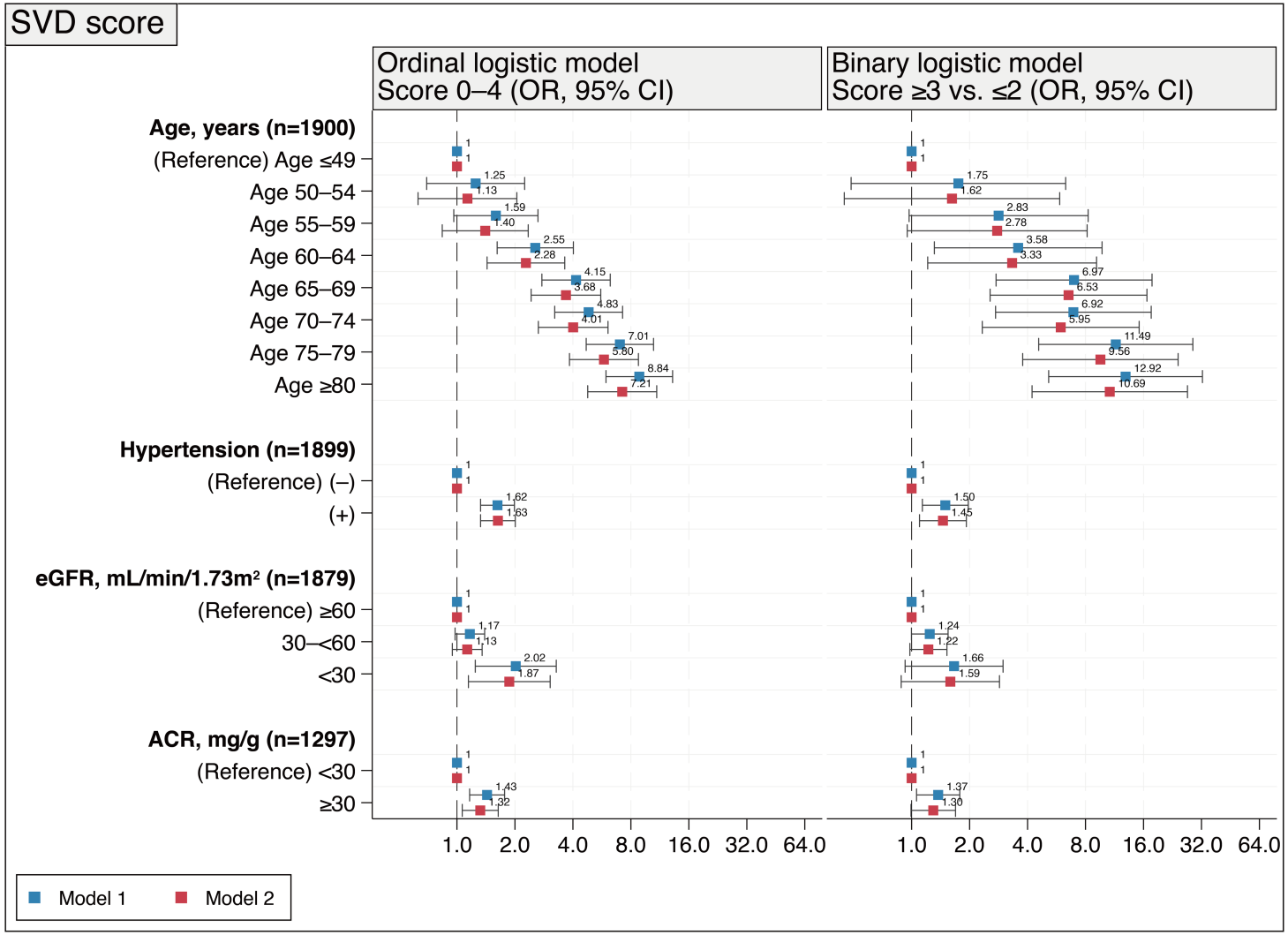
Figure S7. Chronic kidney disease measures and small vessel disease score increment stratified by hypertension



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.