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Letter to the Editor

High Daily Diastolic Blood Pressure Predicts Incident Stroke, Lacune, and Cerebral Microbleeds in CADASIL

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Dear Sir:

In general, elevated levels of systolic and diastolic blood pressure (BP), as well as increased BP variability, are associated with increased burden and progression of cerebral small vessel disease (CSVD).[1,2] Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a hereditary form of CSVD resulting from the *NOTCH3* mutation, can manifest and progress independently of hypertension.[3] However, concurrent hypertension in CADASIL is associated with an augmented risk of stroke and can worsen disease severity, as evidenced by neuroimaging markers such as brain atrophy, microhemorrhages, and impaired white matter integrity.[4-6] However, currently there are no disease-modifying therapies available for CADASIL, and the extent to which daily BP variations or levels can influence the disease course in CADASIL, even in the absence of arterial hypertension, remains unclear. Therefore, we hypothesized that close BP monitoring and aggressive BP control have the potential to aid in the identification of predictors of disease progression in CADASIL. This study aimed to investigate whether various parameters derived from daily home-based automated BP measurements, such as the mean and variability of daily BP, could enhance the prediction of clinical or neuroimaging progression of CADASIL.

Study participants were recruited from the prospective Taiwan CADASIL Registry cohort, which enrolled patients with genetically confirmed cysteine-altering *NOTCH3* variants. The detailed methodology can be found in the Supplementary Methods. Briefly, each enrolled patient was provided with an automated home-based sphygmomanometer (BP A2 Easy; Microlife AG, Widnau, Switzerland) to record BP for at least 90 consecutive days. Patients and their caregivers recorded systolic BP (SBP) and diastolic BP (DBP) twice daily. The mean and standard deviation (SD) of SBP, DBP, and pulse pressure (PP) were used in the analysis. Systolic hypertension was defined as a mean SBP >130 mm Hg and diastolic hypertension as a DBP >80 mm Hg. Patients with available BP records for <50% of the days were excluded.

All patients underwent 1.5-T brain magnetic resonance imaging (MRI) upon enrollment. Follow-up MRIs were performed at intervals of 1–2 years. Visual rating analyses of CSVD markers were performed in accordance with the STandards for ReportIng Vascular changes on nEuroimaging (i.e., STRIVE) criteria, which included white matter hyperintensity, enlarged perivascular space, number of lacunes, and cerebral microbleeds (CMBs).[7] Quantitative analyses of MRI lesions included mean cortical thickness, brain parenchymal fraction, and white matter lesion (WML) volume.

The clinical outcome was stroke incidence. Any incident stroke event was documented and defined as an acute episode of focal neurological dysfunction lasting more than 24 hours with corresponding neuroimaging evidence of cerebral infarction or hemorrhage. The neuroimaging outcome was the progression of MRI markers between baseline and follow-up scans. Because the median annual increases in the number of lacunes and CMBs were 0 and 1, respectively, any incident lacunes or increased CMB numbers ≥2 per year were defined as meaningful neuroimaging outcomes. A Cox regression model was used to test the influence of BP parameters on incident stroke, while logistic regression models were applied for BP parameters and any incident la-

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cune or incident CMB ≥2 per year. Furthermore, a linear mixed model was used to test the associations between changes in neuroimaging markers and each BP parameter.

Of the 128 CADASIL patients with available BP records, 6 were excluded due to <50% of BP records and 31 were excluded due to lack of follow-up MRI, mainly because the follow-up period was too short for the scheduled second MRI. Of the remaining 91 patients (age, 63.2±10.5 years; 65% male), 56% had a history of hypertension and 60% had a history of stroke (Supplementary Table 1). Most of the patients (n=81) carried the *NOTCH3* variant R544C, which is the predominant variant in Taiwan. The others included: one with R110C, one with S118C, two with R131C, one with R141C, two with R332C, one with R1231C, and two with C1250R. The 90-day mean SBP and DBP were 119.3±10.6 mm Hg and 73.6±7.9 mm Hg; 15% and 19% of the patients had systolic or diastolic hypertension, respectively. The median changes in CSVD markers on MRI are shown in Supplementary Table 2. Comparisons between patients with *NOTCH3* R544C and non-R544C variants are presented in Supplementary Table 3.

During a median follow-up of 2.5 years (interquartile range [IQR], 1.8–3.6), there were nine incident stroke events (six ischemic and three hemorrhagic). The mean SBP, DBP, and PP were not significantly different between patients with and without incident stroke (Figure 1 and Table 1). However, diastolic hypertension was more prevalent in patients with incident stroke (55.6% vs. 14.6%; adjusted HR, 6.62; 95% CI, 1.59–27.7) (Table 1). The Kaplan–Meier curve showed that participants with diastolic hypertension had a higher risk of incident stroke (log-rank *P*=0.001) (Supplementary Figure 1). The SD of SBP, DBP, and PP were not associated with the incidence of stroke. Furthermore, although we included 31 patients who did not have follow-up MRI to test the effects of BP on stroke incidence, the results remained unchanged (Supplementary Table 4). However, there were no stroke events among these 31 patients because their follow-up durations were significantly shorter than those of the original patients (median [IQR], 8 [5–15] vs. 27 [22–43] months; *P*<0.001).

Compared to baseline MRI, 26 (28.6%) patients had incident lacune and 37 (41.1%) had increased CMB ≥2 per year on follow-up MRI. The mean DBP was significantly higher in patients with incident lacune (77.1±9.1 vs. 72.2±6.8 mm Hg, *P*=0.01) (Figure 1). A higher mean DBP, larger SD of SBP, DBP, and PP, and diastolic hypertension were associated with incident lacunes (Table 1). Most of the BP parameters were not associated with increased CMB increase ≥2 per year, except diastolic hyperten-

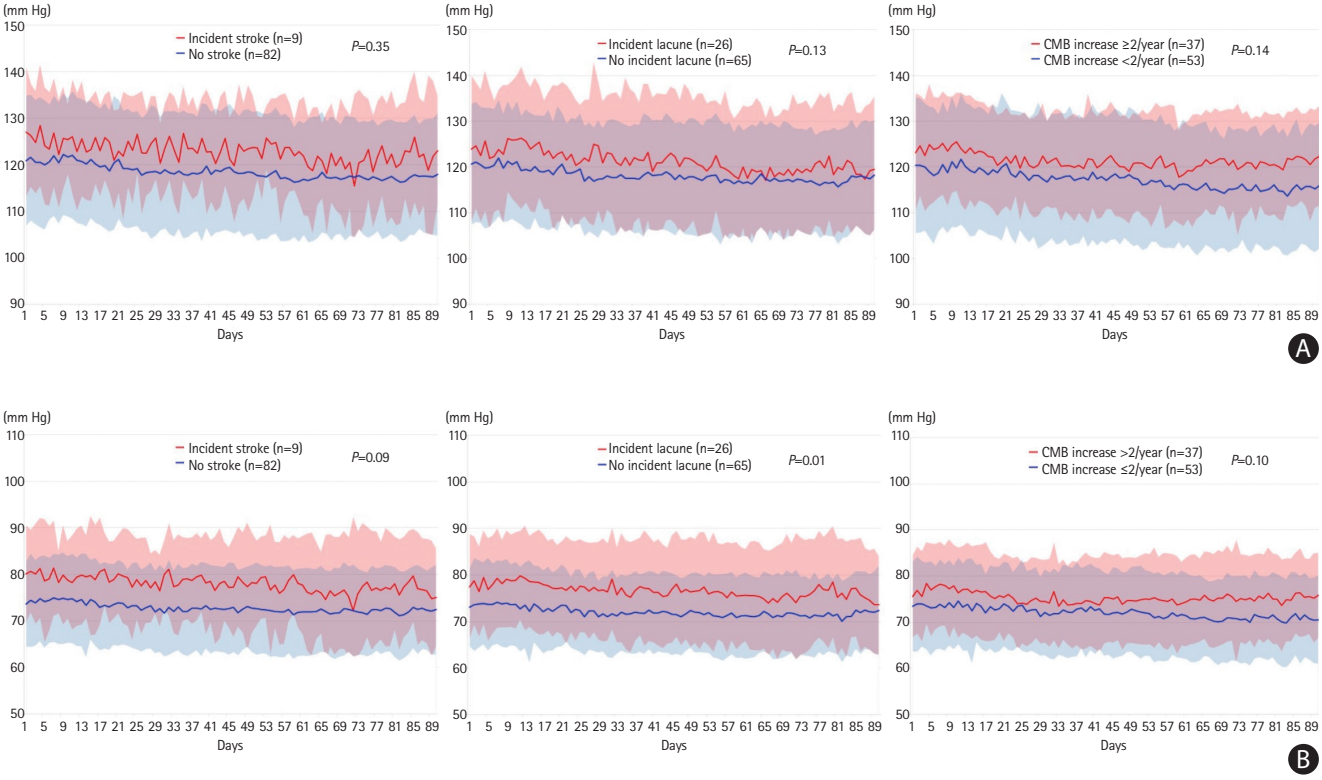

Figure 1. Distribution of 90-day blood pressure and outcomes. (A) The mean systolic blood pressure is not significantly different between patients with and without predefined outcomes. (B) Mean diastolic blood pressure is significantly higher in patients with incident lacune (*P*=0.01) and is borderline significantly higher in patients with cerebral microbleed (CMB) increase ≥2 per year (*P*=0.10) or incident stroke (*P*=0.09) compared to those without these outcomes. The shaded area indicated standard deviations of blood pressure.

Table 1. Effects of blood pressure or hypertension on neuroimaging and clinical outcomes

	Incident stroke			Incident lacune			Increased CMB ≥ 2/year		
	Yes (n=9)	No (n=82)	Adjusted HR (95% CI)*	Yes (n=26)	No (n=65)	Adjusted OR (95% CI)†	Yes (n=37)	No (n=53)	Adjusted OR (95% CI)‡
SBP, mean (mm Hg)§	122.4±9.1	119.0±10.7	1.35 (0.71, 2.59)	122.0±12.3	118.3±9.7	1.25 (0.75, 2.06)	121.3±8.2	118.0±11.9	1.00 (0.58, 1.73)
SBP, SD (mm Hg)	6.7±2.3	7.0±2.4	0.97 (0.70, 1.34)	8.0±2.9	6.5±2.0	1.26 (1.03, 1.55)‖	7.0±2.4	7.0±2.4	0.82 (0.62, 1.07)
DBP, mean (mm Hg)§	77.9±9.2	73.2±7.6	2.13 (0.82, 5.55)	76.8±9.3	72.3±6.9	2.63 (1.23, 5.63)‖	75.4±7.9	72.6±7.7	2.06 (0.91, 4.66)
DBP, SD (mm Hg)	5.6±1.6	5.0±1.3	1.39 (0.90, 2.16)	5.6±1.6	4.8±1.2	1.46 (1.03, 2.06)‖	5.2±1.5	4.9±1.3	0.91 (0.60, 1.38)
PP, mean (mm Hg)§	44.7±5.9	46.1±9.2	0.90 (0.38, 2.13)	45.4±9.2	46.2±8.9	0.64 (0.33, 1.24)	46.1±8.8	45.6±9.0	0.50 (0.22, 1.13)
PP, SD (mm Hg)	4.8±1.3	5.4±1.9	0.70 (0.37, 1.34)	6.3±2.6	5.0±1.3	1.43 (1.08, 1.89)‖	5.2±2.0	5.4±1.8	0.69 (0.45, 1.07)
SBP >130 mm Hg	2 (22.2)	12 (14.6)	1.52 (0.30, 7.75)	5 (19.2)	9 (13.9)	1.23 (0.35, 4.33)	8 (21.6)	6 (11.3)	1.98 (0.45, 8.66)
DBP >80 mm Hg	5 (55.6)	12 (14.6)	6.62 (1.59, 27.7)‖	11 (42.3)	6 (9.2)	9.23 (2.50, 34.1)‖	11 (29.7)	6 (11.3)	5.23 (1.10, 24.8)‖

Values are presented as mean±standard deviation or number (%) unless otherwise indicated.
CMB, cerebral microbleeds; HR, hazard ratio; CI, confidence interval; OR, odds ratio; SBP, systolic blood pressure; SD, standard deviation; DBP, diastolic blood pressure.
*Adjusted for age, sex, hypertension, and history of stroke; †Adjusted for age, sex, hypertension, and baseline lacune number; ‡Adjusted for age, sex, hypertension, and baseline CMB number; §Effect estimates are expressed as a 10-mm Hg increase in blood pressure; ‖Statistically significant.

sion (Table 1). The association between diastolic hypertension and clinical and neuroimaging outcomes remained significant after adjusting for the most common *NOTCH3* R544C variant.

The scatterplots of the 90-day mean BP and the annual changes in neuroimaging markers are presented in Supplementary Figure 2. There was a positive association between mean DBP and increased WML proportion (β=0.005, *P*=0.02), mean DBP and increased number of lacune (relative risk [RR], 1.69; 95% CI, 1.26–2.28) and CMB (RR, 2.43; 95% CI, 1.46–4.05) (Supplementary Table 5).

The present study involved the largest sample size to date of continuous and comprehensive BP records in patients with CADASIL and yielded two main findings. First, although BP in our CADASIL participants was well controlled, since mean 90-day BP recordings largely fell within the target range (<130/80 mm Hg), mild elevations in BP, especially diastolic hypertension, were associated with an increased risk of further events, including incident stroke and progression of neuroimaging abnormalities. Second, 90-day average BP, rather than day-by-day BP variability, was significantly associated with the severity of the neuroimaging markers of CSVD in patients with CADASIL. The limitations of this study include potential BP measurement errors by participants, a relatively small sample size, and the question of generalizability beyond East Asian patients carrying the *NOTCH3* R544C variant.

Previous clinical trials on the effects of BP control on CSVD have typically focused on SBP. Diastolic hypertension, caused by increased peripheral vascular resistance, may represent a group of patients whose vascular elasticity and endothelial function declined earlier than others; therefore, they were at risk of worsening small vessel disease markers and even symptomatic stroke.[8,9] In previous studies, increased DBP was shown to independently influence cardiovascular outcome, including stroke.[8,9] Furthermore, patients with hypertension aged <70 years are at greater risk of WML progression when their DBP increased.[10] Because patients with CADASIL could suffer from cerebrovascular diseases at an earlier age than the general population, more attention should be paid to controlling DBP for these patients. More research or clinical trials to address the issue of effective monitoring and management of BP, especially DBP, are crucial for patients with CADASIL.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2023.02880.

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Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: SCT, YCL (Yi-Chung Lee). Study design: CHC,

SCT, YCL (Yi-Chu Liao), YCL (Yi-Chung Lee). Methodology: CHC, SCT. Data collection: all authors. Investigation: YCL (Yi-Chu Liao), SCT. Statistical analysis: CHC. Writing—original draft: CHC. Writing—review & editing: YCL (Yi-Chu Liao), YWC, CPC, YCL (Yi-Chung Lee), SCT. Funding acquisition: YCL (Yi-Chu Liao), YCL (Yi-Chung Lee), SCT. Approval of final manuscript: all authors.

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Supplementary Methods

Participants

Study participants were recruited from a prospective Taiwan CADASIL Registry (TCR) cohort. The TCR study sites were the National Taiwan University Hospital (NTUH) and the Taipei Veterans General Hospital (VGH-TPE), which are university-affiliated tertiary medical centers. Individuals with clinical and neuroimaging features suggestive of cerebral small vessel disease (CSVD) were screened for cysteine-altered *NOTCH3* variants. The main clinical presentations include stroke, cognitive dysfunction, and gait disturbance, while neuroimaging features suggestive of CSVD include moderate-to-severe leukoaraiosis, multiple lacunes, and mixed locations of cerebral microbleeds (CMBs). Patients with genetically confirmed cysteine-altering *NOTCH3* variants were enrolled and their clinicopathological characteristics, including age, sex, vascular risk factors, history of stroke, cardiovascular medications, and type of blood pressure (BP)-lowering drugs, were documented. Informed consent was obtained from all patients. The research ethics committees of both hospitals approved this study (NTUH: No. 201807044RIND; VGH-TPE: No. 2019-02-025A).

Genetic analysis

In Taiwan, the p.R544C variant in exon 11 of *NOTCH3* accounts for more than 70% of cases of CADASIL.[1] For this reason, all enrolled patients were initially screened for the *NOTCH3* p.R544C variant. If it was not detected, the analysis of *NOTCH3* exons 2 through 24 was performed by Sanger sequencing.[2]

Blood pressure

From February 2019, each patient enrolled in the TCR was provided with a standardized automated, home-based sphygmomanometer (BP A2 Easy, Microlife AG, Widnau, Switzerland) to record their BP for at least 90 consecutive days. Instructions for performing standardized home BP measurements were provided at enrollment. Patients and their caregivers were asked to record their systolic BP (SBP) and diastolic BP (DBP) twice a day, once in the morning (sometimes between 8 AM and 12 PM) and again in the evening (6 PM to 10 PM). An empirical approach was adopted to allow patients to measure their BP only once at a time and on a flexible schedule, without an exact hour requirement. Pulse pressure (PP) was calculated by subtracting the SBP from the corresponding DBP. Average morning and evening BP parameters were used if both were recorded. Parameters used in the analysis included the mean and standard deviation (SD) of the SBP, DBP, and PP. We also applied the cut-off value based on the American College of Cardiology/American Heart Association (ACC/AHA) guidelines to define hypertension, that is, SBP >130 mm Hg for systolic hypertension and DBP >80 mm Hg for diastolic hypertension.[3] Patients recorded BP consecutively for 90 days, and those with available BP records <50% of days were excluded.

Neuroimaging analysis

All patients with TCR underwent 1.5-T brain magnetic resonance imaging (MRI) upon enrollment. Although patients were recruited and MRI was performed at two study sites, a harmonized common scanning protocol was defined that included a high-resolution T1-weighted volumetric scan, T2 and fluid-attenuated inversion recovery (FLAIR)-T2 scans for the evaluation of white matter lesions (WMLs) and detection of lacunes, and a susceptibility-weighted sequence for the detection of CMBs. Follow-up MRI was performed using the same protocol for each patient at intervals of 1–2 years. All images were sent to NTUH for visual ratings and quantitative analyses.

Visual rating analyses of CSVD markers were performed in accordance with the STandards for ReportIng Vascular changes on nEuroimaging (i.e., STRIVE) criteria.[4] The severity of WMLs in the periventricular and deep white matter was evaluated on FLAIR and graded against the Fazekas scale.[5] The presence and number of lacunes were evaluated using T1, T2, and FLAIR images. Enlarged perivascular spaces (EPVS) were visualized on T2-weighted images, and the severity of EPVS in the basal ganglia and centrum semiovale were assessed on a 4-point rating scale.[6] The numbers and distribution of CMBs were evaluated on susceptibility-weighted imaging, documented using the Microbleed Anatomical Rating Scale framework, and classified into lobar and deep regions.[7] All visual rating analyses were performed by CHC and YWC, and any inconsistency was solved with consensus reading. Quantitative analyses of the MRI lesions included mean cortical thickness, brain parenchymal fraction, and WML volume. The mean cortical thickness and estimated total intracranial volume (eTIV) were quantified on T1-weighted structural MRI scans using the pipeline and the output of the FreeSurfer software version 7.2.0.[8] The brain parenchymal fraction, which represents the overall volume of the brain, was calculated by dividing the brain segmentation volume by the eTIV. WMLs were segmented using a lesion growth algorithm implemented in the Lesion Segmentation Tool (LST) toolbox version 3.0.0 (www.statistical-modeling.de/lst.html) for Statistical Parametric Mapping.[9] A FLAIR sequence was used for lesion segmentation, and a T1 image was used as a reference for registration. The final segmented lesions from the output of the LST were visually screened for accuracy, and the WML volumes were expressed in milliliters. To control for variations in head size, WML volumes were adjusted for eTIV

and expressed as the WML proportion (% of eTIV). To account for the possibility of large infarct or hemorrhagic stroke effects, we visually checked the FreeSurfer output. If severe distortion was observed due to a large infarct or intracerebral hemorrhage (ICH), we used only the data from the unaffected hemisphere. For the WML volume, the LST output was visually checked. The gliosis caused by the previous infarct or ICH was manually removed and the WML volume was recalculated.

Outcomes

The clinical outcome was stroke incidence. All enrolled patients with CADASIL were regularly followed up in the outpatient service until November 30, 2022, at a loss to follow-up, or death. Any incident stroke event was documented and defined as an acute episode of focal neurological dysfunction lasting more than 24 hours with corresponding neuroimaging evidence of cerebral infarction or hemorrhage.

Neuroimaging outcome was the progression of MRI markers between baseline and follow-up scans. Because the WML and EPVS scores on the visual rating scale rarely changed over 1–2 years, these two markers were excluded. The number of incident lacunes and CMB detected on follow-up MRI was divided by the interval between scans and expressed as the annual change (n/year). Similarly, annual changes in the proportion of WML, mean cortical thickness, and brain parenchymal fraction were calculated. Because the median annual increases in the number of lacunes and CMBs were 0 and 1, respectively, any incident lacunes or increased CMB numbers ≥2 per year were defined as meaningful neuroimaging outcomes.

Statistical analyses

Descriptive analyses of clinical demographic characteristics, BP parameters, and neuroimaging features were performed. A Cox regression model was used to test the influence of BP parameters on incident stroke and was adjusted for age, sex, hypertension, and history of stroke. Logistic regression models were applied to test the association between the BP parameters and any incident lacune or incident CMB ≥2 per year, with covariates of age, sex, hypertension, and baseline lacune or CMB numbers. In the above models, the mean and SD of SBP, DBP, and PP, as well as systolic hypertension (90-day mean SBP >130 mm Hg) and diastolic hypertension (90-day mean DBP >80 mm Hg) were individually tested as independent variables. For the sensitivity analysis, we included patients who were initially excluded because there was no follow-up MRI to test the effects of BP on incident stroke (clinical outcome).

Furthermore, correlations between BP parameters and annual changes in neuroimaging markers were plotted as scatterplots and tested using unadjusted simple linear regression. A linear mixed model for repeated measures was used to test the associations between the change in WML proportion or mean cortical thickness (dependent variable) and each of the BP parameters (independent variable), adjusted for age, sex, hypertension, study site, and MRI intervals. Due to the skewed distribution and many zero values for the numbers of lacunes and CMBs, a Poisson mixed-effect model (Poisson generalized linear mixed model) was applied to test the associations between the incident lacunes or CMB number and BP parameters and adjusted for age, sex, hypertension, study site, and MRI intervals. The significance level was set at $P<0.05$. No adjustments were made for multiple comparisons because this was an exploratory analysis. All analyses were performed with SAS, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

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Supplementary Table 1. Characteristics of CADASIL patients

Characteristic	Value (n=91)
Age (yr)	63.2±10.5
Male sex	59 (64.8)
Hypertension	51 (56.0)
Diabetes mellitus	20 (22.0)
Hyperlipidemia	41 (45.1)
Atrial fibrillation	7 (7.7)
Coronary artery disease	4 (4.4)
History of stroke	55 (60.4)
Ischemic stroke	38 (41.7)
Intracerebral hemorrhage	21 (23.1)
Use of BP-lowering drugs	48 (52.7)
ACE inhibitor or ARB	38 (41.7)
Beta-blockers	7 (7.7)
Calcium channel blockers	29 (31.9)
Use of antithrombotic agents	54 (59.3)
Use of statin	43 (47.3)
Main symptoms at diagnosis	
Stroke	53 (58.2)
Cognitive decline	9 (9.9)
Gait disturbance	8 (8.8)
Headache or dizziness	7 (7.7)
Pre-symptomatic family members	9 (9.9)
Incidental MRI findings of SVD	5 (5.5)
90-Day BP parameters (mm Hg)	
SBP, mean	119.3±10.6
SBP, SD	6.9±2.4
DBP, mean	73.6±7.9
DBP, SD	5.0±1.4
PP, mean	45.9±8.9
PP, SD	5.3±1.9
Follow-up	
Follow-up duration (mo)	30 (24–44)
Incident stroke	9 (9.9)
Ischemic/hemorrhagic stroke	6/3

Values are presented as mean±standard deviation, count (percentage), or median (interquartile range).
CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; BP, blood pressure; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; MRI, magnetic resonance imaging; SVD, small-vessel disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation.

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Supplementary Table 2. Change in neuroimaging markers

	Baseline MRI	Follow-up MRI	Annual change
PVWM Fazekas score	3 (2–3)	3 (2–3)	-
DWM Fazekas score	3 (2–3)	3 (2–3)	-
EPVS–basal ganglia	3 (2–3)	3 (2–3)	-
EPVS–centrum semiovale	1 (1–2)	1 (1–2)	-
Lacune numbers	5 (2–11)	6 (2–12)	0 (0–1)/0.5±1.3
CMB numbers	8 (2–35)	9 (2–42)	1 (0–4)/2.9±4.1
Lobar CMB numbers	2 (0–12)	3 (0–15)	-
Deep CMB numbers	3 (1–15)	4 (1–20)	-
Infratentorial CMB numbers	1 (0–3)	1 (0–4)	-
WML volume (mL)	39.5±23.8	43.1±25.0	-
WML proportion, % eTIV	2.72±1.59	2.88±1.64	0.23±0.31
Cortical thickness (mm)	2.36±0.13	2.33±0.13	-0.03±0.05
Brain parenchymal fraction, % eTIV	73.00±5.14	72.55±5.27	-0.003±0.02

Values are presented as median (interquartile range) or mean±standard deviation.
MRI, magnetic resonance imaging; PVWM, periventricular white matter; DWM, deep white matter; EPVS, enlarged perivascular space; CMB, cerebral microbleed; WML, white matter lesion; eTIV, estimated total intracranial volume.

Supplementary Table 3. Clinical features and outcomes between *NOTCH3* R544C and non-R544C variant carriers

	R544C (n=81)	Non-R544C (n=10)	*P*
Age (yr)	64.0±9.7	56.5±13.9	0.03
Male sex	53 (65.4)	6 (60.0)	0.74
History of stroke	50 (61.7)	5 (50.0)	0.51
Ischemic stroke	34 (42.0)	4 (40.0)	0.99
Intracerebral hemorrhage	20 (24.7)	1 (10.0)	0.44
MRI markers			
Lacune numbers	5 (2–10)	5 (2–11)	0.94
CMB numbers	9 (2–40)	3 (0–11)	0.08
WML volume (mL)	39.0±23.4	43.6±27.5	0.47
WML proportion, % eTIV	2.67±1.55	3.08±1.98	0.43
Cortical thickness (mm)	2.36±0.11	2.37±0.25	0.17
Brain parenchymal fraction, % eTIV	72.37±4.56	78.71±6.90	<0.01
Outcomes			
Incident stroke	9 (11.1)	0 (0)	0.59
Incident lacune	25 (30.9)	1 (10.0)	0.27
Increased CMB 2/year	36 (44.4)	1 (10.0)	0.04

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
CMB, cerebral microbleed; eTIV, estimated total intracranial volume; MRI, magnetic resonance imaging; WML, white matter lesion.

Supplementary Table 4. Effects of blood pressure or hypertension on clinical outcome when including patients who do not have follow-up MRI in the analysis

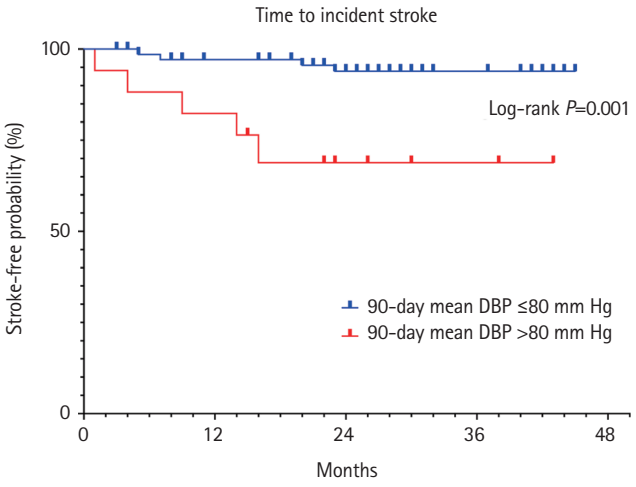
	Incident stroke (updated n=122)		
	Yes (n=9)	No (n=113)	Adjusted HR (95% CI)*
SBP, mean (mm Hg)†	122.4±9.1	119.5±10.5	1.39 (0.71, 2.70)
SBP, SD (mm Hg)	6.7±2.3	8.7±2.5	0.87 (0.62, 1.22)
DBP, mean (mm Hg)†	77.9±9.2	73.6±7.8	1.96 (0.76, 5.08)
DBP, SD (mm Hg)	5.6±1.6	6.1±1.4	1.18 (0.73, 1.91)
PP, mean (mm Hg)†	44.7±5.9	45.9±9.0	0.96 (0.41, 2.26)
PP, SD (mm Hg)	4.8±1.3	7.0±2.1	0.60 (0.32, 1.12)
SBP >130 mm Hg	2 (22.2)	14 (11.5)	2.19 (0.44, 10.88)
DBP >80 mm Hg	5 (55.6)	20 (17.7)	5.59 (1.34, 23.3)‡

Values are presented as mean±standard deviation or number (%) unless otherwise indicated.
MRI, magnetic resonance imaging; HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure; SD, standard deviation; DBP, diastolic blood pressure; PP, pulse pressure.
*Adjusted for age, sex, hypertension, and history of stroke; †Effect estimates are expressed as per 10-mm Hg increase in blood pressure; ‡Statistically significant.

Supplementary Table 5. Association between blood pressure and change in neuroimaging markers in CADASIL patients

Changes of MRI	ΔWML proportion*	ΔCortical thickness*	ΔBrain parenchymal fraction*	ΔLacune†	ΔCMB†
	β (95% CI)	β (95% CI)	β (95% CI)	Relative risk (95% CI)	Relative risk (95% CI)
SBP, mean	0.002 (-0.001, 0.005)	0.02 (-0.003, 0.04)	-0.002 (-0.01, 0.01)	1.26 (1.00, 1.58)‡	1.35 (0.91, 2.00)
SBP, SD	0.005 (-0.008, 0.02)	-0.04 (-0.14, 0.05)	-0.03 (-0.08, 0.01)	1.62 (0.72, 3.60)	2.66 (0.62, 11.4)
DBP, mean	0.005 (0.001, 0.009)‡	0.02 (-0.007, 0.05)	-0.01 (-0.02, 0.01)	1.69 (1.26, 2.28)‡	2.43 (1.46, 4.05)‡
DBP, SD	0.003 (-0.02, 0.02)	-0.09 (-0.24, 0.07)	-0.03 (-0.11, 0.05)	1.76 (0.39, 8.07)	4.29 (0.31, 59.1)
PP, mean	-0.002 (-0.006, 0.002)	0.01 (-0.02, 0.04)	0.005 (-0.01, 0.02)	0.89 (0.65, 1.24)	0.73 (0.48, 1.11)
PP, SD	0.009 (-0.008, 0.03)	-0.06 (-0.17, 0.06)	-0.06 (-0.07, 0.06)	1.48 (0.64, 3.42)	2.07 (0.39, 11.1)

CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; MRI, magnetic resonance imaging; WML, white matter lesion; CMB, cerebral microbleed; CI, confidence interval; SBP, systolic blood pressure; SD, standard deviation; DBP, diastolic blood pressure; PP, pulse pressure. *A linear mixed model was applied and adjusted for age, sex, hypertension, study site, and the interval between the two MRI scans. Effect estimates are expressed per 10-mm Hg increase in blood pressure; †A Poisson mixed-effect model was applied and adjusted for age, sex, hypertension, study site, and interval between the two MRI scans. Effect estimates are expressed per 10-mm Hg increase in blood pressure; ‡Statistically significant.



Supplementary Figure 1. Kaplan–Meier plot for incident stroke. CADASIL patients with mean diastolic blood pressure (DBP) >80 mm Hg had a higher risk of incident stroke.

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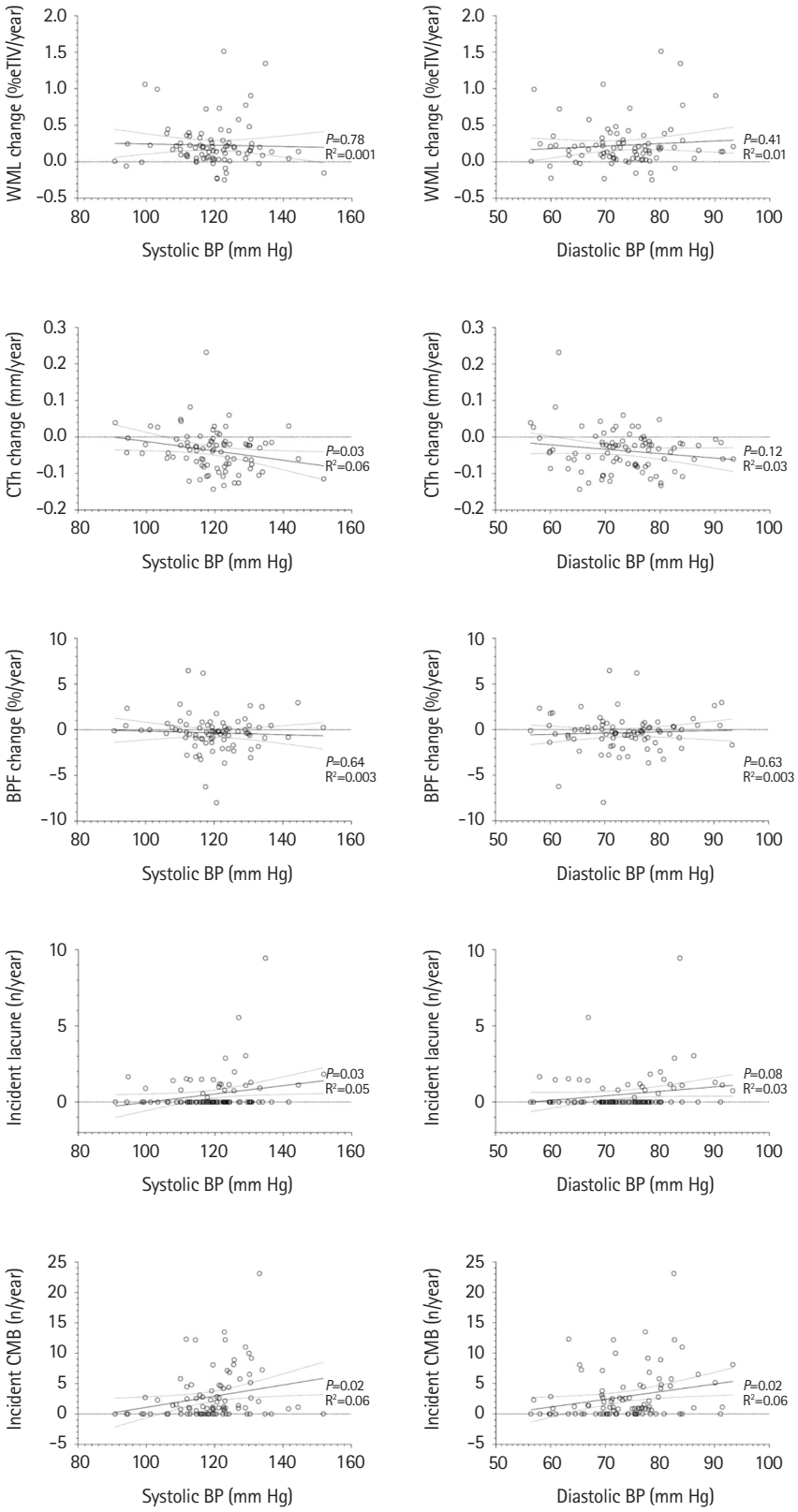

Supplementary Figure 2. Scatter plot of mean blood pressure and annual change of neuroimaging markers. In unadjusted linear regression, significant associations existed between systolic blood pressure (BP) and changes in cortical thickness (P=0.03), incident lacune (P=0.03), and incident cerebral microbleeds (P=0.02), and diastolic BP and incident cerebral microbleeds (P=0.02). WML, white matter lesion; CTh, cortical thickness; BPF, brain parenchymal fraction; CMB, cerebral microbleeds.