Blood pressure variability and leukoaraiosis in acute ischemic stroke

Blood pressure variability and leukoaraiosis in acute ischaemic stroke

Journal:	*International Journal of Stroke*
Manuscript ID	IJS-04-17-5663.R1
Manuscript Type:	Research
Date Submitted by the Author:	08-Jun-2017
Complete List of Authors:	Dickie, David; The University of Edinburgh, Brain Research Imaging Aribisala, Benjamin; The University of Edinburgh, Brain Research Imaging Mair, Grant; University of Edinburgh, Centre for Clinical Brain Sciences Berge, Eivind; Oslo University Hospital, Dept of Internal Medicine Lindley, Richard; The University of Sydney, Sydney Medical School; George Institute for Global Health, Sandercock, Peter; University of Edinburgh, DCN von Kummer, Rüdiger; Technische Universität, Neuroradiology; von Heijne, Anders; Dept of Radiology, Peeters, Andre; UCL St Luc, Neurology; Cala, Lesley; The University of Western Australia Farrall, Andrew; University of Edinburgh, Division of Clinical Neurosciences Morris, Zoe; NHS Lothian Bradey, Nick; James Cook University Hospital, Neurology Potter, Gillian; Greater Manchester Neurosciences Centre, Neuroradiology Adami, Alessandro; Ospedale Sacro Cuore-Don Calabria, Stroke Center Wardlaw, Joanna; University of Edinburgh, Clinical Neurosciences
Keywords:	Blood pressure, variation, Leukoaraiosis, Stroke, ischaemic, computed tomography

Blood pressure variability and leukoaraiosis in acute ischaemic stroke

David Alexander Dickie, PhD[a,b,c,*], Benjamin Aribisala, PhD[a,b,c,*], Grant Mair, MB ChB[a,b,c], Eivind Berge, MD[d], Richard I. Lindley, MD[e], Peter Sandercock, DM[c], Rudiger von Kummer, MD[f], Anders von Heijne, MD[g], Andre Peeters, MD[h], Lesley Cala, MD, FRCR[i], Andrew Farrall, FRCRC[c], Zoe Morris, FRCR[j], Nick Bradey, FRCR[k], Gillian Potter, MD, FRCR[l], Alessandro Adami, MD[m], Joanna M. Wardlaw, MD[a,b,c,+]

[a]*Brain Research Imaging Centre, The University of Edinburgh, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh, EH16 4TJ, United Kingdom.*

[b]*Scottish Imaging Network, A Platform for Scientific Excellence (SINAPSE) collaboration.*

[c]*Centre for Clinical Brain Sciences, Chancellor's building, 49 Little France Crescent, EH16 4SB, United Kingdom.*

[d]*Department of Internal Medicine, Oslo University Hospital, Oslo, Norway.*

[e]*George Institute for Global Health and Discipline of Medicine, University of Sydney, Sydney, New South Wales, Australia.*

[f]*Department of Neuroradiology, University Hospital, Technische Universität Dresden, Germany*

[g]*Danderyd Hospital, Stockholm, Sweden*

[h]*Cliniques Universitaires Saint-Luc, Bruxelles, Belgium*

[i]*School of Pathology and Laboratory Medicine, The University of Western Australia, Crawley, Western Australia*

[j]*NHS Lothian, Edinburgh, Scotland*

[k]*Neuroradiology, James Cook University Hospital, South Tees Hospital NHS Trust, Middlesborough, UK*

[l]*Salford Royal NHS Foundation Trust, Salford, Greater Manchester*

[m]*Stroke Center, Department of Neurology, Ospedale Sacro Cuore-Don Calabria, Via Sempreboni 6, 37024, Negrar, Verona, IT*

*These authors contributed equally.

[+]Corresponding author:

Joanna M. Wardlaw, postal address is affiliation "a".

E-mail address: joanna.wardlaw@ed.ac.uk

Cover title: BP variability and leukoaraiosis in acute stroke

Keywords: Blood pressurise; variation; leukoaraiosis; stroke, ischaemic; computed tomography

Total word count: 3952/4000

Abstract word count: 215/250

Number of figures: 0; number of tables: 2 (2 additional tables in supplement)

Author contributions

David Alexander Dickie, PhD[a,b,c] and Benjamin Aribisala, PhD[a,b,c] performed the analysis and wrote the manuscript. Grant Mair, MB ChB[a,b,c] supported the analysis and edited the manuscript.

Rudiger von Kummer, MD[f], Anders von Heijne, MD[g], Andre Peeters, MD[h], Lesley Cala, MD, FRCR[i], Andrew Farrall, FRCRC[c], Zoe Morris, FRCR[j], Nick Bradey, FRCR[k], Gillian Potter, MD, FRCR[l], and Alessandro Adami, MD[m] performed image analysis and edited the manuscript.

Joanna M. Wardlaw, MD[a,b,c] designed and conceptualised the analysis, oversaw the analysis, and edited the manuscript with support from Eivind Berge, MD[d], Richard I. Lindley, MD[e], and Peter Sandercock, DM[c].

Abstract

Higher blood pressure (BP), BP variability and leukoaraiosis are risk factors for early adverse events and poor functional outcome after ischaemic stroke, but prior studies differed on whether leukoaraiosis was associated with BP variability, including in ischaemic stroke.

In the Third International Stroke Trial, BP was measured in the acute phase of ischaemic stroke immediately prior to randomization, and at 0.5, 1 hour and 24 hours after randomization. Masked neuroradiologists rated index infarct, leukoaraiosis and atrophy on CT using validated methods. We characterised BP variation by coefficient of variance (CV) and three other standard methods. We measured associations between BP, BP variability and leukoaraiosis using generalized estimating equations, adjusting for age, and a number of covariates related to treatment and stroke type/severity.

Amongst 3017 patients, mean (±SD) systolic and diastolic BP decreased from 155(±24)/82(±15)mmHg pre-randomization to 146(±23)/78(±14)mmHg 24 hours later (P<0.005). Mean within-subject CV was 0.09±0.05 for systolic and 0.11±0.06 for diastolic BP. Patients with most leukoaraiosis were older and had higher BP than those with least (P<0.0001). Although statistically significant in simple pairwise comparisons, no measures of BP variability were associated with leukoaraiosis when adjusting for confounding variables (P>0.05), e.g., age.

Our results suggest that BP variability is not a potential mechanism to explain the association between leukoaraiosis and poor outcome after acute stroke.

Introduction

Higher blood pressure (BP) level and BP variability are risk factors for early adverse events and later poor functional outcome after stroke(1, 2)~~; and long-term variability in BP has recently been shown to be a risk factor for cardiovascular events and death after stroke(3)~~. Higher long-term BP has consistently been associated cross-sectionally with a higher burden of leukoaraiosis, which is itself a major risk factor for stroke, dementia, and death(3-8); and independently predicts poor outcome after stroke(9). However, there are conflicting reports on the association between higher long-term BP variability and the burden of leukoaraiosis(6, 7, 10, 11) and short-term BP variability and leukoaraiosis(10, 12, 13). This discord among a relatively small number of studies, mostly with N<250 and only one with greater than 500 participants, is in contrast to the often studied and well characterized associations between higher absolute BP and more leukoaraiosis(14).

The sample sizes in these studies were often relatively small (N<500)(10, 12, 13) and/or were in community-dwelling participants(6, 11), or during long-term follow-up after stroke(7), which might contribute to differing results. We found no previous investigations of the associations between pre-existing leukoaraiosis and variability in BP during the acute phase of stroke. Yet the acute phase of stroke is a time when BP is likely to be highly variable(15, 16).

We previously studied the effect of BP variability(1) and of leukoaraiosis(9) on outcome after ischaemic stroke. Given the independent negative prognostic impacts that we found in these previous studies, we aimed to clarify the relationship between BP variability and leukoaraiosis in the acute phase of ischaemic stroke using data from a large randomized trial, the Third International Stroke Trial (IST-3)(9, 17-19).

Methods

Participants

IST-3 was conducted with 3035 participants recruited from 156 centres in 12 countries(19). All participating centres had a national co-ordinator and local ethics approval. The trial, registered at ISRCTN.com, number ISRCTN25765518, was run according to the local procedures and law of each centre(18). All patients or an assigned patient relative/representative (where patients did not have capacity) gave informed consent. Full details of trial procedures, including imaging assessments, patient characteristics and the main trial results, have been published(9, 17-19).

BP measurement

BP was recorded by trained personnel for trial purposes at five time points: pre-randomization, start of treatment (or immediately after randomization for control patients), and at 30 minutes, 60 minutes, and 24 hours after treatment. We recorded whether BP was treated prior to admission in the trial, within the first 24 hours, and/or between 24 hours and seven days after randomization.

BP variability

We assessed variability in BP via measures of systolic, diastolic, pulse, and mean arterial pressure taken pre-randomization, at the start of treatment, and 30 minutes, 60 minutes, and 24 hours after treatment.

We calculated mean arterial pressure (MAP) via equation 1:

$$\mathrm{MAP}=\mathrm{DBP}+\frac{\mathrm{SBP}-\mathrm{DBP}}{3} \quad (1)$$

According to previous studies(6, 7, 13), we used standard deviation, coefficient of variance (CV), average real variability, and successive variation to quantify variance in each measure of BP.

Average real variability (ARV) was computed for all four measures of BP via equation 2:

$$ARV=\frac{|BP_{start}-BP_{rand}|+|BP_{30m}-BP_{start}|+|BP_{60m}-BP_{30m}|+|BP_{24h}-BP_{60m}|}{4} \quad (2)$$

Successive variability (SV) was computed for all four measures of BP via equation 3:

$$SV=\frac{(BP_{start}-BP_{rand})^2+(BP_{30m}-BP_{start})^2+(BP_{60m}-BP_{30m})^2+(BP_{24h}-BP_{60m})^2}{4} \quad (3)$$

Pre-existing brain damage

Leukoaraiosis, including anterior and posterior (each scored 0-2), burden and whole brain atrophy, were rated by trained neuroradiologists on computed tomography (CT) masked to all clinical details using previously validated procedures(9, 20, 21). Anterior and posterior leukoaraiosis scores were summed to compute a total leukoaraiosis score (on a continuum of 0 to 4; with 4 being the greatest leukoaraiosis burden). Whole brain atrophy was scored for central and cortical structures as none, moderate, or severe, then dichotomised into a single variable as either absent (0) or present in one or both regions (1).

Statistical analyses

All statistical analyses were performed in the Statistical Analysis System (SAS) version 9.4 (© 2002-2012 SAS Institute Inc.). We used longitudinal multiple regression (generalized estimating equations) to model absolute BP (separate models for systolic, diastolic, pulse, and mean arterial pressure) over time according to leukoaraiosis burden and adjusted for age, atrophy, NIHSS, stroke subtype, time to randomization, treatment allocation, and BP lowering treatment before the trial, during the first 24 hours, and between 24 hours and seven days. This analysis is summarised in equation 4:

$$BP=\beta\_Time+\beta\_Age+\beta\_Leukoaraiosis+\beta\_Atrophy+\beta\_NIHSS+\beta\_StrokeSubtype+\beta\_TimeRand+\beta\_TreatmeentAlloc+\beta\_BPlowPrior+\beta\_BPlowDay1+\beta\_BPlowDay2\text{-}7+error \quad (4)$$

We also used generalized estimating equations to measure associations between leukoaraiosis and BP variability with the same adjustment variables. This analysis is summarised in equation 5:

$$Leukoaraiosis=\beta\_DBPV+\beta\_SBPV+\beta\_PPV+\beta\_MAPV+\beta\_Age+\beta\_NIHSS+\beta\_Atrophy+\beta\_StrokeSubtype+\beta\_TimeRand+\beta\_TreatmeentAlloc+\beta\_BPlowPrior+\beta\_BPlowDay1+\beta\_BPlowDay2\text{-}7+error \quad (5)$$

We defined leukoaraiosis as the dependent variable in equation 5 as this allowed all measures of BP (systolic, diastolic, pulse, and mean) to be assessed in one model (rather than four separate models where each measure of variability was the dependent variable). We assessed collinearity using variance inflation factor and stepwise removal of potentially volatile variables. The generalized estimating equations used here are parametric (mean-based) and although leukoaraiosis often has highly skewed distributions, we found this to have a nominal effect on mean-based regression results(14). We used an exchangeable correlation matrix in our generalized estimating equations because repeated BP measures were correlated but not autoregressive. We assessed overfitting by comparing raw and adjusted R-squared. These models were designed to assess the influence of several variables known to have adverse prognostic effects in acute stroke (e.g., atrophy and stroke severity)(9) and whether their effects were attenuated/mediated in fully adjusted models. We determined the influence of adjustment variables by firstly modelling pairwise associations (unadjusted models) between BP variability and leukoaraiosis.

Results

Patient characteristics

Full characteristics of the N=3035 patients, including treatment for hypertension prior to trial admission, stroke subtypes, atrophy and leukoaraiosis CT findings, are provided in supplement; 18 patients did not have CT scans so did not contribute leukoaraiosis or atrophy scores in this analysis. Mean age was 77.3±12.2 years with median NIHSS 11 (IQR=11), and TACI (N=1306, 43%) was the most frequent stroke subtype. BP values by leukoaraiosis group, unadjusted for covariates, are provided in supplement.

Association between leukoaraiosis and acute absolute BP

The following are all adjusted analyses; beta coefficients and *P*-values are in Table 1.

Systolic (155±24 mmHg to 146±23 mmHg) and diastolic (82±15 mmHg to 78±14 mmHg) BP generally fell with time from pre-randomization to 24 hours after start of treatment ($P<0.005$). Systolic BP was 3.58 (95% confidence interval, CI, ±2.5) mmHg lower and diastolic BP was 3.80 (95% CI ±1.5) mmHg lower throughout the measurement period in patients with leukoaraiosis grade zero versus grade four. Systolic BP was higher ($\beta=0.23$, $P<0.0001$) and diastolic BP was lower ($\beta=-0.14$, $P<0.0001$) in older patients.

Mean arterial pressure was lower in those with leukoaraiosis grade zero versus grade four, but not associated with age, while pulse pressure was higher in older people but not associated with leukoaraiosis (Table 1).

Unadjusted associations between leukoaraiosis and acute BP variability

Unadjusted pairwise associations between leukoaraiosis and BP variability (systolic, diastolic, pulse, mean) characterized by CV were not statistically significant ($P>0.05$). All other measures of BP variability (except successive variability in pulse pressure, $P>0.05$) were significantly associated with leukoaraiosis, where greater variability was associated with increased burden of leukoaraiosis, when not adjusting for covariates ($P<0.05$; see supplement).

Adjusted associations between leukoaraiosis and acute BP variability

The following are all adjusted analyses; beta coefficients and *P*-values are in Table 2.

In contrast to the unadjusted pairwise associations, leukoaraiosis was not associated with BP variability in the acute phase of ischaemic stroke, whether measured by CV (column 1 Table 2), standard deviation (column 2 Table 2), average real variability (column 3 Table 2), or successive variability (column 4 Table 2) when adjusting for age, atrophy, stroke severity, subtype, and treatment groups.

Discussion

In this large study including 3017 patients, we found that leukoaraiosis was associated with high absolute BP, but not with BP variability, over the first 24 hours after ischaemic stroke when adjusting for relevant covariates. At first there did appear to be a positive association between leukoaraiosis and acute BP variability measured by standard deviation, average real variability, and successive variability, however these associations disappeared when adjusting for age and other relevant covariates. Therefore, while BP variability is associated with poor outcome in IST-3(1), it is not likely to explain the association between leukoaraiosis and poor outcome after acute stroke, that we also found in IST-3(9). Higher absolute BPs were associated with the presence of grade four leukoaraiosis versus grade zero; but patients with grade four leukoaraiosis did not have higher absolute BP compared to patients with leukoaraiosis grades one to three, after adjusting for age.

Our finding that short-term BP variability in acute ischaemic stroke is not independently associated with leukoaraiosis is consistent with two previous studies (N total=68), including one of non-acute lacunar stroke patients (N=43)(10, 12). Additionally, the lack of association between leukoaraiosis and BP variability is consistent with the largest previous study we found (N=694), that was conducted in community-dwelling subjects(6). However, our finding contrasts with previous smaller studies (N=66; N=210; N=155) of community-dwelling older subjects that found an association between increased variability in short-term BP and leukoaraiosis(13, 22). Additionally, positive associations between leukoaraiosis and BP variability have been found in primary hypertensive (N=487)(23) and cardiovascular disease (N=39)(24) patients. This discord may be due to acute ischaemia masking associations between BP variability and leukoaraiosis, the physiology of patient groups versus community dwelling participants, continual monitoring versus intermittent BP measures, or that previous sample sizes were much smaller (generally N<250) than here. Independent studies of absolute BP and leukoaraiosis may have similar differences in their study design, however, these have still produced generally consistent associations between higher absolute BP and more leukoaraiosis; and the number of these studies far outweighs the number of studies into BP variability and leukoaraiosis(14).

The strengths of our study include the large number of acute ischaemic stroke patients with

BP monitoring within the first 24 hours of stroke at fixed intervals according to standardised protocols; and recording of BP lowering treatment before, during the first 24 hours, and between two and seven days after trial enrolment. IST-3 settings and patients reflect a broad range of hospital environments charged with the care of ischaemic stroke. The number of participants studied here is over four times greater than the largest study of BP variability and leukoaraiosis that we found(6). Finally, we assessed a range of BP variability measures compared with previous studies that used only one measure(11, 12).

Despite these strengths, our study has some limitations. As we used data from a randomized-controlled trial, there is always a risk of confounding. For example, we were not able to control for some vascular risk factors such as cholesterol, which may have an influence on associations between BP and leukoaraiosis(14). MRI has greater sensitivity than CT for detecting leukoaraiosis but CT is much more widely used in acute stroke and detects established leukoaraiosis. We had limited information on BP prior to enrolment in the trial, beyond reported use of antihypertensive treatment, therefore do not know the duration of elevated BP prior to the trial. This means that we cannot ascertain whether those with higher BP and more leukoaraiosis had chronically high BP or only acutely high BP. Continuous monitoring of BP may identify subtle associations between BP variability and leukoaraiosis that we were not able to detect here. Other limitations related to BP measurements and the lack of random allocation to BP lowering treatment in IST-3 have previously been discussed at length(1). Our results may not apply to patients with haemorrhagic stroke as IST-3 only included ischaemic stroke. However, several completed or ongoing trials of BP lowering in haemorrhagic stroke also use similar scan assessments and therefore could assess leukoaraiosis and BP variability.

Notwithstanding, we have shown that patients with leukoaraiosis have high BP but do not have increased BP variability immediately after ischaemic stroke. While additional work is required in this area, our results suggest that BP variability is not a potential mechanism to explain the association between leukoaraiosis and poor outcome after acute ischaemic stroke.

Acknowledgements

The authors greatly thank and acknowledge the patients who participated in IST-3, and the many staff in all participating centres, as listed previously(19).

Sources of funding

Full sources of funding for IST-3 were previously described in the IST-3 protocol paper(18). DAD was funded by Innovate UK (46917-348146).

Conflict of interest

E. Berge is a member of the Second RIGHT-2 advisory committee. R.I. Lindley received support from Boehringer Ingelheim and Covidien. P. Sandercock and J.M. Wardlaw received support from the Medical Research Council, the Stroke Association, the Health Foundation, and Boehringer Ingelheim, and J.M. Wardlaw also received support from Chest Heart Stroke Scotland. All other authors report no conflicts.

References

1. Berge E, Cohen G, Lindley RI, et al. Effects of Blood Pressure and Blood Pressure–Lowering Treatment During the First 24 Hours Among Patients in the Third International Stroke Trial of Thrombolytic Treatment for Acute Ischemic Stroke. Stroke 2015;46(12):3362-9.
2. Ahmed N, Wahlgren N, Brainin M, et al. Relationship of Blood Pressure, Antihypertensive Therapy, and Outcome in Ischemic Stroke Treated With Intravenous Thrombolysis: Retrospective Analysis From Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register (SITS-ISTR). Stroke 2009;40(7):2442-9.
3. Debette S, Seshadri S, Beiser A, et al. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. Neurology 2011;77(5):461-8.
4. Marcus J, Gardener H, Rundek T, et al. Baseline and Longitudinal Increases in Diastolic Blood Pressure Are Associated With Greater White Matter Hyperintensity Volume: The Northern Manhattan Study. Stroke 2011;42(9):2639-41.
5. Debette S, Markus H. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ 2010;341:c3666.
6. Aribisala BS, Morris Z, Eadie E, et al. Blood pressure, internal carotid artery flow parameters, and age-related white matter hyperintensities. Hypertension 2014;63(5):1011-8.
7. Liu W, Liu R, Sun W, et al. Different Impacts of Blood Pressure Variability on the Progression of Cerebral Microbleeds and White Matter Lesions. Stroke 2012;43(11):2916-22.
8. Verhaaren BFJ, Vernooij MW, de Boer R, et al. High Blood Pressure and Cerebral White Matter Lesion Progression in the General Population. Hypertension 2013;61(6):1354-9.
9. The IST-3 collaborative group. Association between brain imaging signs, early and late outcomes, and response to intravenous alteplase after acute ischaemic stroke in the third International Stroke Trial (IST-3): secondary analysis of a randomised controlled trial. The Lancet Neurology 2015;14(5):485-96.
10. Gómez-Angelats E, de La Sierra A, Sierra C, Parati G, Mancia G, Coca A. Blood pressure variability and silent cerebral damage in essential hypertension. Am J Hypertens 2004;17(8):696-700.
11. Liu Z, Zhao Y, Zhang H, et al. Excessive variability in systolic blood pressure that is self-measured at home exacerbates the progression of brain white matter lesions and cognitive impairment in the oldest old. Hypertens Res 2016;39(4):245-53.
12. Martí-Fàbregas J, Valencia C, Pujol J, et al. Blood pressure variability and leukoaraiosis amount in cerebral small-vessel disease. Acta Neurol Scand 2001;104(6):358-63.
13. Tartaro A, Budassi S, Pascali D, et al. Correlation between computed tomography findings of leukoaraiosis and 24-hour blood pressure variability in elderly subjects. Journal of Stroke and Cerebrovascular Diseases 1999;8(2):66-70.
14. Dickie DA, Ritchie SJ, Cox SR, et al. Vascular risk factors and progression of white matter hyperintensities in the Lothian Birth Cohort 1936. Neurobiol Aging 2016;42:116-23.
15. Huang Y, Sharma VK, Robinson T, et al. Rationale, design, and progress of the ENhanced Control of Hypertension ANd Thrombolysis strokE stuDy (ENCHANTED) trial: An international multicenter 2 × 2 quasi-factorial randomized controlled trial of low- vs. standard-dose rt-PA and early intensive vs. guideline-recommended blood pressure lowering in patients with acute ischaemic stroke eligible for thrombolysis treatment. International Journal of Stroke 2015;10(5):778-88.
16. The ENOS Trial Investigators. Efficacy of nitric oxide, with or without continuing

antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): a partial-factorial randomised controlled trial. The Lancet 2015;385(9968):617-28.
17. Sandercock P, Lindley R, Wardlaw J, et al. Update on the third international stroke trial (IST-3) of thrombolysis for acute ischaemic stroke and baseline features of the 3035 patients recruited. Trials 2011;12(1):1-10.
18. Sandercock P, Lindley R, Wardlaw J, et al. The third international stroke trial (IST-3) of thrombolysis for acute ischaemic stroke. Trials 2008;9(1):1-17.
19. The IST-3 collaborative group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. The Lancet 2012;379(9834):2352-63.
20. Wardlaw JM, Farrall AJ, Perry D, et al. Factors Influencing the Detection of Early CT Signs of Cerebral Ischemia: An Internet-Based, International Multiobserver Study. Stroke 2007;38(4):1250-6.
21. Wardlaw JM, von Kummer R, Farrall AJ, Chappell FM, Hill M, Perry D. A Large Web-Based Observer Reliability Study of Early Ischaemic Signs on Computed Tomography. The Acute Cerebral CT Evaluation of Stroke Study (ACCESS). PLoS ONE 2010;5(12):e15757.
22. Yamaguchi Y, Wada M, Sato H, et al. Impact of Ambulatory Blood Pressure Variability on Cerebral Small Vessel Disease Progression and Cognitive Decline in Community-Based Elderly Japanese. Am J Hypertens 2014;27(10):1257-67.
23. Filomena J, Riba-Llena I, Vinyoles E, et al. Short-Term Blood Pressure Variability Relates to the Presence of Subclinical Brain Small Vessel Disease in Primary Hypertension. Hypertension 2015;66(3):634-40.
24. Gunstad J, Cohen RA, Tate DF, et al. Blood pressure variability and white matter hyperintensities in older adults with cardiovascular disease. Blood Press 2005;14(6):353-8.

Table 1. Regression-based associations between absolute BP (dependent variable) and leukoaraiosis (independent variable) with relevant covariates

		Diastolic BP		Systolic BP		Pulse Pressure		Mean arterial pressure	
Parameter	Level	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value
Time (from pre-rand to 24 hours)		**-1.28**	**<0.0001***	**-2.32**	**<0.0001***	**-1.05**	**<0.0001***	**-1.63**	**<0.0001***
Age		**-0.14**	**<0.0001***	**0.23**	**<0.0001***	**0.38**	**<0.0001***	-0.02	0.52
Leukoaraiosis versus grade 4	0	**-3.80**	**<0.0001***	**-3.58**	**0.0042***	0.21	0.85	**-3.73**	**<0.0001***
	1	-1.73	0.06	0.37	0.81	2.09	0.10	-1.03	0.29
	2	-0.44	0.57	0.37	0.78	0.80	0.47	-0.18	0.83
	3	-0.40	0.74	-0.07	0.97	0.31	0.86	-0.30	0.82
No atrophy		0.09	0.89	0.41	0.69	0.33	0.69	0.20	0.77
NIHSS		-0.06	0.13	-0.05	0.46	0.01	0.82	-0.06	0.19
Stroke subtype versus LACI	PACI	-0.54	0.45	-0.55	0.68	0.04	0.97	-0.53	0.52
	POCI	-0.55	0.55	-0.05	0.98	0.53	0.69	-0.39	0.70
	TACI	-0.04	0.96	1.47	0.33	1.56	0.21	0.47	0.62
Time to randomization (hours)		0.21	0.19	0.50	0.08	0.29	0.23	0.31	0.09
Control versus rt-PA		0.62	0.14	0.63	0.37	0.01	0.99	0.63	0.17
BP lowering prior to study		**-1.35**	**0.0092***	-0.92	0.29	0.39	0.57	**-1.21**	**0.0339***
BP lowering in 1st 24 hours		**2.57**	**<0.0001***	**3.83**	**<0.0001***	1.27	0.09	**3.00**	**<0.0001***
BP lowering 24hr-7days		1.04	0.07	**5.24**	**<0.0001***	**4.22**	**<0.0001***	**2.44**	**<0.0001***

Note: BP=blood pressure; SE=standard error; **P*<0.05; NIHSS=National Institutes of Health Stroke Scale; LACI=lacunar infarcts; PACI=partial anterior circulation infarcts; POCI=posterior circulation infarcts, TACI=total anterior circulation infarcts; rt-PA=recombinant tissue-type plasminogen activator.

Beta are not standardised.

Table 2. Regression-based associations between leukoaraiosis (dependent variable) and BP variability (independent variables) with relevant covariates

		Coefficient of variance		Standard deviation		Average real variability		Successive variability	
Parameter	Level	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value
Diastolic BP		-1.71	0.09	0.02	0.38	0.01	0.55	0.00	0.94
Systolic BP		-1.89	0.16	0.01	0.37	0.01	0.31	0.00	0.12
Pulse pressure		0.41	0.30	-0.01	0.23	-0.01	0.20	0.00	0.14
Mean arterial pressure		2.36	0.21	-0.02	0.38	-0.01	0.58	null	.
Age		**0.02**	**<0.0001***	**0.02**	**<0.0001***	**0.03**	**<0.0001***	**0.03**	**<0.0001***
NIHSS		0.00	0.63	0.00	0.70	0.00	0.38	0.00	0.40
No atrophy		**-0.79**	**<0.0001***	**-0.78**	**<0.0001***	**-0.76**	**<0.0001***	**-0.76**	**<0.0001***
Stroke subtype versus LACI	PACI	-0.13	0.09	-0.14	0.09	**-0.18**	**0.0303***	**-0.18**	**0.0339***
	POCI	-0.02	0.82	-0.03	0.79	-0.08	0.48	-0.08	0.50
	TACI	-0.13	0.14	-0.14	0.13	**-0.20**	**0.0347***	**-0.20**	**0.0398***
Time to randomization (hours)		-0.02	0.21	-0.02	0.24	-0.01	0.75	-0.01	0.75
Control versus rt-PA		0.03	0.56	0.03	0.54	0.05	0.29	0.05	0.27
BP lowering prior to study		0.06	0.26	0.06	0.28	0.03	0.58	0.03	0.59
BP lowering in 1st 24 hours		0.10	0.07	0.10	0.06	0.09	0.15	0.08	0.16
BP lowering on days 2-7		-0.04	0.54	-0.04	0.52	0.00	0.96	0.00	0.97

Note: Leukoaraiosis is the dependent variable in this table, all associations shown are with Leukoaraiosis. BP=blood pressure; SE=standard error; **P*<0.05; NIHSS=National Institutes of Health Stroke Scale; LACI=lacunar infarcts; PACI=partial anterior circulation infarcts; POCI=posterior circulation infarcts, TACI=total anterior circulation infarcts; rt-PA=recombinant tissue-type plasminogen activator.

Mean arterial pressure parameter Beta for successive variation was set to null because it is a linear combination of successive variation in diastolic (SV_DBP), systolic BP (SV_SBP), and pulse pressure (SV_PP), i.e., 0.66667 * SV_DBP + 0.33333 * SV_SBP - 0.22222 * SV_PP (see equations 1 and 3).

Beta are not standardised.

Blood pressure variability and leukoaraiosis in acute ischaemic stroke

David Alexander Dickie, PhD[a,b,c,*], Benjamin Aribisala, PhD[a,b,c,*], Grant Mair, MB ChB[a,b,c], Eivind Berge, MD[d], Richard I. Lindley, MD[e], Peter Sandercock, DM[c], Rudiger von Kummer, MD[f], Anders von Heijne, MD[g], Andre Peeters, MD[h], Lesley Cala, MD, FRCR[i], Andrew Farrall, FRCRC[c], Zoe Morris, FRCR[j], Nick Bradey, FRCR[k], Gillian Potter, MD, FRCR[l], Alessandro Adami, MD[m], Joanna M. Wardlaw, MD[a,b,c,+]

[a]*Brain Research Imaging Centre, The University of Edinburgh, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh, EH16 4TJ, United Kingdom.*

[b]*Scottish Imaging Network, A Platform for Scientific Excellence (SINAPSE) collaboration.*

[c]*Centre for Clinical Brain Sciences, Chancellor's building, 49 Little France Crescent, EH16 4SB, United Kingdom.*

[d]*Department of Internal Medicine, Oslo University Hospital, Oslo, Norway.*

[e]*George Institute for Global Health and Discipline of Medicine, University of Sydney, Sydney, New South Wales, Australia.*

[f]*Department of Neuroradiology, University Hospital, Technische Universität Dresden, Germany*

[g]*Danderyd Hospital, Stockholm, Sweden*

[h]*Cliniques Universitaires Saint-Luc, Bruxelles, Belgium*

[i]*School of Pathology and Laboratory Medicine, The University of Western Australia, Crawley, Western Australia*

[j]*NHS Lothian, Edinburgh, Scotland*

[k]*Neuroradiology, James Cook University Hospital, South Tees Hospital NHS Trust, Middlesborough, UK*

[l]*Salford Royal NHS Foundation Trust, Salford, Greater Manchester*

[m]*Stroke Center, Department of Neurology, Ospedale Sacro Cuore-Don Calabria, Via Sempreboni 6, 37024, Negrar, Verona, IT*

*These authors contributed equally.

[+]Corresponding author:

Joanna M. Wardlaw, postal address is affiliation "a".

E-mail address: joanna.wardlaw@ed.ac.uk

Cover title: BP variability and leukoaraiosis in acute stroke

Keywords: Blood pressurise; variation; leukoaraiosis; stroke, ischaemic; computed tomography

Total word count: 3952/4000

Abstract word count: 215/250

Number of figures: 0; number of tables: 2 (2 additional tables in supplement)

Author contributions

David Alexander Dickie, PhD[a,b,c] and Benjamin Aribisala, PhD[a,b,c] performed the analysis and wrote the manuscript. Grant Mair, MB ChB[a,b,c] supported the analysis and edited the manuscript.

Rudiger von Kummer, MD[f], Anders von Heijne, MD[g], Andre Peeters, MD[h], Lesley Cala, MD, FRCR[i], Andrew Farrall, FRCRC[c], Zoe Morris, FRCR[j], Nick Bradey, FRCR[k], Gillian Potter, MD, FRCR[l], and Alessandro Adami, MD[m] performed image analysis and edited the manuscript.

Joanna M. Wardlaw, MD[a,b,c] designed and conceptualised the analysis, oversaw the analysis, and edited the manuscript with support from Eivind Berge, MD[d], Richard I. Lindley, MD[e], and Peter Sandercock, DM[c].

Abstract

Higher blood pressure (BP), BP variability and leukoaraiosis are risk factors for early adverse events and poor functional outcome after ischaemic stroke, but prior studies differed on whether leukoaraiosis was associated with BP variability, including in ischaemic stroke.

In the Third International Stroke Trial, BP was measured in the acute phase of ischaemic stroke immediately prior to randomization, and at 0.5, 1 hour and 24 hours after randomization. Masked neuroradiologists rated index infarct, leukoaraiosis and atrophy on CT using validated methods. We characterised BP variation by coefficient of variance (CV) and three other standard methods. We measured associations between BP, BP variability and leukoaraiosis using generalized estimating equations, adjusting for age, and a number of covariates related to treatment and stroke type/severity.

Amongst 3017 patients, mean (±SD) systolic and diastolic BP decreased from 155(±24)/82(±15)mmHg pre-randomization to 146(±23)/78(±14)mmHg 24 hours later (P<0.005). Mean within-subject CV was 0.09±0.05 for systolic and 0.11±0.06 for diastolic BP. Patients with most leukoaraiosis were older and had higher BP than those with least (P<0.0001). Although statistically significant in simple pairwise comparisons, no measures of BP variability were associated with leukoaraiosis when adjusting for confounding variables (P>0.05), e.g., age.

Our results suggest that BP variability is not a potential mechanism to explain the association between leukoaraiosis and poor outcome after acute stroke.

Introduction

Higher blood pressure (BP) level and BP variability are risk factors for early adverse events and later poor functional outcome after stroke(1, 2). Higher long-term BP has consistently been associated cross-sectionally with a higher burden of leukoaraiosis, which is itself a major risk factor for stroke, dementia, and death(3-8); and independently predicts poor outcome after stroke(9). However, there are conflicting reports on the association between higher long-term BP variability and the burden of leukoaraiosis(6, 7, 10, 11) and short-term BP variability and leukoaraiosis(10, 12, 13). This discord among a relatively small number of studies, mostly with N<250 and only one with greater than 500 participants, is in contrast to the often studied and well characterized associations between higher absolute BP and more leukoaraiosis(14).

The sample sizes in these studies were often relatively small (N<500)(10, 12, 13) and/or were in community-dwelling participants(6, 11), or during long-term follow-up after stroke(7), which might contribute to differing results. We found no previous investigations of the associations between pre-existing leukoaraiosis and variability in BP during the acute phase of stroke. Yet the acute phase of stroke is a time when BP is likely to be highly variable(15, 16).

We previously studied the effect of BP variability(1) and of leukoaraiosis(9) on outcome after ischaemic stroke. Given the independent negative prognostic impacts that we found in these previous studies, we aimed to clarify the relationship between BP variability and leukoaraiosis in the acute phase of ischaemic stroke using data from a large randomized trial, the Third International Stroke Trial (IST-3)(9, 17-19).

Methods

Participants

IST-3 was conducted with 3035 participants recruited from 156 centres in 12 countries(19). All participating centres had a national co-ordinator and local ethics approval. The trial, registered at ISRCTN.com, number ISRCTN25765518, was run according to the local procedures and law of each centre(18). All patients or an assigned patient relative/representative (where patients did not have capacity) gave informed consent. Full details of trial procedures, including imaging assessments, patient characteristics and the main trial results, have been published(9, 17-19).

BP measurement

BP was recorded by trained personnel for trial purposes at five time points: pre-randomization, start of treatment (or immediately after randomization for control patients), and at 30 minutes, 60 minutes, and 24 hours after treatment. We recorded whether BP was treated prior to admission in the trial, within the first 24 hours, and/or between 24 hours and seven days after randomization.

BP variability

We assessed variability in BP via measures of systolic, diastolic, pulse, and mean arterial pressure taken pre-randomization, at the start of treatment, and 30 minutes, 60 minutes, and 24 hours after treatment.

We calculated mean arterial pressure (MAP) via equation 1:

$$\text{MAP}=\text{DBP}+\frac{\text{SBP-DBP}}{3} \quad (1)$$

According to previous studies(6, 7, 13), we used standard deviation, coefficient of variance (CV), average real variability, and successive variation to quantify variance in each measure of BP.

Average real variability (ARV) was computed for all four measures of BP via equation 2:

$$ARV=\frac{|BP_{start}-BP_{rand}|+|BP_{30m}-BP_{start}|+|BP_{60m}-BP_{30m}|+|BP_{24h}-BP_{60m}|}{4} \quad (2)$$

Successive variability (SV) was computed for all four measures of BP via equation 3:

$$SV=\frac{(BP_{start}-BP_{rand})^2+(BP_{30m}-BP_{start})^2+(BP_{60m}-BP_{30m})^2+(BP_{24h}-BP_{60m})^2}{4} \quad (3)$$

Pre-existing brain damage

Leukoaraiosis, including anterior and posterior (each scored 0-2), burden and whole brain atrophy, were rated by trained neuroradiologists on computed tomography (CT) masked to all clinical details using previously validated procedures(9, 20, 21). Anterior and posterior leukoaraiosis scores were summed to compute a total leukoaraiosis score (on a continuum of 0 to 4; with 4 being the greatest leukoaraiosis burden). Whole brain atrophy was scored for central and cortical structures as none, moderate, or severe, then dichotomised into a single variable as either absent (0) or present in one or both regions (1).

Statistical analyses

All statistical analyses were performed in the Statistical Analysis System (SAS) version 9.4 (© 2002-2012 SAS Institute Inc.). We used longitudinal multiple regression (generalized estimating equations) to model absolute BP (separate models for systolic, diastolic, pulse, and mean arterial pressure) over time according to leukoaraiosis burden and adjusted for age, atrophy, NIHSS, stroke subtype, time to randomization, treatment allocation, and BP lowering treatment before the trial, during the first 24 hours, and between 24 hours and seven days. This analysis is summarised in equation 4:

$$BP=\beta\_Time+\beta\_Age+\beta\_Leukoaraiosis+\beta\_Atrophy+\beta\_NIHSS+\beta\_StrokeSubtype+\beta\_TimeRand+\beta\_TreatmeentAlloc+\beta\_BPlowPrior+\beta\_BPlowDay1+\beta\_BPlowDay2\text{-}7+error \quad (4)$$

We also used generalized estimating equations to measure associations between leukoaraiosis and BP variability with the same adjustment variables. This analysis is summarised in equation 5:

$$Leukoaraiosis=\beta\_DBPV+\beta\_SBPV+\beta\_PPV+\beta\_MAPV+\beta\_Age+\beta\_NIHSS+\beta\_Atrophy+\beta\_StrokeSubtype+\beta\_TimeRand+\beta\_TreatmeentAlloc+\beta\_BPlowPrior+\beta\_BPlowDay1+\beta\_BPlowDay2\text{-}7+error \quad (5)$$

We defined leukoaraiosis as the dependent variable in equation 5 as this allowed all measures of BP (systolic, diastolic, pulse, and mean) to be assessed in one model (rather than four separate models where each measure of variability was the dependent variable). We assessed collinearity using variance inflation factor and stepwise removal of potentially volatile variables. The generalized estimating equations used here are parametric (mean-based) and although leukoaraiosis often has highly skewed distributions, we found this to have a nominal effect on mean-based regression results(14). We used an exchangeable correlation matrix in our generalized estimating equations because repeated BP measures were correlated but not autoregressive. We assessed overfitting by comparing raw and adjusted R-squared. These models were designed to assess the influence of several variables known to have adverse prognostic effects in acute stroke (e.g., atrophy and stroke severity)(9) and whether their effects were attenuated/mediated in fully adjusted models. We determined the influence of adjustment variables by firstly modelling pairwise associations (unadjusted models) between BP variability and leukoaraiosis.

Results

Patient characteristics

Full characteristics of the N=3035 patients, including treatment for hypertension prior to trial admission, stroke subtypes, atrophy and leukoaraiosis CT findings, are provided in supplement; 18 patients did not have CT scans so did not contribute leukoaraiosis or atrophy scores in this analysis. Mean age was 77.3±12.2 years with median NIHSS 11 (IQR=11), and TACI (N=1306, 43%) was the most frequent stroke subtype. BP values by leukoaraiosis group, unadjusted for covariates, are provided in supplement.

Association between leukoaraiosis and acute absolute BP

The following are all adjusted analyses; beta coefficients and *P*-values are in Table 1.

Systolic (155±24 mmHg to 146±23 mmHg) and diastolic (82±15 mmHg to 78±14 mmHg) BP generally fell with time from pre-randomization to 24 hours after start of treatment ($P<0.005$). Systolic BP was 3.58 (95% confidence interval, CI, ±2.5) mmHg lower and diastolic BP was 3.80 (95% CI ±1.5) mmHg lower throughout the measurement period in patients with leukoaraiosis grade zero versus grade four. Systolic BP was higher ($\beta=0.23$, $P<0.0001$) and diastolic BP was lower ($\beta=-0.14$, $P<0.0001$) in older patients.

Mean arterial pressure was lower in those with leukoaraiosis grade zero versus grade four, but not associated with age, while pulse pressure was higher in older people but not associated with leukoaraiosis (Table 1).

Unadjusted associations between leukoaraiosis and acute BP variability

Unadjusted pairwise associations between leukoaraiosis and BP variability (systolic, diastolic, pulse, mean) characterized by CV were not statistically significant ($P>0.05$). All other measures of BP variability (except successive variability in pulse pressure, $P>0.05$) were significantly associated with leukoaraiosis, where greater variability was associated with increased burden of leukoaraiosis, when not adjusting for covariates ($P<0.05$; see supplement).

Adjusted associations between leukoaraiosis and acute BP variability

The following are all adjusted analyses; beta coefficients and *P*-values are in Table 2.

In contrast to the unadjusted pairwise associations, leukoaraiosis was not associated with BP variability in the acute phase of ischaemic stroke, whether measured by CV (column 1 Table 2), standard deviation (column 2 Table 2), average real variability (column 3 Table 2), or successive variability (column 4 Table 2) when adjusting for age, atrophy, stroke severity, subtype, and treatment groups.

Discussion

In this large study including 3017 patients, we found that leukoaraiosis was associated with high absolute BP, but not with BP variability, over the first 24 hours after ischaemic stroke when adjusting for relevant covariates. At first there did appear to be a positive association between leukoaraiosis and acute BP variability measured by standard deviation, average real variability, and successive variability, however these associations disappeared when adjusting for age and other relevant covariates. Therefore, while BP variability is associated with poor outcome in IST-3(1), it is not likely to explain the association between leukoaraiosis and poor outcome after acute stroke, that we also found in IST-3(9). Higher absolute BPs were associated with the presence of grade four leukoaraiosis versus grade zero; but patients with grade four leukoaraiosis did not have higher absolute BP compared to patients with leukoaraiosis grades one to three, after adjusting for age.

Our finding that short-term BP variability in acute ischaemic stroke is not independently associated with leukoaraiosis is consistent with two previous studies (N total=68), including one of non-acute lacunar stroke patients (N=43)(10, 12). Additionally, the lack of association between leukoaraiosis and BP variability is consistent with the largest previous study we found (N=694), that was conducted in community-dwelling subjects(6). However, our finding contrasts with previous smaller studies (N=66; N=210; N=155) of community-dwelling older subjects that found an association between increased variability in short-term BP and leukoaraiosis(13, 22). Additionally, positive associations between leukoaraiosis and BP variability have been found in primary hypertensive (N=487)(23) and cardiovascular disease (N=39)(24) patients. This discord may be due to acute ischaemia masking associations between BP variability and leukoaraiosis, the physiology of patient groups versus community dwelling participants, continual monitoring versus intermittent BP measures, or that previous sample sizes were much smaller (generally N<250) than here. Independent studies of absolute BP and leukoaraiosis may have similar differences in their study design, however, these have still produced generally consistent associations between higher absolute BP and more leukoaraiosis; and the number of these studies far outweighs the number of studies into BP variability and leukoaraiosis(14).

The strengths of our study include the large number of acute ischaemic stroke patients with

BP monitoring within the first 24 hours of stroke at fixed intervals according to standardised protocols; and recording of BP lowering treatment before, during the first 24 hours, and between two and seven days after trial enrolment. IST-3 settings and patients reflect a broad range of hospital environments charged with the care of ischaemic stroke. The number of participants studied here is over four times greater than the largest study of BP variability and leukoaraiosis that we found(6). Finally, we assessed a range of BP variability measures compared with previous studies that used only one measure(11, 12).

Despite these strengths, our study has some limitations. As we used data from a randomized-controlled trial, there is always a risk of confounding. For example, we were not able to control for some vascular risk factors such as cholesterol, which may have an influence on associations between BP and leukoaraiosis(14). MRI has greater sensitivity than CT for detecting leukoaraiosis but CT is much more widely used in acute stroke and detects established leukoaraiosis. We had limited information on BP prior to enrolment in the trial, beyond reported use of antihypertensive treatment, therefore do not know the duration of elevated BP prior to the trial. This means that we cannot ascertain whether those with higher BP and more leukoaraiosis had chronically high BP or only acutely high BP. Continuous monitoring of BP may identify subtle associations between BP variability and leukoaraiosis that we were not able to detect here. Other limitations related to BP measurements and the lack of random allocation to BP lowering treatment in IST-3 have previously been discussed at length(1). Our results may not apply to patients with haemorrhagic stroke as IST-3 only included ischaemic stroke. However, several completed or ongoing trials of BP lowering in haemorrhagic stroke also use similar scan assessments and therefore could assess leukoaraiosis and BP variability.

Notwithstanding, we have shown that patients with leukoaraiosis have high BP but do not have increased BP variability immediately after ischaemic stroke. While additional work is required in this area, our results suggest that BP variability is not a potential mechanism to explain the association between leukoaraiosis and poor outcome after acute ischaemic stroke.

Acknowledgements

The authors greatly thank and acknowledge the patients who participated in IST-3, and the many staff in all participating centres, as listed previously(19).

Sources of funding

Full sources of funding for IST-3 were previously described in the IST-3 protocol paper(18). DAD was funded by Innovate UK (46917-348146).

Conflict of interest

E. Berge is a member of the Second RIGHT-2 advisory committee. R.I. Lindley received support from Boehringer Ingelheim and Covidien. P. Sandercock and J.M. Wardlaw received support from the Medical Research Council, the Stroke Association, the Health Foundation, and Boehringer Ingelheim, and J.M. Wardlaw also received support from Chest Heart Stroke Scotland. All other authors report no conflicts.

References

1. Berge E, Cohen G, Lindley RI, et al. Effects of Blood Pressure and Blood Pressure–Lowering Treatment During the First 24 Hours Among Patients in the Third International Stroke Trial of Thrombolytic Treatment for Acute Ischemic Stroke. Stroke 2015;46(12):3362-9.
2. Ahmed N, Wahlgren N, Brainin M, et al. Relationship of Blood Pressure, Antihypertensive Therapy, and Outcome in Ischemic Stroke Treated With Intravenous Thrombolysis: Retrospective Analysis From Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register (SITS-ISTR). Stroke 2009;40(7):2442-9.
3. Debette S, Seshadri S, Beiser A, et al. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. Neurology 2011;77(5):461-8.
4. Marcus J, Gardener H, Rundek T, et al. Baseline and Longitudinal Increases in Diastolic Blood Pressure Are Associated With Greater White Matter Hyperintensity Volume: The Northern Manhattan Study. Stroke 2011;42(9):2639-41.
5. Debette S, Markus H. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ 2010;341:c3666.
6. Aribisala BS, Morris Z, Eadie E, et al. Blood pressure, internal carotid artery flow parameters, and age-related white matter hyperintensities. Hypertension 2014;63(5):1011-8.
7. Liu W, Liu R, Sun W, et al. Different Impacts of Blood Pressure Variability on the Progression of Cerebral Microbleeds and White Matter Lesions. Stroke 2012;43(11):2916-22.
8. Verhaaren BFJ, Vernooij MW, de Boer R, et al. High Blood Pressure and Cerebral White Matter Lesion Progression in the General Population. Hypertension 2013;61(6):1354-9.
9. The IST-3 collaborative group. Association between brain imaging signs, early and late outcomes, and response to intravenous alteplase after acute ischaemic stroke in the third International Stroke Trial (IST-3): secondary analysis of a randomised controlled trial. The Lancet Neurology 2015;14(5):485-96.
10. Gómez-Angelats E, de La Sierra A, Sierra C, Parati G, Mancia G, Coca A. Blood pressure variability and silent cerebral damage in essential hypertension. Am J Hypertens 2004;17(8):696-700.
11. Liu Z, Zhao Y, Zhang H, et al. Excessive variability in systolic blood pressure that is self-measured at home exacerbates the progression of brain white matter lesions and cognitive impairment in the oldest old. Hypertens Res 2016;39(4):245-53.
12. Martí-Fàbregas J, Valencia C, Pujol J, et al. Blood pressure variability and leukoaraiosis amount in cerebral small-vessel disease. Acta Neurol Scand 2001;104(6):358-63.
13. Tartaro A, Budassi S, Pascali D, et al. Correlation between computed tomography findings of leukoaraiosis and 24-hour blood pressure variability in elderly subjects. Journal of Stroke and Cerebrovascular Diseases 1999;8(2):66-70.
14. Dickie DA, Ritchie SJ, Cox SR, et al. Vascular risk factors and progression of white matter hyperintensities in the Lothian Birth Cohort 1936. Neurobiol Aging 2016;42:116-23.
15. Huang Y, Sharma VK, Robinson T, et al. Rationale, design, and progress of the ENhanced Control of Hypertension ANd Thrombolysis strokE stuDy (ENCHANTED) trial: An international multicenter 2×2 quasi-factorial randomized controlled trial of low- vs. standard-dose rt-PA and early intensive vs. guideline-recommended blood pressure lowering in patients with acute ischaemic stroke eligible for thrombolysis treatment. International Journal of Stroke 2015;10(5):778-88.
16. The ENOS Trial Investigators. Efficacy of nitric oxide, with or without continuing

antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): a partial-factorial randomised controlled trial. The Lancet 2015;385(9968):617-28.
17. Sandercock P, Lindley R, Wardlaw J, et al. Update on the third international stroke trial (IST-3) of thrombolysis for acute ischaemic stroke and baseline features of the 3035 patients recruited. Trials 2011;12(1):1-10.
18. Sandercock P, Lindley R, Wardlaw J, et al. The third international stroke trial (IST-3) of thrombolysis for acute ischaemic stroke. Trials 2008;9(1):1-17.
19. The IST-3 collaborative group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. The Lancet 2012;379(9834):2352-63.
20. Wardlaw JM, Farrall AJ, Perry D, et al. Factors Influencing the Detection of Early CT Signs of Cerebral Ischemia: An Internet-Based, International Multiobserver Study. Stroke 2007;38(4):1250-6.
21. Wardlaw JM, von Kummer R, Farrall AJ, Chappell FM, Hill M, Perry D. A Large Web-Based Observer Reliability Study of Early Ischaemic Signs on Computed Tomography. The Acute Cerebral CT Evaluation of Stroke Study (ACCESS). PLoS ONE 2010;5(12):e15757.
22. Yamaguchi Y, Wada M, Sato H, et al. Impact of Ambulatory Blood Pressure Variability on Cerebral Small Vessel Disease Progression and Cognitive Decline in Community-Based Elderly Japanese. Am J Hypertens 2014;27(10):1257-67.
23. Filomena J, Riba-Llena I, Vinyoles E, et al. Short-Term Blood Pressure Variability Relates to the Presence of Subclinical Brain Small Vessel Disease in Primary Hypertension. Hypertension 2015;66(3):634-40.
24. Gunstad J, Cohen RA, Tate DF, et al. Blood pressure variability and white matter hyperintensities in older adults with cardiovascular disease. Blood Press 2005;14(6):353-8.

Table 1. Regression-based associations between absolute BP (dependent variable) and leukoaraiosis (independent variable) with relevant covariates

		Diastolic BP		Systolic BP		Pulse Pressure		Mean arterial pressure	
Parameter	Level	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value
Time (from pre-rand to 24 hours)		**-1.28**	**<0.0001***	**-2.32**	**<0.0001***	**-1.05**	**<0.0001***	**-1.63**	**<0.0001***
Age		**-0.14**	**<0.0001***	**0.23**	**<0.0001***	**0.38**	**<0.0001***	-0.02	0.52
Leukoaraiosis versus grade 4	0	**-3.80**	**<0.0001***	**-3.58**	**0.0042***	0.21	0.85	**-3.73**	**<0.0001***
	1	-1.73	0.06	0.37	0.81	2.09	0.10	-1.03	0.29
	2	-0.44	0.57	0.37	0.78	0.80	0.47	-0.18	0.83
	3	-0.40	0.74	-0.07	0.97	0.31	0.86	-0.30	0.82
No atrophy		0.09	0.89	0.41	0.69	0.33	0.69	0.20	0.77
NIHSS		-0.06	0.13	-0.05	0.46	0.01	0.82	-0.06	0.19
Stroke subtype versus LACI	PACI	-0.54	0.45	-0.55	0.68	0.04	0.97	-0.53	0.52
	POCI	-0.55	0.55	-0.05	0.98	0.53	0.69	-0.39	0.70
	TACI	-0.04	0.96	1.47	0.33	1.56	0.21	0.47	0.62
Time to randomization (hours)		0.21	0.19	0.50	0.08	0.29	0.23	0.31	0.09
Control versus rt-PA		0.62	0.14	0.63	0.37	0.01	0.99	0.63	0.17
BP lowering prior to study		**-1.35**	**0.0092***	-0.92	0.29	0.39	0.57	**-1.21**	**0.0339***
BP lowering in 1st 24 hours		**2.57**	**<0.0001***	**3.83**	**<0.0001***	1.27	0.09	**3.00**	**<0.0001***
BP lowering 24hr-7days		1.04	0.07	**5.24**	**<0.0001***	**4.22**	**<0.0001***	**2.44**	**<0.0001***

Note: BP=blood pressure; SE=standard error; **P*<0.05; NIHSS=National Institutes of Health Stroke Scale; LACI=lacunar infarcts; PACI=partial anterior circulation infarcts; POCI=posterior circulation infarcts, TACI=total anterior circulation infarcts; rt-PA=recombinant tissue-type plasminogen activator.

Beta are not standardised.

Table 2. Regression-based associations between leukoaraiosis (dependent variable) and BP variability (independent variables) with relevant covariates

		Coefficient of variance		Standard deviation		Average real variability		Successive variability	
Parameter	Level	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value
Diastolic BP		-1.71	0.09	0.02	0.38	0.01	0.55	0.00	0.94
Systolic BP		-1.89	0.16	0.01	0.37	0.01	0.31	0.00	0.12
Pulse pressure		0.41	0.30	-0.01	0.23	-0.01	0.20	0.00	0.14
Mean arterial pressure		2.36	0.21	-0.02	0.38	-0.01	0.58	null	.
Age		**0.02**	**<0.0001***	**0.02**	**<0.0001***	**0.03**	**<0.0001***	**0.03**	**<0.0001***
NIHSS		0.00	0.63	0.00	0.70	0.00	0.38	0.00	0.40
No atrophy		**-0.79**	**<0.0001***	**-0.78**	**<0.0001***	**-0.76**	**<0.0001***	**-0.76**	**<0.0001***
Stroke subtype versus LACI	PACI	-0.13	0.09	-0.14	0.09	**-0.18**	**0.0303***	**-0.18**	**0.0339***
	POCI	-0.02	0.82	-0.03	0.79	-0.08	0.48	-0.08	0.50
	TACI	-0.13	0.14	-0.14	0.13	**-0.20**	**0.0347***	**-0.20**	**0.0398***
Time to randomization (hours)		-0.02	0.21	-0.02	0.24	-0.01	0.75	-0.01	0.75
Control versus rt-PA		0.03	0.56	0.03	0.54	0.05	0.29	0.05	0.27
BP lowering prior to study		0.06	0.26	0.06	0.28	0.03	0.58	0.03	0.59
BP lowering in 1st 24 hours		0.10	0.07	0.10	0.06	0.09	0.15	0.08	0.16
BP lowering on days 2-7		-0.04	0.54	-0.04	0.52	0.00	0.96	0.00	0.97

Note: Leukoaraiosis is the dependent variable in this table, all associations shown are with Leukoaraiosis. BP=blood pressure; SE=standard error; **P*<0.05; NIHSS=National Institutes of Health Stroke Scale; LACI=lacunar infarcts; PACI=partial anterior circulation infarcts; POCI=posterior circulation infarcts, TACI=total anterior circulation infarcts; rt-PA=recombinant tissue-type plasminogen activator.

Mean arterial pressure parameter Beta for successive variation was set to null because it is a linear combination of successive variation in diastolic (SV_DBP), systolic BP (SV_SBP), and pulse pressure (SV_PP), i.e., 0.66667 * SV_DBP + 0.33333 * SV_SBP - 0.22222 * SV_PP (see equations 1 and 3).

Beta are not standardised.