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Citation for published version:

Dickie, DA, Aribisala, B, Mair, G, Berge, E, Lindley, RI, Sandercock, P, von Kummer, R, von Heijne, A, Peeters, A, Cala, L, Farrall, A, Morris, Z, Bradey, N, Potter, G, Adami, A & Wardlaw, J 2017, 'Blood pressure variability and leukoaraiosis in acute ischemic stroke', *International Journal of Stroke*.
<https://doi.org/10.1177/1747493017729267>

Digital Object Identifier (DOI):

[10.1177/1747493017729267](https://doi.org/10.1177/1747493017729267)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

International Journal of Stroke

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Blood pressure variability and leukoaraiosis in acute ischaemic stroke

Journal:	<i>International Journal of Stroke</i>
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

1 Blood pressure variability and leukoaraiosis in acute ischaemic stroke

2

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36 Cover title: BP variability and leukoaraiosis in acute stroke

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

1 Total word count: 3952/4000

2 Abstract word count: 215/250

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

4

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14 manuscript.

15 Joanna M. Wardlaw, MD^{a,b,c} designed and conceptualised the analysis, oversaw the analysis,
16 and edited the manuscript with support from Eivind Berge, MD^d, Richard I. Lindley, MD^e,
17 and Peter Sandercock, DM^c.

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1 **Abstract**

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

5

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

13

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

21

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

24

25

1 Introduction

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

13

14 The sample sizes in these studies were often relatively small ($N < 500$)(10, 12, 13) and/or were
15 in community-dwelling participants(6, 11), or during long-term follow-up after stroke(7),
16 which might contribute to differing results. We found no previous investigations of the
17 associations between pre-existing leukoaraiosis and variability in BP during the acute phase
18 of stroke. Yet the acute phase of stroke is a time when BP is likely to be highly variable(15,
19 16).

20

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

26

27

1 **Methods**

2 *Participants*

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

10

11 *BP measurement*

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

17

18 *BP variability*

19 We assessed variability in BP via measures of systolic, diastolic, pulse, and mean arterial
20 pressure taken pre-randomization, at the start of treatment, and 30 minutes, 60 minutes, and
21 24 hours after treatment.

22

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

24

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

25

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

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

2

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

3

4

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

6

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

7

8

9 *Pre-existing brain damage*

10 Leukoaraiosis, including anterior and posterior (each scored 0-2), burden and whole brain
 11 atrophy, were rated by trained neuroradiologists on computed tomography (CT) masked to all
 12 clinical details using previously validated procedures(9, 20, 21). Anterior and posterior
 13 leukoaraiosis scores were summed to compute a total leukoaraiosis score (on a continuum of
 14 0 to 4; with 4 being the greatest leukoaraiosis burden). Whole brain atrophy was scored for
 15 central and cortical structures as none, moderate, or severe, then dichotomised into a single
 16 variable as either absent (0) or present in one or both regions (1).

17

18 *Statistical analyses*

19 All statistical analyses were performed in the Statistical Analysis System (SAS) version 9.4
 20 (© 2002-2012 SAS Institute Inc.). We used longitudinal multiple regression (generalized
 21 estimating equations) to model absolute BP (separate models for systolic, diastolic, pulse, and
 22 mean arterial pressure) over time according to leukoaraiosis burden and adjusted for age,
 23 atrophy, NIHSS, stroke subtype, time to randomization, treatment allocation, and BP
 24 lowering treatment before the trial, during the first 24 hours, and between 24 hours and seven
 25 days. This analysis is summarised in equation 4:

26

$$\text{BP} = \beta_{\text{Time}} + \beta_{\text{Age}} + \beta_{\text{Leukoaraiosis}} + \beta_{\text{Atrophy}} + \beta_{\text{NIHSS}} + \beta_{\text{StrokeSubtype}} + \beta_{\text{TimeRand}} + \beta_{\text{TreatmentAlloc}} + \beta_{\text{BPlowPrior}} + \beta_{\text{BPlowDay1}} + \beta_{\text{BPlowDay2-7}} + \text{error} \quad (4)$$

1

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

5

$$\text{Leukoaraiosis} = \beta_{\text{DBPV}} + \beta_{\text{SBPV}} + \beta_{\text{PPV}} + \beta_{\text{MAPV}} + \beta_{\text{Age}} + \beta_{\text{NIHSS}} + \beta_{\text{Atrophy}} + \beta_{\text{StrokeSubtype}} + \beta_{\text{TimeRand}} + \beta_{\text{TreatmentAlloc}} + \beta_{\text{BPlowPrior}} + \beta_{\text{BPlowDay1}} + \beta_{\text{BPlowDay2-7}} + \text{error} \quad (5)$$

6

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

21

1 **Results**

2 *Patient characteristics*

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

9

10 *Association between leukoaraiosis and acute absolute BP*

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

12 Systolic (155 ± 24 mmHg to 146 ± 23 mmHg) and diastolic (82 ± 15 mmHg to 78 ± 14 mmHg)
13 BP generally fell with time from pre-randomization to 24 hours after start of treatment
14 ($P < 0.005$). Systolic BP was 3.58 (95% confidence interval, CI, ± 2.5) mmHg lower and
15 diastolic BP was 3.80 (95% CI ± 1.5) mmHg lower throughout the measurement period in
16 patients with leukoaraiosis grade zero versus grade four. Systolic BP was higher ($\beta = 0.23$,
17 $P < 0.0001$) and diastolic BP was lower ($\beta = -0.14$, $P < 0.0001$) in older patients.

18

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

22

23 *Unadjusted associations between leukoaraiosis and acute BP variability*

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

30

1

2 *Adjusted associations between leukoaraiosis and acute BP variability*3 The following are all adjusted analyses; beta coefficients and *P*-values are in Table 2.

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

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For Review Only

1 Discussion

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

13

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

31

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

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

8
9 Despite these strengths, our study has some limitations. As we used data from a randomized-
10 controlled trial, there is always a risk of confounding. For example, we were not able to
11 control for some vascular risk factors such as cholesterol, which may have an influence on
12 associations between BP and leukoaraiosis(14). MRI has greater sensitivity than CT for
13 detecting leukoaraiosis but CT is much more widely used in acute stroke and detects
14 established leukoaraiosis. We had limited information on BP prior to enrolment in the trial,
15 beyond reported use of antihypertensive treatment, therefore do not know the duration of
16 elevated BP prior to the trial. This means that we cannot ascertain whether those with higher
17 BP and more leukoaraiosis had chronically high BP or only acutely high BP. Continuous
18 monitoring of BP may identify subtle associations between BP variability and leukoaraiosis
19 that we were not able to detect here. Other limitations related to BP measurements and the
20 lack of random allocation to BP lowering treatment in IST-3 have previously been discussed
21 at length(1). Our results may not apply to patients with haemorrhagic stroke as IST-3 only
22 included ischaemic stroke. However, several completed or ongoing trials of BP lowering in
23 haemorrhagic stroke also use similar scan assessments and therefore could assess
24 leukoaraiosis and BP variability.

25
26 Notwithstanding, we have shown that patients with leukoaraiosis have high BP but do not
27 have increased BP variability immediately after ischaemic stroke. While additional work is
28 required in this area, our results suggest that BP variability is not a potential mechanism to
29 explain the association between leukoaraiosis and poor outcome after acute ischaemic stroke.

30

1 **Acknowledgements**

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

4

5 **Sources of funding**

6 Full sources of funding for IST-3 were previously described in the IST-3 protocol paper(18).

7 DAD was funded by Innovate UK (46917-348146).

8

9 **Conflict of interest**

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

15

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

Parameter	Level	Diastolic BP		Systolic BP		Pulse Pressure		Mean arterial pressure	
		Beta	<i>P</i> -value	Beta	<i>P</i> -value	Beta	<i>P</i> -value	Beta	<i>P</i> -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 1 st 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*

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

6 Beta are not standardised.

7

8

9

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

Parameter	Level	Coefficient of variance		Standard deviation		Average real variability		Successive variability	
		Beta	<i>P</i> -value	Beta	<i>P</i> -value	Beta	<i>P</i> -value	Beta	<i>P</i> -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 1 st 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

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

6 Mean arterial pressure parameter Beta for successive variation was set to null because it is a linear combination of successive variation in
7 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
8 equations 1 and 3).

9 Beta are not standardised.

10

1 Blood pressure variability and leukoaraiosis in acute ischaemic stroke

2

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36 Cover title: BP variability and leukoaraiosis in acute stroke

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

1 Total word count: 3952/4000

2 Abstract word count: 215/250

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

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16 and edited the manuscript with support from Eivind Berge, MD^d, Richard I. Lindley, MD^e,
17 and Peter Sandercock, DM^c.

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1 **Abstract**

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

5

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

13

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

21

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

24

25

1 **Introduction**

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

12

13 The sample sizes in these studies were often relatively small ($N < 500$)(10, 12, 13) and/or were
14 in community-dwelling participants(6, 11), or during long-term follow-up after stroke(7),
15 which might contribute to differing results. We found no previous investigations of the
16 associations between pre-existing leukoaraiosis and variability in BP during the acute phase
17 of stroke. Yet the acute phase of stroke is a time when BP is likely to be highly variable(15,
18 16).

19

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

25

26

1 **Methods**

2 *Participants*

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

10

11 *BP measurement*

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

17

18 *BP variability*

19 We assessed variability in BP via measures of systolic, diastolic, pulse, and mean arterial
20 pressure taken pre-randomization, at the start of treatment, and 30 minutes, 60 minutes, and
21 24 hours after treatment.

22

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

24

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

25

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

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

2

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

3

4

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

6

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

7

8

9 *Pre-existing brain damage*

10 Leukoaraiosis, including anterior and posterior (each scored 0-2), burden and whole brain
 11 atrophy, were rated by trained neuroradiologists on computed tomography (CT) masked to all
 12 clinical details using previously validated procedures(9, 20, 21). Anterior and posterior
 13 leukoaraiosis scores were summed to compute a total leukoaraiosis score (on a continuum of
 14 0 to 4; with 4 being the greatest leukoaraiosis burden). Whole brain atrophy was scored for
 15 central and cortical structures as none, moderate, or severe, then dichotomised into a single
 16 variable as either absent (0) or present in one or both regions (1).

17

18 *Statistical analyses*

19 All statistical analyses were performed in the Statistical Analysis System (SAS) version 9.4
 20 (© 2002-2012 SAS Institute Inc.). We used longitudinal multiple regression (generalized
 21 estimating equations) to model absolute BP (separate models for systolic, diastolic, pulse, and
 22 mean arterial pressure) over time according to leukoaraiosis burden and adjusted for age,
 23 atrophy, NIHSS, stroke subtype, time to randomization, treatment allocation, and BP
 24 lowering treatment before the trial, during the first 24 hours, and between 24 hours and seven
 25 days. This analysis is summarised in equation 4:

26

$$\begin{aligned} \text{BP} = & \beta_{\text{Time}} + \beta_{\text{Age}} + \beta_{\text{Leukoaraiosis}} + \beta_{\text{Atrophy}} + \beta_{\text{NIHSS}} + \beta_{\text{StrokeSubtype}} + \quad (4) \\ & \beta_{\text{TimeRand}} + \beta_{\text{TreatmentAlloc}} + \beta_{\text{BPlowPrior}} + \beta_{\text{BPlowDay1}} + \\ & \beta_{\text{BPlowDay2-7}} + \text{error} \end{aligned}$$

1

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

5

$$\begin{aligned} \text{Leukoaraiosis} = & \beta_{\text{DBPV}} + \beta_{\text{SBPV}} + \beta_{\text{PPV}} + \beta_{\text{MAPV}} + \beta_{\text{Age}} + \beta_{\text{NIHSS}} + \beta_{\text{Atrophy}} + \quad (5) \\ & \beta_{\text{StrokeSubtype}} + \beta_{\text{TimeRand}} + \beta_{\text{TreatmentAlloc}} + \beta_{\text{BPlowPrior}} + \beta_{\text{BPlowDay1}} + \\ & \beta_{\text{BPlowDay2-7}} + \text{error} \end{aligned}$$

6

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

21

1 **Results**

2 *Patient characteristics*

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

9

10 *Association between leukoaraiosis and acute absolute BP*

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

12 Systolic (155 ± 24 mmHg to 146 ± 23 mmHg) and diastolic (82 ± 15 mmHg to 78 ± 14 mmHg)
13 BP generally fell with time from pre-randomization to 24 hours after start of treatment
14 ($P < 0.005$). Systolic BP was 3.58 (95% confidence interval, CI, ± 2.5) mmHg lower and
15 diastolic BP was 3.80 (95% CI ± 1.5) mmHg lower throughout the measurement period in
16 patients with leukoaraiosis grade zero versus grade four. Systolic BP was higher ($\beta = 0.23$,
17 $P < 0.0001$) and diastolic BP was lower ($\beta = -0.14$, $P < 0.0001$) in older patients.

18

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

22

23 *Unadjusted associations between leukoaraiosis and acute BP variability*

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

30

1

2 *Adjusted associations between leukoaraiosis and acute BP variability*3 The following are all adjusted analyses; beta coefficients and *P*-values are in Table 2.

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

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For Review Only

1 Discussion

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

13

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

31

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

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

8

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

25

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

30

1 **Acknowledgements**

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

4

5 **Sources of funding**

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

8

9 **Conflict of interest**

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

15

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

Parameter	Level	Diastolic BP		Systolic BP		Pulse Pressure		Mean arterial pressure	
		Beta	<i>P</i> -value	Beta	<i>P</i> -value	Beta	<i>P</i> -value	Beta	<i>P</i> -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 1 st 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*

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

6 Beta are not standardised.

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

Parameter	Level	Coefficient of variance		Standard deviation		Average real variability		Successive variability	
		Beta	<i>P</i> -value	Beta	<i>P</i> -value	Beta	<i>P</i> -value	Beta	<i>P</i> -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 1 st 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

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

6 Mean arterial pressure parameter Beta for successive variation was set to null because it is a linear combination of successive variation in
7 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
8 equations 1 and 3).

9 Beta are not standardised.

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