





Cilostazol and isosorbide mononitrate for the prevention of progression of : baseline data and statistical analysis plan for the Lacunar Intervention Trial-2 (LACI-2) (ISRCTN14911850)

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ABSTRACT

Background Cerebral small vessel disease (SVD) causes lacunar strokes (25% of all ischaemic strokes), physical frailty and cognitive impairment and vascular and mixed dementia. There is no specific treatment to prevent progression of SVD.

Methods The LACunar Intervention Trial-2 is an investigator-initiated prospective randomised open-label blinded-endpoint phase II feasibility study assessing cilostazol and isosorbide mononitrate for preventing SVD progression. We aimed to recruit 400 patients with clinically evident lacunar ischaemic stroke and randomised to cilostazol, isosorbide mononitrate, both or neither, in addition to guideline secondary ischaemic stroke prevention, in a partial factorial design. The primary outcome is feasibility of recruitment and adherence to medication; key secondary outcomes include: drug tolerability; recurrent vascular events, cognition and function at 1 year after randomisation; and safety (bleeding, falls, death). Data are number (%) and median (IQR).

Results The trial commenced on 5 February 2018 and ceased recruitment on 31 May 2021 with 363 patients randomised, with the following baseline characteristics: average age 64 (56.0, 72.0) years, female 112 (30.9%), stroke onset to randomisation 79.0 (27.0, 244.0) days, hypertension 267 (73.6%), median blood pressures 143.0 (130.0, 157.0)/83.0 (75.0, 90.0) mm Hg, current smokers 67 (18.5%), educationally achieved end of school examinations (A-level) or higher 118 (32.5%), modified Rankin scale 1.0 (0.0, 1.0), National Institutes Health stroke scale 1.0 (1.4), Montreal Cognitive Assessment 26.0 (23.0, 28.0) and total SVD score on brain imaging 1.0 (0.0, 2.0). This publication summarises the baseline data and presents the statistical analysis plan.

Summary The trial is currently in follow-up which will complete on 31 May 2022 with results expected in October 2022.

Trial registration number ISRCTN14911850.

INTRODUCTION

Cerebral small vessel disease (SVD) is a major cause of stroke (lacunar ischaemic stroke), intracerebral haemorrhage and vascular and mixed dementias.¹ It is most commonly

due to an intrinsic disorder of the brain's small perforating arterioles with endothelial dysfunction manifesting as impaired vasoreactivity, vascular stiffness, blood–brain barrier leakage and perivascular inflammation.¹ Currently, there is no specific secondary prevention for lacunar ischaemic stroke or SVD-associated cognitive decline.² Combined aspirin and clopidogrel increased bleeding³ and intensive antihypertensive therapy did not reduce recurrence or prevent cognitive decline⁴ in lacunar ischaemic stroke.

However, there are other potential interventions that might prevent SVD or reduce its development and progression, including: drugs that modulate the blood–brain barrier or lower blood lipids, immunosuppressive agents, neurotrophins, peroxisome proliferator-activated receptor-gamma agonists, rho-kinase antagonists, vitamins, anti-inflammatory agents and xanthine oxidase inhibitors.^{2,5} Additionally, drugs that modulate the nitric oxide (NO)-cyclic guanylate cyclase-phosphodiesterase-5 and prostacyclin (PGI₂)-cyclic adenylylase-cyclase-phosphodiesterase-3 systems are attractive since they mimic key endogenous vaso-regulators.² Both NO and PGI₂ have vasodilator, antiplatelet, antileucocyte,⁶ antismooth muscle and proendothelial effects. NO may be administered orally as substrate (L-arginine or inorganic nitrate), organic nitrates (such as isosorbide mononitrate, ISMN) or drugs that inhibit PDE5 (such as dipyridamole⁷ or sildenafil) to increase and preserve levels of the NO second messenger, cyclic guanylate monophosphate. Although PGI₂ has to be administered intravenously, PDE3 may be inhibited with cilostazol,⁸ which preserves levels of the PGI₂ second messenger, cyclic adenylylase monophosphate; cilostazol has showed promise in secondary prevention

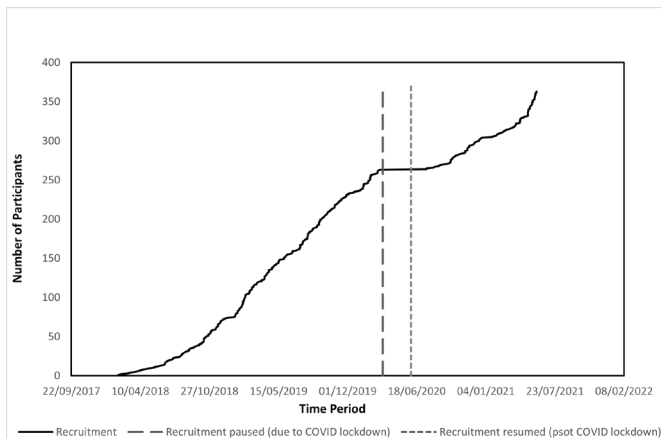


Figure 1 Recruitment by time.

trials in ischaemic stroke, which included large proportions of patients with lacunar stroke subtype⁸; and is widely used in East Asia. In addition, in experimental models, cilostazol reversed impaired oligodendrocyte precursor cell maturation which occurs when endothelial cells are dysfunctional thus potentially reducing myelin damage and facilitating its repair,⁹ and increased the astrocyte-to-neuron lactate shuttle thus increasing energy supply and prolonging neuronal survival.¹⁰ Both actions are potentially relevant to reducing brain damage in SVD.

SVD can present clinically as lacunar ischaemic stroke, cognitive impairment, mobility and/or mood disorders, or be covert and detected on incidentally on brain imaging.¹

Table 1 Continued

Variable	N	Participants	cSVD	Score*
		All	None/mild	Moderate to severe
ACE-inhibitors		132 (36.4)	32 (32.3)	100 (37.9)
Angiotensin-II RA		54 (14.9)	14 (14.1)	40 (15.2)
Renin inhibitor		0 (0.0)	0 (0.0)	0 (0.0)
Beta-RA		41 (11.3)	10 (10.1)	31 (11.7)
CCB		164 (45.2)	33 (33.3)	131 (49.6)
Diuretic		51 (14.0)	13 (13.1)	38 (14.4)
Alpha-RA		17 (4.7)	3 (3.0)	14 (5.3)
Centrally active		2 (0.6)	1 (1.0)	1 (0.4)
Antiplatelet	363	352 (97.0)	97 (98.0)	255 (96.6)
Lipid lowering	363	341 (93.9)	91 (91.9)	250 (94.7)
Proton pump inhibitor	363	128 (35.3)	30 (30.3)	98 (37.1)
PDE5 inhibitor	363	7 (1.9)	3 (3.0)	4 (1.5)
Grapefruit juice more than once a week	363	15 (0.04)	3 (0.03)	12 (0.04)
Other drugs	363	236 (65.0)	67 (67.7)	169 (64.0)
Nor of drugs taken/day	363	4.0 (3.0, 4.0)	3.0 (3.0, 4.0)	4.0 (3.0, 5.0)

Data are number (%), median (IQR).
 *According to scan read at site.
 †Minimisation variable.
 ‡School exams at age 16 (O-level/GCSE or equivalent) and 18 (A-level or equivalent).
 CCB, calcium channel blocker; F/T, full time; P/T, part time; RA, receptor antagonist; SVD, small vessel disease; TIA, transient ischaemic attack.

Table 1 Baseline characteristics by small vessel disease score as determined by recruiting site

Variable	N	Participants	cSVD	Score*
		All	None/mild	Moderate to severe
No of patients, N		363	99	264
Demographics				
Age, years†	363	64.0(56.0, 72.0)	62.0(54.0, 69.0)	65.0(57.5, 73.0)
≤70 years (%)	363	251 (69.1)	78 (78.8)	173 (65.5)
Sex, female (%)	363	112 (30.9)	28 (28.3)	84 (31.8)
modified Rankin Scale (/6)	363	1.0(0.0, 1.0)	1.0(0.0, 1.0)	1.0(0.0, 1.0)
>1 (%)‡	363	85 (23.4)	23 (23.2)	62 (23.5)
Onset to randomisation (days)†	363	79.0(27.0, 244.0)	73.0(27.0, 244.0)	84.5(28.5, 246.5)
≤100 (%)	363	206 (56.7)	64 (64.6)	142 (53.8)
Age completing education (years)	363	16.0(15.0, 18.0)	16.0(15.0, 17.0)	16.0(15.0, 18.0)
Highest education level (%)‡ test				
Primary school	363	2 (0.6)	0 (0.0)	2 (0.8)
Secondary school	363	129 (35.5)	36 (36.4)	93 (35.2)
O-level/GCSE or equivalent‡	363	114 (31.4)	34 (34.3)	80 (30.3)
A-level or equivalent‡	363	54 (14.9)	17 (17.2)	37 (14.0)
College or university undergraduate	363	37 (10.2)	7 (7.1)	30 (11.4)
College or university postgraduate	363	27 (7.4)	5 (5.1)	22 (8.3)
Lifestyle				
Smoking (%)†				
Current	363	67 (18.5)	17 (17.2)	50 (18.9)
Past	363	154 (42.4)	36 (36.4)	118 (44.7)
Never	363	142 (39.1)	46 (46.5)	96 (36.4)
Medical history (%)				
Hypertension	363	267 (73.6)	58 (58.6)	209 (79.2)
Hypertension, drug treated	363	258 (71.1)	55 (55.6)	203 (76.9)
Hyperlipidaemia	363	281 (77.4)	75 (75.8)	206 (78.0)
Hyperlipidaemia, drug treated	363	278 (76.6)	75 (75.8)	203 (76.9)
Diabetes mellitus	363	80 (22.0)	20 (20.2)	60 (22.7)
Insulin	363	18 (5.0)	5 (5.1)	13 (4.9)
Oral agents	363	58 (16.0)	18 (18.2)	40 (15.2)
Lifestyle	363	24 (6.6)	3 (3.0)	21 (8.0)
Atrial fibrillation	363	5 (1.4)	1 (1.0)	4 (1.5)
Heart failure	363	4 (1.1)	0 (0.0)	4 (1.5)
Previous stroke	363	25 (6.9)	2 (2.0)	23 (8.7)
Prior TIA	363	29 (8.0)	5 (5.1)	24 (9.1)
Family history, young stroke	363	55 (15.2)	16 (16.2)	39 (14.8)
Current medications (%)				
Anticoagulants	363	5 (1.4)	1 (1.0)	4 (1.5)
Antibiotics	363	2 (0.6)	0 (0.0)	2 (0.8)
Antihypertensive	363	277 (76.3)	67 (67.7)	210 (79.5)

Continued

Table 2 Baseline clinical and investigation characteristics by small vessel disease score as determined by recruiting site

Variable	N	Participants	cSVD	Score*	P value
		All	None/mild	Moderate to severe	
No of patients, N		363	99	264	
Clinical data (%)					
SBP mm Hg†	363	143.0 (130.0, 157.0)	143.0 (128.0, 160.0)	143.0 (131.0, 155.5)	0.94
DBP mm Hg	363	83.0 (75.0, 90.0)	82.0 (75.0, 90.0)	83.0 (75.5, 90.0)	0.89
NIHSS (/42)†	363	0.0 (0.0, 2.0)	0.0 (0.0, 1.0)	0.0 (0.0, 2.0)	0.34
Duration of symptoms (days)	145	2.0 (1.0, 5.0)	2.0 (1.0, 7.0)	2.0 (1.0, 5.0)	0.30
Ongoing symptoms	363	218 (60.1)	58 (58.6)	160 (60.6)	0.73
Weakness, side of weakness	363	288 (79.3)	80 (80.8)	208 (78.8)	0.67
Left (%)	363	148 (40.8)	37 (37.4)	111 (42.0)	
Right (%)	363	138 (38.0)	43 (43.4)	95 (36.0)	
Both (%)	363	2 (0.6)	0 (0.0)	2 (1.0)	
Sensory loss, side of loss	363	148 (40.8)	43 (43.4)	105 (39.8)	0.53
Left (%)	363	74 (20.4)	19 (19.2)	55 (20.8)	
Right (%)	363	71 (19.6)	24 (24.2)	47 (17.8)	
Both (%)	363	3 (0.8)	0 (0.0)	3 (1.1)	
Ataxia	363	84 (23.1)	17 (17.2)	67 (25.4)	0.010
Left (%)	363	41 (11.3)	5 (5.1)	36 (13.6)	
Right (%)	363	39 (10.7)	12 (12.1)	27 (10.2)	
Neglect/inattention	363	6 (1.7)	1 (1.0)	5 (1.9)	0.56
Dysphasia	363	19 (5.2)	6 (6.1)	13 (4.9)	0.67
Dysarthria	363	111 (30.6)	28 (28.3)	83 (31.4)	0.56
Visual loss	363	11 (3.0)	6 (6.1)	5 (1.9)	0.039
Cognition					
MOCA total (/30)	363	26.0 (23.0, 28.0)	26.0 (23.0, 28.0)	26.0 (24.0, 28.0)	0.098
≤24 (%)	363	119 (32.8)	39 (39.4)	80 (30.3)	0.10
Trail making test part B					
Time (seconds)	359	110.0 (75.0, 170.0)	112.0 (74.0, 168.0)	108.0 (76.0, 171.0)	0.73
Points	359	25.0 (23.0, 25.0)	25.0 (23.0, 25.0)	25.0 (23.0, 25.0)	0.39
Investigations (%)					
Type of scan after index stroke (%)					
CT only	363	101 (27.8)	40 (40.4)	61 (23.1)	0.001
MRI only	363	43 (11.8)	9 (9.1)	34 (12.9)	0.32
Both	363	219 (60.3)	50 (50.5)	169 (64.0)	0.019
Stroke-CT scan (days)	320	1.0 (0.0, 1.0)	0.0 (0.0, 1.0)	1.0 (0.0, 1.0)	0.26
Stroke-MRI scan (days)	262	3.0 (1.0, 9.0)	2.0 (1.0, 5.0)	3.0 (1.0, 11.0)	0.13
Acute stroke lesion present*	363	296 (81.5)	68 (68.7)	228 (86.4)	<0.001
Lesion side of brain, left (%)*	363	164 (45.2)	45 (45.5)	119 (45.1)	0.95
SVD score 1 (%)*	363	206 (56.7)	0 (0.0)	206 (78.0)	–
WMH/hypoattenuations, yes (%)*	363	179 (49.3)	0 (0.0)	179 (67.8)	–
Total SVD score*†	363	1.0 (0.0, 2.0)	0.0 (0.0, 0.0)	1.0 (1.0, 2.0)	–
SVD moderate/severe (%)*	363	264 (72.7)	0 (0.0)	264 (100.0)	–
Carotid stenosis (%)	363	315 (86.8)	90 (90.9)	225 (85.2)	0.16
Degree of stenosis left <50%	363	312 (86.0)	90 (90.9)	222 (84.1)	
Degree of stenosis right <50%	363	309 (85.1)	90 (90.9)	219 (83.0)	
ECG (%)					
Sinus	360	347 (96.4)	94 (95.9)	253 (96.6)	0.93

Continued

Table 2 Continued

Variable	N	Participants	cSVD	Score*	P value
		All	None/mild	Moderate to severe	
AF	360	0 (0.0)	0 (0.0)	0 (0.0)	
Other	360	13 (3.6)	4 (4.1)	9 (3.4)	
Haemoglobin, g/L	361	14.2 (13.3, 15.2)	14.3 (13.2, 15.3)	14.2 (13.3, 15.2)	0.55
Creatinine (µmol/l)	363	77.0 (66.0, 90.0)	82.0 (69.0, 91.0)	76.0 (66.0, 90.0)	0.21
eGFR (mL/min)	362	75.0 (75.0, 78.0)	75.0 (75.0, 81.0)	75.0 (75.0, 75.0)	0.10

Data are number (%), median (IQR).

*According to scan read at site.

†Minimisation variable.

F/T, full time; NIHSS, National Institutes Health stroke scale; P/T, part time; SVD, small vessel disease; WMH, white matter hyperintensity.

These presentations are associated with increased short and long-term risk of recurrent stroke, cognitive decline, dementia and functional impairments.^{11–15} However, although these clinical outcomes are highly relevant to patients and clinical services,^{15 16} the data on their rates long term, individually or in combination, are sparse, precluding reliable sample size estimations for clinical trials in SVD.¹⁷ Furthermore, it was unclear if patients with clinically evident lacunar ischaemic stroke could be identified with key prognostic variables determined accurately in routine clinical practice, or recruited in sufficient numbers rapidly enough, to make a clinical trial in stroke presentations of SVD feasible in a practical time period. This is because lacunar ischaemic stroke may be confused clinically with mild cortical ischaemic stroke,¹⁸ MRI is not always available acutely nor positive for small subcortical stroke,¹⁹ and long-term outcomes vary with severity of SVD lesions on brain imaging,^{13–15} making it necessary to minimise the randomisation on SVD severity.²⁰ Since lacunar ischaemic stroke is currently managed according to guidelines covering the whole of secondary prevention of ischaemic stroke (representing best medical care) and there is no justification currently for withholding secondary prevention, any novel drugs should be tested against a background of guideline secondary ischaemic stroke prevention.

The LACunar Intervention Trial-2 (LACI-1/2) series of trials are assessing the feasibility of recruiting patients with clinically evident lacunar ischaemic stroke and tolerability of treatment with ISMN and cilostazol,^{17 21–24} while also gathering data on outcome event rates, with the aim of testing these agents in a large phase III efficacy trial. In LACI-1, short-term administration of cilostazol and ISMN in addition to best medical care were well tolerated when the dose was escalated, without safety concerns, in patients with clinically evident lacunar ischaemic stroke²³; additionally, these drugs appeared to reduce arterial stiffness without effects on platelet function²² and appeared to improve cerebrovascular function.²⁴

The present trial, LACI-2, is testing the long-term feasibility and tolerability of administering cilostazol and ISMN to patients with clinically evident lacunar ischaemic stroke given on top of guideline secondary ischaemic

stroke prevention while assessing safety and gathering data on clinically relevant outcome event rates.¹⁷ Here, we present the statistical analysis plan (SAP) and baseline data of LACI-2.

METHODS

The LACunar Intervention Trial-2 (LACI-2) is a UK-based investigator-initiated, prospective, randomised, partial factorial, open-label, blinded-endpoint phase II feasibility trial of cilostazol and/or ISMN. Patients with clinically evident lacunar ischaemic stroke, with no limit on the time interval since the stroke, with capacity to consent and who were independent in activities of daily living, were randomised to cilostazol, ISMN, both or neither in a partial factorial design. Patients with contraindications to one of the trial drugs could be randomised to the other drug alone. Randomised treatment was given in all patients in addition to guideline stroke prevention therapies, typically clopidogrel or aspirin, antihypertensive drugs and statins. Patients requiring oral anticoagulation were excluded.

Full details of regulatory approvals, patient assessment, inclusion and exclusion criteria, randomisation, minimisation criteria (age, baseline modified Rankin scale (mRS), National Institutes Health stroke scale (NIHSS), time from stroke to randomisation, highest educational attainment, smoking, systolic BP), dose-escalation scheme, short-term and long-term assessments are given in the protocol paper.¹⁷

The presence of an infarct relevant to the clinical presentation and a simplified estimate of total SVD lesion severity score, adapted for use on CT or MRI and by people not expert in brain imaging of SVD,^{17 21} were determined at the recruiting site. All diagnostic CT or MRI, scans obtained at any stroke recurrence and 1-year follow-up MRI, were collected by the trial office for central adjudication.

The primary outcome is feasibility of recruitment and adherence to medication. Key secondary outcomes include recruitment of hospital sites and participants, drug tolerability, symptoms (such as headache, nausea, palpitations) which might deter drug adherence, safety

(bleeding, falls, death), recurrent vascular events (including stroke and myocardial infarction), cognition and function over 1 year of follow-up. Imaging outcomes (white matter hyperintensity (WMH) severity, new cortical or subcortical infarcts, lacunes, haemorrhage, microbleeds) are assessed with MRI at 1 year. Details of central CT and MRI adjudication are given in the LACI-2 protocol paper.¹⁷

LACI-2 will provide outcome event rates and hence information to estimate sample size, recruitment and trial procedures for a phase III trial based in clinical outcomes. Further information is given in online supplemental file and published protocol.¹⁷

We present here a complete listing of baseline data; data are number (%) and median (IQR), unless otherwise stated.

The full details of the SAP^{25 26} are given in the accompanying online supplemental file, Appendix S1 and is presented prior to locking of the study database so that analyses are not data driven or reported selectively.²⁷ The SAP also lists planned secondary analyses and substudies, and follows the layout suggested in guidelines.^{25 26}

RESULTS

The trial commenced in February 2018; recruitment was suspended due to COVID-19 restrictions on 17 March 2020 by the Sponsor and reopened on 10 June 2020; however, the additional delays in reinstating site approvals meant that there was a total of 4 months without recruitment. Following a 6-month extension, recruitment stopped on 31 May 2021 to allow a year of follow-up prior to close, a total of 40 months (36 months excluding COVID-19 suspension, figure 1).

Of a planned 400 participants, 363 (91%) were recruited from 26 UK hospitals. At baseline, the average age was 64 (range 31–87) years (table 1). There were 112 (31%) female patients, the median NIHSS was 0 (0, 0), the mRS was 2 in 85 (23%) patients, and the time from stroke onset to randomisation was 79.0 (27.0, 244.0) days (table 1). The median age for completing education was 16 years, with 118 (33%) participants having one or more A-level equivalent or above qualifications. Vascular risk factor rates included median blood pressure of 143.0 (130.0, 157.0)/83.0 (75.0, 90.0) mm Hg, current smoking in 67 (19%), drug-treated hypertension in 258 (71%), drug-treated hyperlipidaemia in 278 (77%), diabetes mellitus in 80 (22%), atrial fibrillation in 5 (1%), carotid stenosis of >50% left 3 (0.8%), right 6 (1.7%) and history of previous stroke in 25 (7%) (table 2).

Baseline clinical findings included persistent unilateral weakness in 288 (79%), sensory change in 148 (41%), neglect/inattention in 6 (2%), dysphasia in 19 (5%) and visual disturbance in 11 (3%) (table 2). On cognitive testing, the median Montreal Cognitive Assessment score was 26.0 (23.0, 28.0) with 119 (33%) having a score below 25 signifying cognitive impairment. The median score on

the trail making test, part B, a test of executive function, was 25.0 (23.0, 25.0) points.

A majority of participants, 219 (60%), had both an admission CT scan and MRI brain imaging (320, 88%, had CT and 229, 65%, had MRI) (table 2). Imaging findings as reported by the recruiting site included an acute ischaemic stroke lesion thought to be consistent with the lacunar stroke symptoms in 296 (82%), WMHs present in 179 (49%) and median modified total SVD score of 1.0 (0.0, 2.0).

On central adjudication, a visible index infarct was present in 319 (88%) and averaged 10×8×10 mm in size (table 3). Only one scan was considered to be normal, that is, to have neither an acute infarct responsible for the recent stroke symptoms or any background changes of SVD or atrophy. Microbleeds were present in 20% of patients in mainly lobar (28%), deep (41%) or mixed lobar/deep (31%) locations (table 4). Atrophy was present in 75% of participants. WMHs were present in 95% of participants: 76% had up to Fazekas 2 periventricular and 82% had up to Fazekas 2 deep WMH scores. Sixty-two per cent of participants had one or more old vascular lesions including lacunes present in 96% (table 5).

In univariate analyses and in comparison with participants with lower SVD scores (table 1), those with moderate or severe SVD scores were older and more likely to have had a previous stroke, be taking antihypertensive drugs and have ataxia, and less likely to have visual loss. Additionally, participants with more severe SVD scores were more likely to have had MRI at diagnosis and to have a relevant acute ischaemic stroke lesion present on imaging (table 3). Similarly, in comparison with participants with a low SVD score, those with a moderate/high score had more atrophy, WMHs and their severity (table 4), and the presence of old vascular lesions (table 5).

DISCUSSION

SVD is common worldwide and, so far, whether presenting covertly or with stroke, cognitive or physical impairment, or neuropsychiatric symptoms,²⁸ has no demonstrated interventions that prevent or limit its development and progression.^{2-4 16} The LACI trials are assessing the tolerability and feasibility of recruiting patients, the outcome event rates, and tolerability and safety of treatment with ISMN and cilostazol^{17 21-24} in addition to guideline secondary stroke prevention, with the aim of testing these agents in a large phase III efficacy trial.

The baseline characteristics presented here show that LACI-2 is representative of patients with clinically evident lacunar ischaemic stroke, a marker of SVD. In particular, the average age was younger than for other types of ischaemic stroke at 64 years,²⁹ there was a preponderance of males (69%)³⁰ and most participants had relatively few physical signs or impairments resulting from their stroke.¹⁵ A majority of participants were diagnosed with hypertension and taking antihypertensive medication, and most were taking antiplatelet or lipid lowering drugs

Table 3 Adjudicated baseline imaging characteristics by small vessel disease score as determined by recruiting site

Variable	N	All	SVD	Score	P value
			Low	Moderate-severe	
Patients randomised		363	99	264	
Scan					
Scan type (%)					
CT	363	320 (88.2)	90 (90.9)	230 (87.1)	0.32
Time to CT (days)	320	1.0 (0.0, 1.0)	0.0 (0.0, 1.0)	1.0 (0.0, 1.0)	0.19
MRI	362	263 (72.5)	60 (60.6)	203 (76.9)	0.0020
Time to MRI (days)	263	3.0 (1.0, 9.0)	2.0 (1.0, 5.0)	3.0 (1.0, 11.0)	0.097
Scan quality (%)					0.28
Good		237 (65.3)	66 (66.7)	171 (64.8)	
Moderate		118 (32.5)	29 (29.3)	89 (33.7)	
Poor		8 (2.2)	4 (4.0)	4 (1.5)	
Index lesion (%)					
Normal scan		1 (0.3)	1 (1.0)	0 (0.0)	1.00
Lesion present (type)					0.0006
Primary infarct		319 (87.9)	77 (77.8)	242 (91.7)	
Primary haemorrhage		0 (0.0)	0 (0.0)	0 (0.0)	
Mimic		0 (0.0)	0 (0.0)	0 (0.0)	
No acute lesion visible		43 (11.8)	21 (21.2)	22 (8.3)	
Infarct side of brain	320				0.22
Right		142 (44.4)	29 (37.7)	113 (46.5)	
Left		175 (54.7)	48 (62.3)	127 (52.3)	
Both		3 (0.9)	0 (0.0)	3 (1.2)	
Location (%)	320				
Small subcortical infarct		311 (97.2)	72 (93.5)	239 (98.4)	0.33
Internal capsule		110 (34.4)	21 (27.3)	89 (36.6)	
External capsule		4 (1.3)	1 (1.3)	3 (1.2)	
Lentiform nucleus		31 (9.7)	7 (9.1)	24 (9.9)	
Internal border zone		0 (0.0)	0 (0.0)	0 (0.0)	
Centrum semiovale		83 (25.9)	23 (29.9)	60 (24.7)	
Thalamus		64 (20.0)	17 (22.1)	47 (19.3)	
Cerebellum		0 (0.0)	0 (0.0)	0 (0.0)	
Brainstem lesion (pons)		18 (5.6)	3 (3.9)	15 (6.2)	
Medulla		1 (0.3)	0 (0.0)	1 (0.4)	
Non-small subcortical infarct					
MCA territory	320	9 (2.8)	4 (5.2)	5 (2.1)	0.23
PCA territory	320	2 (0.6)	1 (1.3)	1 (0.4)	0.42
Infarct size (mm)	320				
A/P		10.0 (8.0, 12.0)	10.0 (8.0, 12.0)	10.0 (8.0, 12.0)	0.97
R/L		9.0 (6.0, 11.0)	9.0 (6.0, 10.0)	9.0 (6.0, 11.0)	0.91
Cranio-caudal		10.0 (8.0, 15.0)	10.0 (8.0, 12.0)	10.0 (8.0, 15.0)	0.15

Data are number (%), median (IQR) or mean (SD). The number of participants with data is 363 unless stated.

Index lesion=main cause of stroke symptoms.

Index small subcortical infarct=acute lacunar.

Non-small subcortical infarct=large artery cortical or large subcortical or posterior circulation.

SVD, small vessel disease.

Table 4 Adjudicated baseline imaging characteristics (microhaemorrhages, atrophy, white matter hyperintensities and perivascular spaces) by small vessel disease score as determined by recruiting site

Variable	N	SVD		Score		P value
		All	Low	Moderate-severe		
Patients randomised	363	99	264			
Microhaemorrhages	196	39 (19.9)	9 (20.9)	30 (19.6)		0.85
No microhaemorrhages (%)	39					0.18
1		9 (23.1)	5 (55.6)	4 (13.3)		
2		7 (17.9)	3 (33.3)	4 (13.3)		
3		5 (12.8)	0 (0.0)	5 (16.7)		
4		2 (5.1)	0 (0.0)	2 (6.7)		
≥5		15 (38.5)	1 (11.1)	14 (46.7)		
Type of microhaemorrhages (%)	39					0.61
Lobar		11 (28.2)	2 (22.2)	9 (30.0)		
Deep		16 (41.0)	5 (55.6)	11 (36.7)		
Both		12 (30.8)	2 (22.2)	10 (33.3)		
Superficial siderosis present	41	2 (4.9)	0 (0.0)	2 (6.3)		1.00
Siderosis focal		2 (100.0)	0 (0.0)	2 (100.0)		1.00
Siderosis disseminated		0 (0.0)	0 (0.0)	0 (0.0)		–
Siderosis location						1.00
Left		1 (50.0)	0 (0.0)	1 (50.0)		
Right		0 (0.0)	0 (0.0)	0 (0.0)		
Both		1 (50.0)	0 (0.0)	1 (50.0)		
Atrophy (%)						
Brain volume reduction	362	272 (75.1)	63 (64.3)	209 (79.2)		0.0036
Central brain tissue volume	272					0.42
Moderate		199 (73.2)	50 (79.4)	149 (71.3)		
Severe		64 (23.5)	11 (17.5)	53 (25.4)		
Cortical brain tissue volume	272					0.12
Moderate		203 (74.6)	43 (68.3)	160 (76.6)		
Severe		5 (1.8)	0 (0.0)	5 (2.4)		
WMH (%)						
WMH present	362	342 (94.5)	87 (88.8)	255 (96.6)		0.0038
Anterior white matter lucency	342					
Adjoining ventricles		116 (33.9)	32 (36.8)	84 (32.9)		0.51
Covering ventricle to cortex		56 (16.4)	6 (6.9)	50 (19.6)		0.0057
Posterior white matter lucency	342					
Adjoining ventricles		114 (33.3)	27 (31.0)	87 (34.1)		0.60
Covering ventricle to cortex		55 (16.1)	10 (11.5)	45 (17.6)		0.18
Anterior and/or Posterior white matter lucency	342					
Adjoining ventricles		136 (39.8)	36 (41.4)	100 (39.2)		0.72

Continued

Table 4 Continued

Variable	N	SVD		Score		P value
		All	Low	Moderate-severe		
Covering ventricle to cortex		68 (19.9)	11 (12.6)	57 (22.4)		0.050
Periventricular WMH Fazekas score	342					<0.0001
1		131 (38.3)	48 (55.2)	83 (32.5)		
2		129 (37.7)	32 (36.8)	97 (38.0)		
3		80 (23.4)	7 (8.0)	73 (28.6)		
Deep WMH Fazekas score	342					0.0002
1		178 (52.0)	59 (67.8)	119 (46.7)		
2		102 (29.8)	14 (16.1)	88 (34.5)		
3		42 (12.3)	5 (5.7)	37 (14.5)		
Periventricular and/or Deep WMH Fazekas score	342					<0.0001
1		123 (36.0)	46 (52.9)	77 (30.2)		
2		137 (40.1)	34 (39.1)	103 (40.4)		
3		82 (24.0)	7 (8.0)	75 (29.4)		
Enlarged PVS (%), MRI only	194					
Enlarged PVS		194 (100.0)	43 (100.0)	151 (100.0)		1.00
Basal ganglia score						
≤10		62 (32.0)	23 (53.5)	39 (25.8)		0.0008
11–20		74 (38.1)	16 (37.2)	58 (38.4)		
20–40		36 (18.6)	4 (9.3)	32 (21.2)		
>40		22 (11.3)	0 (0.0)	22 (14.6)		
Centrum semiovale score						
≤10		30 (15.5)	10 (23.3)	20 (13.2)		0.30
11–20		52 (26.8)	13 (30.2)	39 (25.8)		
20–40		82 (42.3)	15 (34.9)	67 (44.4)		
>40		30 (15.5)	5 (11.6)	25 (16.6)		

Data are number (%), median (IQR) or mean (SD). The number of participants with data is 363 unless stated. PVS, perivascular spaces; WMH, white matter hyperintensities.

as guideline secondary prevention of ischaemic stroke. Many were ex-smokers or current smokers. Very few had atrial fibrillation or carotid stenosis (about 1%) reflecting that, while emboli can enter and intracranial large artery atheroma may obstruct perforating cerebral arterioles, these are rare in, and uncommon causes of, lacunar ischaemic stroke.^{29 31}

A minority of participants had clinical cortical features such as dysphasia (19, 5.2%), neglect (6, 2%) or hemianopia (11, 3%), reflecting the overlap in symptoms between cortical and lacunar ischaemic stroke,¹⁸ and potential difficulty of recruiting pure lacunar syndrome populations on the basis of clinical syndrome and CT scanning in busy regional hospital stroke services. Nonetheless, it is reassuring that very few patients were found to have a primary cortical infarct on central expert scan

Table 5 Adjudicated baseline imaging characteristics (old vascular and non-stroke lesions) by small vessel disease score as determined by recruiting site

Variable	N	All	SVD		P value
			Low	Moderate-severe	
Patients randomised		363	99	264	
Old vascular lesions (%)	362	224 (61.9)	38 (38.8)	186 (70.5)	<0.0001
Old cortical infarct	224	11 (4.9)	1 (2.6)	10 (5.4)	0.70
Old striatocapsular infarct	224	2 (0.9)	1 (2.6)	1 (0.5)	0.31
Old borderzone infarct	224	2 (0.9)	1 (2.6)	1 (0.5)	0.31
Old lacunar infarct	224	216 (96.4)	36 (94.7)	180 (96.8)	0.54
No of lacunes (%)	224				0.11
1		40 (17.9)	10 (26.3)	30 (16.1)	
2		46 (20.5)	8 (21.1)	38 (20.4)	
3		42 (18.8)	8 (21.1)	34 (18.3)	
4		26 (11.6)	6 (15.8)	20 (10.8)	
≥5		62 (27.7)	4 (10.5)	58 (31.2)	
Old brainstem/cerebellar non-lacunar infarcts	224	35 (15.6)	2 (5.3)	33 (17.7)	0.083
Probable old haemorrhage	224	4 (1.8)	0 (0.0)	4 (2.2)	1.00
Non-stroke lesions (%)					
Non-stroke lesion present	362	13 (3.6)	3 (3.1)	10 (3.8)	1.00
Classification of non-stroke (%)	13				
Cerebral tumour		2 (15.4)	0 (0.0)	2 (20.0)	1.00
Aneurysm		1 (7.7)	0 (0.0)	1 (10.0)	1.00
Vascular malformation		1 (7.7)	1 (33.3)	0 (0.0)	1.00
Other non-stroke classification		8 (61.5)	2 (66.7)	6 (60.0)	1.00

Data are number (%), median (IQR), or mean (SD). The number of participants with data is 363 unless stated.

read (3%), the remaining 97% having either a recent small subcortical (ie, acute lacunar) infarct as the primary cause of symptoms, or no definite visible relevant lacunar infarct but no alternative cause for their symptoms.

On adjudicated brain imaging, most participants (264, 73%) were judged to have a moderate to severe SVD score by the recruiting hospital, consistent with patients with lacunar ischaemic stroke, and demonstrating that a simplified version of the SVD score, suitable for use on CT or MRI, can be applied in busy stroke services.³²

The trial is in follow-up and once this is completed, the database will be cleaned and locked. Therefore there may be minor changes in the baseline data between that provided here and in subsequent publications. Analysis will follow the SAP given here as an online supplemental file. If reasonable drug adherence and safety are confirmed, then a phase III trial will be

designed and submitted for funding using the vascular and cognitive outcome event rates to power the next phase of the trial.

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Contributors JMW is the chief investigator, obtained ethics and regulatory approvals; PMB is Director of the Nottingham Stroke Trials Unit. KO is the current trial manager, responsible for daily running of the trial including regulatory compliance; FD is a Principle Investigator; AAM provides statistical expertise; IM and LJW are the trial statisticians; PMB drafted the manuscript; all other authors commented and edited it; all authors approved the final version for submission. JMW is the guarantor for the trial.

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