Research Article

PRESERVE: Randomized trial of intensive vs standard blood pressure control in small vessel disease

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ABSTRACT

Background and Purpose: In cerebral small vessel disease cerebral blood flow and autoregulation are impaired and therefore excessive blood pressure reduction could possibly accelerate white matter damage and worsen outcome. The trial determined, in severe symptomatic cerebral small vessel disease, whether intensive blood pressure lowering resulted in progression of white matter damage assessed using diffusion tensor imaging.

Methods: Randomised, parallel, multicentre controlled, blinded-outcomes clinical trial. 111 participants with magnetic resonance imaging confirmed symptomatic lacunar infarct and confluent white matter hyperintensities, were recruited and randomised to "standard" (systolic=130-140mmHg) (N=56) or "intensive" (systolic<125mmHg) (N=55) blood pressure targets.

The primary endpoint was change in diffusion tensor imaging white matter mean diffusivity peak height between baseline and 24 months. Secondary endpoints were other magnetic resonance imaging markers and cognition.

Results: Patients were mean 68 years and 60% male. Mean (SD) blood pressure reduced by -15.3 (15.4) and -23.1 (22.04) mmHg in the standard/intensive groups, respectively ($p<0.001$). There was no difference between treatment groups for the primary endpoint: standard, adjusted mean (SE)= $12.5\text{x}10^{-3}$ ($0.2\text{x}10^{-3}$); intensive, $12.5\text{x}10^{-3}$ ($0.02\text{x}10^{-3}$), $p= 0.92$. In the whole population over 24 months follow-up, there was a significant deterioration in white matter microstructure but no detectable decrease in cognition.

Conclusions: Intensive blood pressure lowering in severe cerebral small vessel disease was not associated with progression of white matter damage on diffusion tensor imaging or magnetic resonance imaging. In a multicentre study setting over two years multimodal diffusion tensor imaging- magnetic resonance imaging was more sensitive to detecting change than cognitive testing.

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Abbreviations/ Acronyms	**Meaning**
AEs	Adverse events
ANCOVA	Analysis of covariance analysis
BP	Blood pressure
DTI	Diffusion Tensor Imaging
FA	Fractional anisotropy
FLAIR	Fluid-attenuated inversion recovery
ITT	Intention-to-treat analysis
MD	Mean diffusivity
MRI	Magnetic Resonance Imaging
NBV	Normalized brain volume
SAEs	Serious adverse events
SVD	Small vessel disease
WM	White matter volume
WMH	White matter hyperintensities lesion

INTRODUCTION

Cerebral Small Vessel Disease (SVD) accounts for 20% of ischaemic strokes, and is the most common cause of vascular cognitive impairment (VCI).[1] Hypertension is a major risk factor for SVD,[2] and reducing blood pressure (BP) is associated with reduced risk of SVD.[3] However, how low BP should be reduced in patients with symptomatic SVD is uncertain.

On the one hand, recent trials have reported intensive BP lowering, targeting a systolic BP of 120-125 mmHg is associated with reduced cardiovascular events in primary prevention[4], and reduced stroke risk in secondary prevention in stroke patients.[5] However it has been argued that excessive BP lowering could be harmful in established SVD.[6] Reduced cerebral blood flow,[7,8] and impaired cerebral autoregulation,[9] occur in SVD. Excessive BP lowering, in the presence of impaired autoregulation, could further reduce cerebral blood flow, accelerate white matter damage and worsening cognition.[10] Cerebral autoregulation is particularly impaired in patients with severe SVD, who have confluent white matter hyperintensities (WMH) and multiple lacunar infarcts,[9,10] and therefore this group have been suggested to be particularly vulnerable to excessive BP reduction. The SPS3 trial, found no difference in cognitive decline rates with intensive BP lowering,[11] but many patients had mild SVD.

Clinical trial design to assess interventions in SVD has been challenging. Neuropsychological tests to monitor cognitive change are insensitive to change over time periods of 2-3 years often used in clinical trials, with change only detected on longer follow-up.[11.12] MRI may represent a useful surrogate marker. The SPRINT-MRI study reported intensive BP lowering was associated with reduced WMH lesion progression, but this was in hypertensive patients without symptomatic SVD.[3] Diffusion Tensor Imaging (DTI), is more sensitive to change in white matter structure and in SVD correlates with cognition better than WMH volume.[13,14]

Using DTI, white matter abnormalities can be detected in SVD not only within WMH but also in normal-appearing white matter on T2-MRI,[13,14,15] DTI abnormalities predict long-term dementia risk.[16] Decline in DTI parameters has been detected over periods as short as 1-2 years.[17] However no multicentre randomised clinical trials have used DTI as a surrogate marker.

The PRESERVE trial was designed to determine whether intensive BP lowering was associated with increased white matter damage assessed by DTI, with the primary endpoint being DTI mean diffusivity peak height, which has been shown to be the DTI parameter most sensitive to change in a longitudinal SVD study.[18]

MATERIALS and METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study design

PRESERVE was a two-years, multicentre, randomised clinical trial in 6 university hospitals which tested "intensive" vs. "standard" BP treatment regimens in severe SVD. The full protocol is available: http://www.neurology.cam.ac.uk/wp-content/uploads/2014/04/PRESERVE-Protocol-Version-5-13-December-2013.pdf.

Study participants

Inclusion criteria were clinical lacunar stroke with an anatomically corresponding lacunar infarct on MRI, in addition to confluent WMH graded ≥2 on the Fazekas scale.[19] Patients

were ≥40 years with hypertension defined as systolic BP >140mmHg, or 125-140mmHg while on antihypertensive medication. Participants were recruited at least three months post-stroke. Exclusion criteria were: known single gene disorder causing SVD, cause of stroke other than SVD (e.g. carotid or vertebral stenosis >50%, cortical infarction, dementia, life expectancy >2 years, symptomatic postural hypotension, women of childbearing potential, and inability to fulfil study data collection.

Standard Protocol Approvals, Registrations, and Patient Consents

All patients gave informed written consent. The study was approved by Harrow NRES ethics committee (REC number:11/LO/0458). The trial was registered with NIHR Clinical Research Network (CRN number:10962). accessible at https://www.ukctg.nihr.ac.uk/ and ISRCTN37694103.

Screening and randomisation

PRESERVE had a parallel trial design. After recruitment, participants were randomised (stratified by centre) with random allocation concealed until the intervention was assigned to "Standard" (systolic BP target 130-140mmHg) or "Intensive" (systolic BP target <125mmHg) treatment arms by the local clinician in a 1:1 ratio via a centralised, online system (at Mental Health & Neuroscience Clinical Trials Unit, Kings College London).

Outcome measures

The initial endpoint was a global cognitive score with DTI-MRI as a secondary endpoint. There was a pre-planned review following the expected publication of the SPS3 cognition

study which published in 2014.[11] This showed that in SPS3 cognitive change could not be detected over two years in 2916 participants with lacunar stroke. Following this, the steering committee met, and with funders agreement, halted recruitment to the cognitive only arm which had a planned sample size of 422, and only recruited to the DTI-MRI arm (which had a sample size of 180), with the primary endpoint of the overall study becoming DTI. There were no interim analyses. Treatment allocation was known to the participants and clinical staff, but analysis of MRI and cognitive outcomes was performed blind to treatment allocation.

Follow-up Assessments

All subjects were seen at 1, 3, 6, 12, 18 and 24 months for clinical assessment and BP monitoring. Additional clinic or telephone BP check-ups were performed as necessary. During clinic visits, BP was measured in sitting position 3 times following a 10 minutes rest period in a quiet room. Recorded BP was mean of the 2nd and 3rd measures. At each check-up, an increase in antihypertensive medication was prescribed if the participant's BP was above study target, and so long as hypotensive symptoms did not prevent it. Results presented, and used in analysis, are clinic BP readings.

MRI was performed at baseline and at two years. Cognitive assessments were performed at baseline, one and two years.

Treatment intervention

Treatment algorithms for intensive and standard BP lowering protocols consistent with the British Hypertension Society/NICE guidance on drug treatment of hypertension were used.[20]

Final treatment decisions were made by the local study principal investigator. No treatment changes were before the baseline MRI scan.

Adverse event recording

At each participant visit, adverse events (AEs) and serious adverse events (SAEs) were recorded. In addition, participants were asked specifically about falls or postural-related dizziness. Stroke and death outcome events were recorded on a proforma, and reviewed by two adjudicators blinded to treatment.

Cognitive Testing

The cognitive test battery included tests sensitive to impairments in processing speed and executive function characteristic of SVD with additional memory testing; details of individual cognitive tests have been published previously.[21] Assessment included the WAIS-III Digit Symbol Coding test (DSC), Trail Making Test (TMT), phonemic verbal fluency task(FAS), semantic verbal fluency task (animals), and Rey Auditory Verbal Learning Test (RAVLT). Premorbid IQ was estimated using the restandardised National Adult Reading Test (NART-R). Cognitive testing was performed on the same day as MRI, or as close as possible.

Performance across neuropsychological tests was made comparable by transforming raw scores into z-scores using age-scaled normative data.[21] Tasks were grouped into three domains (**Processing Speed**: WAIS-III coding total correct, TMT-A time to complete, **Executive function**: TMT-B time to complete**,** total correct for "FAS" letter fluency and animal fluency, and **Verbal Memory**: RAVLT "immediate" and "delayed" recall). Individual task z-scores were averaged across these groupings to create overall domain scores, and all domain scores averaged to create a **Global Cognition** domain.

Where data were missing due to subjects being unable to complete a task, the lowest available Z score was given; this applied to 33 individual tasks, across 6 participants (5.4% of sample). If data were missing for any other reason, domain scores were calculated without that task; this applied to 14 participants (12.6% of sample).

MRI Acquisition

Across 6 centres, eight 3-Tesla MR scanners were used (3 Philips Acheiva TX, 1 Philips Acheiva, 1 Philips Ingenia, 1 Siemens Verio, 1 Siemens Prisma, 1 Siemens Magnetom Prisma^{fit}). 3D T1-weighted (T1W), DTI, T2*-weighted (T2*W), and Fluid Attenuated Inversion Recovery (FLAIR) scans were acquired. Rigorous quality control was implemented to ensure standardisation of sequence acquisition parameters. T1W scans were acquired at 1mm^3 isotropic voxel resolution and TR and TE optimised to ensure comparable T1 weighting and tissue contrast. DTI scans (2mm^3 isotropic voxel resolution) had similar TEs and long TRs to avoid T1 relaxation effects. In addition to b=0 s mm^{-2} acquisitions, all DTI acquisitions included 32 equally spaced, non-collinear diffusion gradient directions (b=1000 smm^{-2}) to ensure identical angular resolution and noise characteristics. T2*W sequences were TE matched and kept similar TR to ensure comparable weighting. FLAIR sequences had identical inversion times and were TE matched with long enough TR's to ensure no T1 weighting. Exact scanner and sequence details have been published.[21]

MR Image analysis

All MRI analysis was centralised and performed blind to patient identity.

WMH: WMH were defined as areas of increased signal on FLAIR (and segmented by a single trained rater using a semi-automated, contouring technique in Jim image analysis

software version 7.0_5 (Xinapse Systems Limited, http://www.xinapse.com/j-im-7-software/). Whole brain WMH lesions maps were generated and WMH lesion load score calculated as percentage of WMH lesion volume against whole brain volume. On 10 different SVD scans, inter-rater reliability and intra-rater reliability was assessed; intraclass correlation coefficients were 0.988 and 0.998 respectively.

LACUNES:

Lacunes were defined as cerebrospinal fluid (CSF)-filled cavities at least 3 mm in diameter. Additional features such as T2-hyperintense rims, shape and location were also considered to differentiate lacunes from similar imaging features such as perivascular spaces. The same single rater identified lacunes after training by a consultant neuroradiologist using a combination of T1W, T2*W and FLAIR scans.

CEREBRAL MICROBLEEDS: Microbleeds were detected on gradient recalled echo images as focal regions of low signal<10mm in diameter by a single trained rater using the Microbleed Anatomical Rating Scale (MARS)[22]. Only definite CMB, as defined by MARS criteria, were included in the analysis.

BRAIN VOLUME: T1W scans were intensity non-uniformity corrected using "N4ITK" and segmented into grey matter (GM), white matter (WM) and CSF tissue probability maps (TPM) using SPM12b (Statistical Parametric Mapping, http://www.fil.ion.ucl. SIENAX (FMRIB Software Library, https://fsl.fmrib.ox.ac.uk/fsl) was applied to T1W scans giving a scaling factor describing variation of brain size relative to skull size. Native space brain volumes were multiplied by this scaling factor to provide normalised brain volumes (NBV).

DTI HISTOGRAM ANALYSIS: FSL software (FMRIB's Diffusion Toolbox, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT) was used for DTI pre-processing. Briefly; A binary brain mask in DTI space was calculated for each subject using BET on the same b=0 acquisition. Fractional anisotropy (FA) and mean diffusivity (MD) maps were calculated using DTIFIT. Based on a diffusivity threshold,[23] spurious CSF voxels were removed from tissue masks were considered to contain CSF and excluded. For each participant, FMRIB Linear Image Registration Tool (FLIRT, FMRI Software Library, FSL version 4.1, http://www.fmrib.ox.ac.uk/fsl) was used to register FLAIR to T1W images, and T1W to b0 images. These affine transformation matrices were concatenated to create a FLAIR-to-DTI transformation. TPM's and WMH lesion masks were registered into DTI space using the T1W-to-DTI (trilinear interpolation), and FLAIR-to-DTI (nearest neighbour interpolation) transforms for TPMs and binary WMH lesion masks, respectively.

A hard segmentation method was applied to generate maps of tissue classes. This was achieved by voxel-wise comparison of the GM, WM and CSF TPMs, with each voxel being assigned to the highest probability tissue class. Histogram analysis was performed on white matter FA and MD maps. Normalised histograms with 1000 bins (FA range 0-1, bin width 0.001; MD range 0-4mm^2s^{-1} $x10^{-3}$, bin width 0.004mm^2s^{-1} $x10^{-3}$) were computed and median, peak height and peak value FA and MD were extracted from histograms.

Sample size

A sample size of 160 completed scans, with 180 recruited to account for an attrition rate of 12.5%, was planned to allow detection of difference on DTI with $p<0.05$, and power of 0.9 based on an FA SD in control group of $6.0x10^{-3}$ and difference between 2 interventions of

$3.1x10^{-3}$. Recruitment was stopped at 111 due to slower than expected recruitment, and a fixed duration grant, which meant recruitment could not be continued beyond this number.

Statistical Analyses

All analyses were performed using R 3.4 software (r-project.org, R Foundation for Statistical Computing, Austria). Linear mixed effects model were computed employing the lmer function in the lme4 package[24]. Demographic variables and risk factors were compared between groups employing t-tests, Mann-Whitney, or chi-square tests as appropriate. Differences in MRI and DTI marker between baseline and 24 months were tested using paired t-test and Wilcoxon Signed Rank test. Changes in cognition across time were assessed through a linear mixed model with visit as a fixed factor. Change in systolic and diastolic BP was compared across visits by a linear mixed model with visit as a fixed factor. To test whether change in BP was dependent on the treatment group, a fixed interaction term between visit and treatment group was added to the model.

The primary analysis was intention to treat (ITT). The DTI marker for the primary endpoint was chosen as MD peak height because this was shown to be most sensitive to change in longitudinal study in SVD, and predicted to allow detection of treatment effects with lowest sample size.[18] To assess treatment effect at 24 months while accounting for baseline values, analysis of covariance (ANCOVA) was employed, with study site added as a factor. WMH lesion volume was log transformed to normalise the distribution. Differences between treatment groups in lacune and CMB count were tested using permutation ANCOVA. For cognition linear mixed models were employed to examine whether change in cognition was dependent on treatment group. The interaction between the fixed factors study visit and treatment group was included to estimate treatment effects. A per-protocol analysis was

performed, limited to subjects who reached their BP target at 3 months, defined as systolic BP<125 mmHg in the intensive group, and ≥130 in the standard group. To determine any relationship between change in BP and MRI markers, multivariable regression was conducted between change in systolic BP and change in the imaging markers while accounting for study site. The effect of time on change in BP was estimated over the 24 months employing a linear mixed model. The intercept and slope of each patient's linear trajectory were allowed to vary with both fixed and random effects. Fixed effects variations were modelled by the trial's duration and random effect variation allowed for the remaining inter-individual differences. The proportions of patients with side effects were compared by Fisher's exact test.

RESULTS

Recruitment took place from 29.02.2012-30.10.2015; follow-up was completed on 1.11.2017. Patient flow is shown in Figure 1. 111 participants (56 standard, 55 intensive) were recruited. One subject did not meet MRI criteria on baseline central MRI review and was withdrawn. Three died during follow up, 1 developed other serious illness and could not continue, 6 withdrew consent, and 2 were lost to follow-up. Baseline MRI was not performed in one, and follow-up MRI not performed in two. Therefore, 90 subjects remained with baseline and follow-up MRI scans. Of these, DTI sequences were available for 86 (42 standard, 44 intensive). After excluding 5 scans (3 standard, 2 intensive) of inadequate quality for DTI analysis, 81 pairs remained for the analysis (intensive 42, standard 39). There were no differences in baseline demographics, or cardiovascular risk factors between the treatment arms (Table 1). There was no difference in baseline cognition measured by Montreal Cognitive Assessment between the 81 participants who had data included in the primary endpoint analysis and those that did not (Included: Mean (SD) = 24.87 (3.60); Not included: Mean (SD)= 25.33 (2.73).

Blood Pressure changes in the Treatment Arms

Target BP difference was achieved by 3 months (intensive 127mmHg, standard 140mmHg), and maintained for two years (Figure 2A to B). Mean (SD) systolic blood pressure (BP) was reduced by -15.3 (15.4) and by -23.1 (22.0) mmHg in the standard/intensive groups, respectively ($p< 0.001$).

Primary endpoint

On ITT analysis there was no difference between treatment groups for the primary endpoint MD peak height: standard, adjusted mean (SE)= $12.5x10^{-3}$ ($0.2x10^{-3}$); intensive, $12.5x10^{-3}$ ($0.2x10^{-3}$), p=0.92. (Table 2). No other DTI measure showed any treatment effect (Table I).

Secondary endpoints

There was no difference between treatment arms in WMH lesion volume, brain volume WMH lesion volume, lacune count, or cerebral microbleeds (Table 2).

Cognition

There was no difference in change in global cognition, or any cognitive subdomains, between groups (Figure I). Change in cognition did not depend on the treatment group for global cognition ($F_{(2,\ 196.64)}$= 0.42, p= 0.66), executive function ($F_{(2,\ 197.04)}$= 1.01, p= 0.37), processing speed ($F_{(2,\ 196.69)}$= 0.55, p= 0.58) or verbal memory ($F_{(2,\ 195.37)}$ = 1.12, p= 0.33) (Figure I).

Per-Protocol analysis

There were 32 patients in the intensive arm and 47 patients in the standard arm reached their BP target level at 3 months. 26 patients in the intensive treatment group and 33 patients in the

standard treatment group had complete DTI data at both time points for the per-protocol analysis. There was no difference between treatment groups in the primary DTI endpoint or any secondary imaging endpoints (Table 3). No other DTI measure showed any treatment effect (Table II). Change in cognition did also not depend on the treatment group for global cognition ($F_{(2,\ 142.85)}$= 0.12, p= 0.89), executive function ($F_{(2,\ 143.29)}$= 0.33, p= 0.72), processing speed ($F_{(2,\ 142.42)}$= 0.21, p= 0.81) or verbal memory ($F_{(2,\ 141.33)}$= 0.62, p= 0.54) (Figure II).

Relationship between change in BP and change in imaging parameters

Across the whole population a greater reduction in systolic BP was correlated with less progression of WMH lesion volume. (β=0.369 (0.097), p=0.00027) (Figure 3). No similar relationship was seen for DTI, brain volume, lacune count or cerebral microbleeds.

Change in cognition and MRI markers in the whole cohort

A significant decrease in MD peak height was detectable over the two-years period. Brain volume, WMH volume, lacune count, and microbleeds also all significantly progressed (Table III). In contrast no decrease in any cognition domain was detectable (Table IV). A small but significant increase in verbal memory (P=0.002) and global cognition (p= 0.01) occurred. We explored different imputation methods to manage missing cognitive data points but the results were similar (Table IV, Table V).

Adverse Events

The number of patients with any side effect was 45 in the intensive arm and 36 in the standard arm (*OR (95%CI)*= 2.48 (0.96, 6.73), p= 0.05), and with any serious adverse event was intensive 13, standard 8 (*OR (95%CI)*= 0.54 (0.18, 1.57), p= 0.23). There was no

difference between groups in the number of falls (intensive 21 standard 14; *OR (95%CI)*= 0.54 (0.22, 1.31), *p*= 0.16), or postural related dizziness (intensive 27 standard 22; *OR (95%CI)*= 0.67 (0.30, 1.52), *p*= 0.34). A list of all reported side effects per treatment group can be found in Table VI. During follow-up there were 3 strokes, and 1 death in the intensive, and 3 strokes, and 2 deaths in the standard arms.

Anonymized data will be shared by request to the corresponding author from any qualified investigator.

DISCUSSION

We found no significant difference in the primary endpoint of white matter integrity, measured by DTI, between patients randomised to intensive versus standard BP lowering. The results demonstrate that BP lowering in patients with severe SVD is feasible and does not appear to increase white matter damage. This is important because BP lowering not only protects the brain, but also reduces risk of cardiovascular endpoints in other vascular beds.

On secondary analysis, we found a significant negative correlation between degree of BP lowering and WMH progression, with more intensive lowering associated with less progression. This suggests that intensive BP lowering might be protective, but should be interpreted cautiously as it was a secondary analysis.

Previous longitudinal studies have demonstrated cognitive endpoints are insensitive to change in SVD over periods of 1-2 years.[11,12] Consistent with this we found no reduction in cognition, but detected a small improvement in memory, likely due to practice effects.

In contrast longitudinal studies have shown MRI markers, particularly DTI, are sensitive to change over 1–2 years.[18] Studies to date have been single centre, and observational. PRESERVE is the first multicentre clinical trial to apply DTI in this setting. The results show significant changes in DTI parameters could be detected over 2 years follow up. The data is consistent with results from the cerebral blood flow PRESERVE substudy,[25] in which intensive BP lowering did not reduce cerebral perfusion compared with standard BP treatment. There were also significant changes in conventional MRI parameters including WMH volume, brain volume, and lacunes. This suggests MRI markers may be more sensitive outcome measures for use in phase 2 clinical trials in SVD. However implementation of DTI across multiple sites and scanners does present challenges, and significant between sites differences in DTI parameters have been demonstrated in some[26] but not all[27] studies assessing reproducibility. We implemented a standard protocol, which was established on scanners at study initiation and no major scanner upgrades occurred during the study. We also entered study site as a covariate in analysis. In a study of the baseline data we showed similar correlations between DTI parameters and cognition across all sites.[21] Nevertheless site and scanner differences may have reduced power to detect a treatment effect.

This study has limitations. Although overall mean BP was reduced in the intensive arm to 125 mmHg systolic, in some patients target BP was not reached. However, per protocol analysis limited to patients reaching target blood pressure at 3 months revealed similar results. Careful quality control of DTI imaging was ensured across different scanners. However, despite a significant inverse relationship between degree of BP reduction and progression of WMH, there was no similar relationship for DTI. It is possible that WMH represents a more robust marker for multicentre studies; further data is required to evaluate this. A further limitation is the failure to recruit the planned sample size of 180, which could

have missed smaller treatment effects. This reduced the power to detect the planned difference from 0.9 to 0.49 at a significance level of 0.05.

SUMMARY

This study demonstrates feasibility of intensive blood pressure lowering in subjects with severe SVD without worsening white matter microstructure, although this result requires further validation in a larger study. Furthermore, it demonstrates that in a multicentre setting MRI markers are more sensitive to change over short time periods than cognitive testing in SVD.

Authors

Obtained funding: Markus HS, O'Brien JT, Morris RG, Barrick TR, Blamire AM, Ford GA; Study design: Markus HS, O'Brien JT, Morris RG, Barrick TR, Blamire AM, Ford GA; Data acquisition: Markus HS, Khan U, Hassan A, Harkness K, O'Brien JT, Morris RG, Blamire AM, Tozer DJ, Ford GA; Data analysis: Markus HS, Egle M, Morris RG, Blamire AM, Tozer DJ, Ford GA. Neuroradiological analysis and training: Mackinnon A; Image analysis: Croall ID, Sari H, Blamire AM, Tozer DJ; Initial draft of manuscript: Markus HS, Egle M; Revision of manuscript draft: Markus HS, Croall ID, Sari H, Khan U, Hassan A, Harkness K, Mackinnon A, O'Brien JT, Morris RG, Barrick TR, Blamire AM, Tozer DJ, Ford GA. Overall study supervision: Markus HS, Ford GA.

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Supplementary Material List:

Figure I – II

Table I - VI

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Table 1. Baseline demographics and risk factors for patients with complete DTI data in the two treatment arms.

Demographics	Standard (N= 39)	Intensive (N= 42)	p-value
Age, (years)	69.58 (9.35)	68.13 (8.66)	0.47
Male Sex	23 (59%)	25 (59%)	1
Systolic BP (mmHg)	147.77 (11.53)	149.29 (14.8)	0.61
Hypercholesterolaemia	32 (82%)	31 (74%)	0.43
Current smoker	6 (15%)	5 (12%)	0.75
Former smoker	15 (39%)	14 (33%)	0.64
Diabetes mellitus	1 (3%)	1 (2%)	1
Myocardial infarction, CABG, or coronary angioplasty	2 (5%)	2 (5%)	1
Peripheral vascular disease	1 (3%)	1 (2%)	1
History of treated depression	7 (18%)	6 (14%)	0.77

Values are mean(SD) or number(%)
Hypercholesterolaemia is defined as on drug treatment. There were no differences between the treatment groups

Table 2. MRI measures at baseline and 2 years in the two treatment groups- intention to treat analysis

	Raw, Mean (SD, IQR)				***Change Mean (SD, IQR) (%)***	
MRI parameter	**Standard**		**Intensive**		**Standard**	**Intensive**
	Baseline	24 months	Baseline	24 months	Baseline – 24 months	Baseline – 24 months
DTI – MD peak height (mm^2/s)	$13.5x10^{-3}$ ($2.6x10^{-3}$)	$12.7x10^{-3}$ ($2.6x10^{-3}$)	$13.2x10^{-3}$ ($2.3x10^{-3}$)	$12.3x10^{-3}$ ($2.1x10^{-3}$)	$-0.8x10^{-3}$ ($1.4x10^{-3}$) (-5.9)	$-0.9x10^{-3}$ ($1.0x10^{-3}$) (-6.8)
NBV (whole brain, ml)	1368.0 (131.0)	1342.5 (135.1)	1340.9 (92.2)	1304.3 (97.0)	-25.5 (27.8) (-1.9)	-36.6 (31.9) (-2.7)
WMH lesion volume (%brain)	3.2 (2.1)	3.7 (2.4)	3.5 (2.4)	3.9 (2.6)	0.5 (0.8) (15.6)	0.4 (0.8) (11.4)
Lacunes (count)	4.3 (4.1, 5.0*)	5.8 (5.2, 7.0*)	4.4 (5.3, 4.0*)	6.5 (6.6, 8.0*)	1.5 (2.4, 3*) (34.9)	2.1 (3.6, 3*) (47.7)
Cerebral microbleeds (count)	4.0 (8.0, 5.0*)	4.6 (9.1, 5.8*)	4.0 (6.9, 6.8*)	4.4 (7.7, 4.75*)	0.6 (1.6, 1*) (15.0)	0.4 (2.2, 1*) (10.0)
	Adjusted, Mean (SE) (95% CI) at 24 months ‖				***p-value***	
MRI parameter	Standard		Intensive			
DTI – MD peak height (mm^2/s)	$12.5x10^{-3}$ ($0.2x10^{-3}$) ($12.1x10^{-3}$- $12.8x10^{-3}$)		$12.5x10^{-3}$ ($0.2x10^{-3}$) ($12.2x10^{-3}$- $12.8x10^{-3}$)		0.92†	
NBV (whole brain, ml)	1327.2 (45.5) (1318.2 – 1336.3)		1318.3 (43.5) (1309.6 – 1326.9)		0.16†	
WMH lesion volume (%brain) ‡	0.59 (0.02) (0.56 – 0.62)		0.56 (0.02) (0.53 – 0.59)		0.17†	
Lacunes (count)	6.1 (0.4) (5.3 – 6.9)		6.2 (0.4) (5.5- 7.0)		> 0.05§	
Cerebral microbleeds (count)	4.7 (0.3) (4.2 – 5.2)		4.3 (0.3) (3.8 – 4.8)		> 0.05§	

MD=Mean diffusivity; NBV= Normalised whole brain volume; WMH= White matter hyperintensity, (%)= Percentage change

*Interquartile range additionally computed for count data.

† Analysis of covariance testing the difference between treatment groups at 24 months while adjusting for the baseline measure and study site

‡ MRI variable log10 transformed

§ Permutational analysis of covariance testing the difference between treatment groups at 24 months while adjusting by the baseline measure and study site

‖ Means, standard errors and 95% confidence intervals adjusted by the baseline measure and study site

Table 3. Imaging marker at baseline and 2 years in the two treatment groups- per-protocol analysis

	Raw, Mean (SD)				***Change Mean (SD) (%)***	
MRI parameter	**Standard**		**Intensive**		**Standard**	**Intensive**
	Baseline	24 months	Baseline	24 months	Baseline – 24 months	Baseline – 24 months
DTI-MD peak height (mm^2/s)	$13.1x10^{-3}$ ($2.2x10^{-3}$)	$12.5x10^{-3}$ ($2.6x10^{-3}$)	$13.1x10^{-3}$ ($2.5x10^{-3}$)	$12.2x10^{-3}$ ($2.0x10^{-3}$)	$-0.06x10^{-3}$ ($0.1x10^{-3}$) (-0.5)	$-0.09x10^{-3}$ ($0.1x10^{-3}$) (-0.7)
NBV (whole brain, ml)	1358.6 (124.9)	1330.9 (127.7)	1347.9 (94.9)	1313.4 (102.0)	-27.7 (28.4) (-2.0)	-34.5 (32.5) (-2.6)
WMH lesion volume (%brain)	3.3 (2.1)	3.8 (2.5)	3.7 (2.4)	4.1 (2.6)	0.6 (0.7) (18.2)	0.4 (0.9) (10.8)
Lacunes (count)	4.6 (4.1)	6.1 (5.0)	4.9 (6.4)	6.3 (7.1)	1.5 (2.3, 3*) (32.6)	1.4 (2.2, 2*) (28.6)
Cerebral microbleeds (count)	4.3 (8.6)	4.9 (9.6)	4.6 (7.5)	4.9 (8.0)	0.6 (1.7, 1*) (14.0)	0.3 (2.2, 1*) (6.5)

	Adjusted, Mean (SE) (95% CI) at 24 months ‖		***p-value***
MRI parameter	**Standard**	**Intensive**	
DTI-MD peak height (mm^2/s)	$12.4x10^{-3}$ ($0.2x10^{-3}$) ($12.0x10^{-3}$ - $12.8x10^{-3}$)	$12.3x10^{-3}$ ($0.2x10^{-3}$) ($11.9x10^{-3}$ - $12.7x10^{-3}$)	0.70†
NBV (whole brain, ml)	1324.8 (50.4) (1314.7- 1334.9)	1320.1 (56.3) (1309.7-1332.2)	0.61†
WMH lesion volume (%brain) ‡	0.61 (0.02) (0.57- 0.64)	0.56 (0.02) (0.53- 0.60)	0.07†
Lacunes (count)	6.4 (0.4) (5.6- 7.1)	6.0 (0.4) (5.2- 6.8)	>0.05§
Cerebral microbleeds (count)	5.0 (0.3) (4.4- 5.6)	4.7 (0.4) (4.0- 5.4)	>0.05§

MD=Mean diffusivity; NBV= Normalised whole brain volume; WMH= White matter hyperintensity, (%)= Percentage change

*Interquartile range additionally computed for count data.
† Analysis of covariance testing the difference between treatment groups at 24 months while adjusting for the baseline measure and study site
‡ MRI variable log10 transformed
§ Permutational analysis of covariance testing the difference between treatment groups at 24 months while adjusting by the baseline measure and study site
‖ Means, standard errors and 95% confidence intervals adjusted by the baseline measure and study site

Title and Figure legends:

FIGURE 1: An overview of the patient flow. The inner boxes show the number of patients enrolled in the clinical trial at each TP after being randomised. The primary analysis included all patients (intention-to-treat). Of the 111 patients randomised, 108 patients had a baseline scan and were cognitively tested. Between baseline and 24 months 18 patients were lost due to withdrawal of consent (N= 5), death (N= 3), no follow-up (N= 2), developing other serious illness (N= 1), no scans being performed (N= 7).

FiGURE 2: Change in systolic and diastolic BP (blood pressure) over the 24 months. The mean and 95% confidence interval are displayed at each time point.

Panel A: change in systolic BP over time, Panel B: Change in diastolic BP over time

FIGURE 3: Relationship between change on systolic BP and change in WMH lesion volume. Dotted symbols refer to a single centre and lines represent relationship for individual centres; one centre only recruited one patient and there is not represented by a line.