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Association of Blood Pressure Lowering Intensity With White Matter Network Integrity in Patients With Cerebral Small Vessel Disease

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Abstract

Background and Objectives:

Diffusion tensor imaging (DTI) networks integrate damage from a variety of pathological processes in cerebral small vessel disease (SVD) and may be a sensitive marker to detect treatment effects. We determined whether brain network analysis could detect treatment effects in the PRESERVE trial dataset, in which intensive versus standard blood pressure (BP) lowering was compared. The primary endpoint of DTI had not shown treatment differences.

Methods:

Subjects with lacunar stroke were randomised to standard (systolic 130-140 mmHg), or intensive (systolic </= 125 mmHg) BP lowering and followed for 2-years with MRI at baseline and at 2 years. Graph-theory based metrics were derived from DTI data to produce a measure of network integrity weighted global efficiency, and compared to individual MRI markers of DTI, brain volume and white matter hyperintensities.

Results:

Data were available in 82 subjects; standard n=40 (mean age 66.3±1.5), intensive n=42 (69.6±1.0). Mean (SD) systolic blood pressure was reduced by 13(14) and 23(23) mmHg in the standard and intensive groups respectively (P<0.001 between groups). Significant differences in diffusion network metrics were found, with improved network integrity (weighted global efficiency, P=0.002) seen with intensive BP lowering. In contrast there were

no significant differences in individual MRI markers including DTI histogram metrics, brain volume or white matter hyperintensities.

Discussion:

Brain network analysis may be a sensitive surrogate marker in trials in small vessel disease. This work suggests that measures of brain network efficiency may be more sensitive to the effects of blood pressure control treatment than conventional DTI metrics.

Trial Registration Information:

The trial is registered with the ISRCTN Registry (ISRCTN37694103; https://doi.org/10.1186/ISRCTN37694103) and the NIHR Clinical Research Network (CRN 10962; https://public-odp.nihr.ac.uk/QvAJAXZfc/opendoc.htm?document=crncc_users%5Cfind%20a%20clinical%20research%20study.qvw&lang=en-US&host=QVS%40crn-prod-odp-pu&anonymous=true)

Classification of Evidence:

This study provides Class II evidence that intensive BP lowering in patients with small vessel disease results in improved brain network function when assessed by DTI based brain network metrics.

Introduction

Cerebral Small Vessel Disease (SVD) accounts for 20% of all ischaemic strokes and is the most common pathology underlying vascular cognitive impairment and dementia.[1] Hypertension is a major risk factor for SVD, and lower blood pressure in midlife is associated with a reduced risk of small vessel disease.[2] More intensive blood pressure lowering to a target of 120-125mmHg systolic has been shown to reduce radiological SVD in patients without stroke,[3] but it is uncertain whether similar intensive targets should be applied to patients with symptomatic SVD. Patients with severe SVD have reduced cerebral blood flow

and impaired cerebral autoregulation[4,5] and excessive blood pressure reduction could lead to hypoperfusion, and as a result accelerate white matter (WM) damage and worsen clinical outcomes.[6]

Cognitive testing has been shown to be insensitive to change in patients with SVD over the follow-up durations of 2-3 years used in clinical trials.[7] This had led to the use of MRI as a surrogate marker to evaluate treatment efficacy in phase 2 trials in SVD, with a number of MRI imaging biomarkers including white matter hyperintensities (WMH), brain atrophy and Diffusion tensor imaging (DTI) showing sensitivity to detect change over 2-3 years period.[8] DTI is particularly sensitive to diffuse white matter damage in SVD, and predicts future dementia risk.[9] The PRESERVE multicentre randomised clinical trial determined the effect of intensive systolic blood pressure (BP) lowering to 125mmHg systolic, as compared to standard BP lowering to 140 mmHg, on white matter ultrastructure in SVD, using DTI (change in white matter mean diffusivity histogram peak height over 2 years) as the primary endpoint, but did not detect differences between the treatment groups, possibly due to it not reaching the planned sample size.[10]

Recently structural brain networks, which can be derived using tractography performed on DTI data, have been shown to be disrupted in SVD, with the degree of disruption correlating with cognitive impairment[11,12] and predicting future dementia risk.[13] Network disruption mediates the effect of a number of SVD pathologies on cognition, including WMH, lacunes and DTI white matter microstructural alterations.[11] Thus network analysis might provide a single measure which integrates the different pathologies in SVD, adding additional information to the degree of white matter ultrastructural damage assessed on DTI, and could represent a useful surrogate marker in clinical trials in SVD.

The aim of this, secondary, study was to determine whether network analysis was more sensitive method to detect treatment effects, in this case the effect of intensive blood pressure lowering, than the primary study endpoint. As such the primary question this study was designed to answer was: Whether network metrics based on DTI based brain networks could detect treatment effects in the PRESERVE trial dataset, in which intensive versus standard BP lowering was compared in subjects with established SVD.

Methods

Standard Protocol Approvals, Registrations and Patient Consent

PRESERVE was a two-year, multicentre, randomised clinical trial comparing "intensive" vs. "standard" blood pressure treatment options in patients with severe small vessel disease. The full protocol and statistical analysis plan were previously published[14]. As part of a multimodal 3T MRI acquisition, diffusion data were acquired at baseline and at the 2 years follow-up visit. A detailed description of the PRESERVE clinical trial including the MRI protocol has already been reported.[10,15] The trial is registered: Clinical Trial registration: ISRCTN37694103.[16] and CRN Number: 10962, accessible at.[17] Informed participant consent was obtained in line with the Declaration of Helsinki and the study was approved by the local ethics committee (North London REC3 (REC number 11/LO/0458)).

Participants and data acquired

Participants were included who had a clinical lacunar stroke with an anatomically corresponding lacunar infarct on MRI, in addition to confluent WMH graded as ≥ 2 on the Fazekas scale.[18] 111 patients with SVD were randomised to "standard" (systolic = 130-140 mmHg) or "intensive" (systolic ≤ 125 mmHg) blood pressure targets with 56 patients in the

standard arm and 55 patients in the intensive arm. Participants were randomized (stratified by centre) with random allocation concealed until the intervention was assigned by the local clinician in a 1:1 ratio via a centralized, online system (at Mental Health & Neuroscience Clinical Trials Unit, Kings College London). Due to the nature of the treatment groups local clinicians were then aware of group allocation. At each clinical check-up (1, 3, 6, 12, 18 and 24 months from the baseline visit), an increase in antihypertensive medication was prescribed if the BP was above study target (i.e. >125 mmHg in the standard group and above >140 mmHg in the intensive group), unless hypotensive symptoms prevented further BP lowering.

Across six centres, eight 3-Tesla MR scanners were used (3 Philips Acheiva TX, and one each of Philips Acheiva, Philips Ingenia, Siemens Verio, Siemens Prisma, 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. 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. Full details of MR sequences, and analysis methods of the MR data have been published[15], brief details of the relevant sequences are shown in **Table 1**. All MR analysis was performed centrally, and blinded to subject identify and treatment arm.

MRI data analysis and construction of brain networks

WMH were defined as areas of increased signal on FLAIR images, segmented by a single trained rater using a semi-automated contouring technique in Jim version 7.0_5 (Xinapse Systems Limited[19]). A WMH lesion load score was calculated as the percentage of WMH lesion volume against whole brain volume.

Lacunes were defined as cerebrospinal fluid filled cavities at least 3mm in diameter using a combination of T1W, T2*W and FLAIR scans. Additional features such as T2-hyperintense rims, shape and location were also considered to differentiate lacunes from similar imaging features.

T1W scans were intensity non-uniformity corrected and segmented into grey matter (GM), WM and CSF tissue probability maps (TPM) using SPM12b.[20] Brain volume was calculated from the GM and WM TPMs. These volumes were normalised by applying SIENAX[21] to the T1W scans giving a scaling factor. The brain volumes were multiplied by this scaling factor to provide normalised brain volumes.

Diffusion data were pre-processed to correct for geometric distortions and eddy currents and a diffusion tensor model fit at each voxel using the Oxford Centre for Functional MRI of the Brain Software library (FSL)[22] to produce Fractional Anisotropy (FA) and Mean Diffusivity (MD) maps. T1W images were brain-extracted using the FSL tool BET[23] and coregistered into MNI space using Advanced-Normalization tools (ANTS).[24] Non-diffusion weighted b=0 s mm^{-2} (B0) images were registered onto the brain-extracted T1W images using the FSL tool flirt. This transform was used to generate WM masks for the diffusion data. Histogram analysis was performed on FA and MD maps in white matter. 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 were extracted from these for

both FA and MD. In addition 90 seed regions were defined from the Desikan-Killiany parcellation of the cerebral cortex and subcortical nuclei[25] using the automatic-anatomical labelling (AAL) template without the cerebellum and brainstem in Montreal Neurological Institute (MNI) space. Inverse warps/matrices from the registration of the B0 to T1W space and then from T1W space to MNI space were used to transform the AAL seed masks into native diffusion space for each subject and time-point.

Deterministic whole brain tractography was run on the principal eigenvectors of the diffusion tensor using MRtrix.[26] In brief, this algorithm fits a diffusion tensor to the local (trilinear-interpolated) diffusion data at each streamline step and the streamline trajectory is then determined as the principal eigenvector of that tensor.[27] The following additional settings were used: step size = 0.5mm, maximum angle theta between successive steps: 45 degrees, minimum length of any track: 20 mm, maximum length of any track: 250mm, tensor FA cut-off threshold for terminating tracks: 0.15, integration method used to fit streamlines to the tensor field: 4th-order Runge-Kutta integration, grid size: 4, streamlines terminating in their region of origin were removed. From the whole brain deterministic tractogram, connections were generated between each pair of seed masks. Two brain regions A and B were considered to be connected with each other if one or more streamlines terminating in region A also terminated in region B. Streamlines were seeded within voxel on an evenly-spaced super-resolution grid ($0.5mm^3$), due to this the strength of connectivity between each pair of seeds was calculated as the streamline count between regions adjusted for the length of the streamline in mm. This was done by scaling each contribution to the connectome edge by the inverse of the streamline length due to the presence of multiple seeding points in each streamline.

On the basis of this strength of connectivity the connectome was reconstructed as an undirected graph, and the adjacency matrix was created as a symmetric matrix where each element represents the strength of connectivity between each pair of brain regions. From the adjacency matrix graph-theoretical network metrics were calculated using the brain graph package[28] and igraph package available in R[29]. Given that there are a large number of network metrics, which are often highly correlated we chose to focus on weighted average global efficiency and weighted averaged local efficiency. In brief, global efficiency indicates how well connected all nodes of the brain network are relative to an idealized brain network where each and every node is connected. Local efficiency tells us how resistant the brain network is against failure in information processing on a small scale.

The connectome-based network analysis workflow, described above, is summarized in (**Fig 1**).

Data analysis

The primary analysis was intention-to-treat group. In addition, a secondary per-protocol analysis was performed that included only patients reaching the BP target as previously defined.[10] Statistical analysis was carried out using R (version 3.2.3) and the statistical models package (stats models) as implemented in python.[30] During the exploratory data analysis carried out on the diffusion network metrics, we noticed a large amount of outliers both longitudinally and cross-sectionally exceeding the 3-sigma rule (see also the dispersion plots shown in (**Fig 2**). We therefore decided to use permutational tests to assess the effects against bias and because permutational analysis of covariance models are robust against both outliers and violation of the assumption of normality.

Permutational repeated measures ANCOVA with study site as covariate and treatment group (standard vs. intensive) as explanatory factor was used to test for significant group effects and group by time point interactions. Within this framework main effects of time-point correspond to longitudinal effects on diffusion metrics irrespective of group, main effects of treatment group correspond to group differences irrespective of time point, and time-point by treatment group interactions correspond to the longitudinal effects of the therapeutic intervention on diffusion network metrics. This model has greater statistical power to detect any effect when compared with analysis of covariance with baseline as covariate or analysis of variance carried out on the differences between baseline and follow-up (so called delta values).

To assess whether any associations were merely due to network metrics acting as a non-specific measure of SVD severity, we also co-varied for WMH volume as a measure of SVD severity.

Data Availability

The data supporting the findings of the study may be obtained from the corresponding author upon reasonable request from a qualified researcher.

Results

Recruitment took place from 29/02/2012-30/10/2015; follow-up was completed on 1/11/2017. Participants were recruited from six secondary care stroke services sites across the UK. One subject did not meet MRI criteria on baseline central MRI review and was withdrawn. Three died during follow up, one developed other serious illness and could not continue, six withdrew consent, and two were lost to follow-up. Baseline MRI was not performed in two, and follow-up MRI not performed in six participants. Therefore, 90 subjects remained with baseline and follow-up MRI scans. After excluding scans of inadequate quality for DTI analysis, 40 patients in the standard arm and 42 patients in the intensive arm were included in the graph theoretical data analysis, assessment of image quality was made blinded to subject number and treatment group. A subject flow diagram representing the above can be seen in[10] figure 1.

There was no difference in demographics between those included (n=82) and excluded (n=8) in the study in demographics, cognition or MRI metrics (age: 68±12 vs. 66±6, p=0.33, NART: 116±9 vs. 116±12, p=0.96, Global Cognition: -0.78±0.99 vs. -0.49±0.61, p=0.42, systolic BP, 147±21 vs. 155±16, p=0.22, CMB: 4±8 vs. 3±5, p=00.59, lacunes 4±3 vs. 4±8, p0.93, lesion load: 3.4%±2.3 vs. 3.5%±2.3, p=0.87, normalised brain volume 1333ml±185 vs. 1406ml±137, p=0.17). In the 82 patients whose data included in this analysis, there was no difference in baseline BP (**Table 2**). Target BP difference was achieved by 3 months (intensive 127mmHg, standard 140mmHg), and maintained for two years (as shown in **Fig 3**). Mean (SD) systolic blood pressure (BP) was reduced by -13(14) and -23(23) mmHg in the standard/intensive groups, respectively (difference between groups p<0.001). The number reaching BP targets at 3 months and included in the per protocol analysis were: standard arm 35/40, intensive arm 28/42.

Permutational repeated-measures ANCOVA with study site as a covariate showed intensive blood pressure lowering was associated with no progression of network disruption over the two years follow-up and even a possible improvement, while standard blood pressure lowering was associated with a decline in network metrics (see **Table 3**): weighted global efficiency (p = 0.002, **Fig 2 A**), weighted local efficiency (p = 0.002, **Fig 2 B**), where a reduction in the efficiency was seen over two years for the standard treatment regime with a corresponding increase in the intensive group. The figure shows the behaviour of the individual subjects (colour coded by site) and the mean change as the thick line surrounded by the standard error (shaded area).

To assess whether the associations seen in table 3 were merely due to network metrics acting as a non-specific measure of SVD severity, we also co-varied for WMH lesion volume as a measure of SVD severity, entering both the magnitude of lesion load at baseline (intercept) and the longitudinal change (slope) of the lesion load as covariates into the repeated-measures model. The directionality and effects of treatment regimen on the network metrics remained after this analysis; weighted global efficiency (p = 0.007), weighted local efficiency (p = 0.005).

In contrast to the significant difference between treatment groups on network analysis we found no difference when using conventional DTI parameters in a histogram-based analysis. Permutational repeated-measures ANCOVA with study site as a covariate did not show any significant effects of treatment regimen for the following histogram metrics in the normal appearing white matter: FA peak height (permutational p = 0.99), MD peak height (p =

0.99), FA peak location (p = 0.244), MD peak location (p = 0.99), median FA (p = 0.071), median MD (p = 0.99).

Similarly, no significant overall effects of treatment regimen were found for normalized brain volumes, lesion volumes, and microbleeds, including the following: normalized whole brain volume (p = 0.076), normalized grey matter volume (p = 0.941), normalized white matter volume (p = 0.222), WMH lesion load (p = 0.415), lacunes (p = 0.863), and microbleeds (p = 0.278).

On per-protocol analysis only including subjects reaching their blood pressure target, there were similar results. There were significant effects of treatment regimen (i.e. standard vs. intensive intention-to-treat groups) for weighted local efficiency (p = 0.016), but not weighted global efficiency (p = 0.055) (see **Table 4**) with the same directionality of changes seen as in the whole group analysis.

Classification of Evidence

The primary question this study was designed to answer was: Whether network metrics based on DTI based brain networks could detect treatment effects in the PRESERVE trial dataset, in which intensive versus standard BP lowering was compared in subjects with established SVD. This study provides Class II evidence that intensive BP lowering in patients with small vessel disease results in improved brain network function when assessed by DTI based brain network metrics. It used a well designed randomized controlled trial dataset but was a post-hoc analysis and not the primary endpoint. It is found that intensive BP lowering results in improved brain network function when measured with global and local efficiency.

Discussion

In this analysis of the PRESERVE dataset, using diffusion network metrics as the outcome measure, intensive blood pressure reduction of systolic BP to 125mmHg was associated with reduced white matter damage in patients with severe SVD. Our results suggest network metrics may be a more sensitive surrogate marker for multi-centre clinical trials in patients with SVD than conventional DTI analyses. It also suggests that intensive blood pressure lowering is beneficial even in patients with severe SVD, extending data demonstrating its efficacy in primary prevention and in patients with milder SVD.

Network disruption has been shown to mediate the effect of a number of SVD pathologies including WMH, diffuse white matter damage on DTI, lacunes and cerebral microbleeds, on cognitive impairment.[11,12] It may therefore provide a more comprehensive measure of SVD pathology than a simple DTI metric, and this may explain its greater sensitivity to detecting a treatment effect in the PRESERVE dataset. In this analysis it provided greater sensitivity than white matter mean diffusivity peak height, a metric derived from DTI histogram analysis, which was the primary endpoint of PRESERVE trial.[10]

Our results show that both global and local efficiency showed progressive deterioration in this standard BP arm, while they showed no deterioration and even a possible improvement in the intensive BP arm. This is consistent with intensive BP lowering leading to an improvement in network integrity. Why intensive blood pressure lowering would lead to an improvement, rather than stabilization, of network metrics is unclear. One possible explanation is that the reduction in blood pressure reduces inflammation, which has been shown to be present in SVD[31,32], resulting in less cell swelling and tissue infiltration and this could lead to an overall increase in network strength as brain regions would appear to be

more connected, rather than a genuine increase in connectivity. It has previously been hypothesised that antihypertensive therapy may reduce ischaemia-induced neuroinflammation in patients with stroke.[33] Alternatively it is possible that the changes seen are due to remyelination and repair of the axons as inflammatory episodes are reduced or stopped. This would indicate a genuine increase in tissue health leading to greater connectivity.

This paper provides further support for the beneficial effect of intensive blood pressure lowering in patients with SVD. The SPRINT trial, in the setting of primary prevention, showed intensive blood pressure lowering to 125 mmHg systolic was associated with a reduction in both cardiovascular events,[34] and a reduction in the combined endpoint of dementia and mild cognitive impairment.[35] An MRI substudy of SPRINT demonstrated intensive blood pressure lowering was also associated with reduced progression of radiological small vessel disease, as determined by WMH.[3] The SPS3 trial, in patients with lacunar stroke, showed no significant difference in recurrent stroke rate with intensive blood pressure lowering, but the researchers suggested a possible trend in stroke reduction.[36] Therefore increasing evidence suggests more intensive blood pressure lowering may reduce cardiovascular events and possibly also dementia. However there has been concern that in patients with severe SVD, in whom reduced cerebral blood flow and impaired cerebral autoregulation have been found, this could result in a drop in cerebral blood flow, which in itself could result in increased white matter damage and impaired cognition. This analysis provides support for intensive blood pressure lowering, even in patients with severe SVD.

Cognitive endpoints have been shown to be insensitive to change in clinical trials in SVD. This has led to increasing interest in the use of MRI surrogate markers to assess efficacy in phase 2 trials, prior to large phase 3 studies with dementia as the clinical endpoint. A number

of MRI markers have been suggested as useful surrogates including WMH, white matter ultrastructural change on DTI, and brain volume.[8] Our study suggests that a measure which integrates a number of the underlying SVD radiological pathologies, which network metrics do, may be a sensitive marker. In particular network analysis was more powerful than conventional DTI markers.

Our study has a number of strengths. It is one of the few studies in SVD to use a randomised controlled trial methodology to evaluate a surrogate marker. We found consistent results across both the intention to treat and per protocol analysis. All MR analyses were preformed blinded to treatment allocation. However, it also has limitations. This was a secondary analysis of a clinical trial dataset for which the primary endpoint was a simple DTI histogram metric. The original sample size of the PRESERVE trial was 180 and only 111 patients were recruited to the MRI arm, the smaller sample size and exclusions do reduce the power of the study. A post-hoc power calculation indicates that the power of the study ranges between 58% and 73% for the analyses and parameters. The per-protocol analysis produced weaker results than the intention-to-treat analysis; this is most likely to be caused by the reduced number of subjects in the per-protocol analysis. A number of subjects which go the 'wrong way' in both groups; may be for a number of reasons. This may just be natural variation in the dataset, which would suggest that although network measures can detect treatment effects across groups they are less useful in detecting change in individual subjects. effect it may not be applicable to all subjects.

In conclusion, intensive systolic blood pressure lowering to a target of 125 mmHg was associated with less progression of white matter damage as assessed by network metrics. This supports the use of intensive blood pressure targets even in patients with severe SVD. Diffusion network metrics may be a more sensitive surrogate marker for multi-centre clinical

trials in patients with small vessel disease, than conventional DTI analyses and other MRI measures.

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http://links.lww.com/WNL/C249

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Figure Legends and Titles

Figure 1. Tractography based image processing pipeline

Connectome-based network analysis workflow in the MRI branch of the PRESERVE clinical trial investigating longitudinal effects on networks metrics at baseline and the follow-up visit at 2 years. A shows the AAL atlas overlaid on the MRI, B the streamline construction, C the whole brain tractography and D the reconstructed connectome used to calculate the measures such as global efficiency.

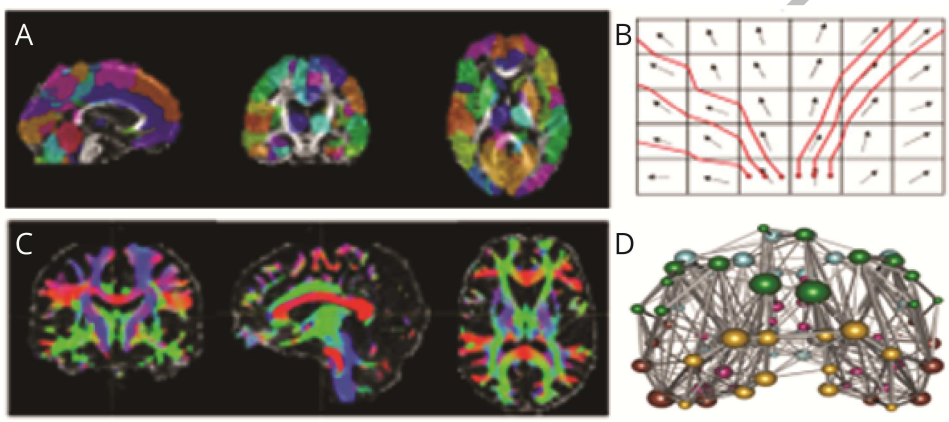


Figure 2. Change in global and local efficiency between timepoints

Longitudinal plots showing the change in weighted global efficiency (A) and weighted local efficiency (B) in response to antihypertensive therapy in the intention-to-treat group showing the differences in behaviours between the two treatment groups. Pairs of dots relate to individual subjects, they are coloured by study site. - The triangles and thick line show the mean behaviour for the group and the shaded area around the mean line is the standard error.

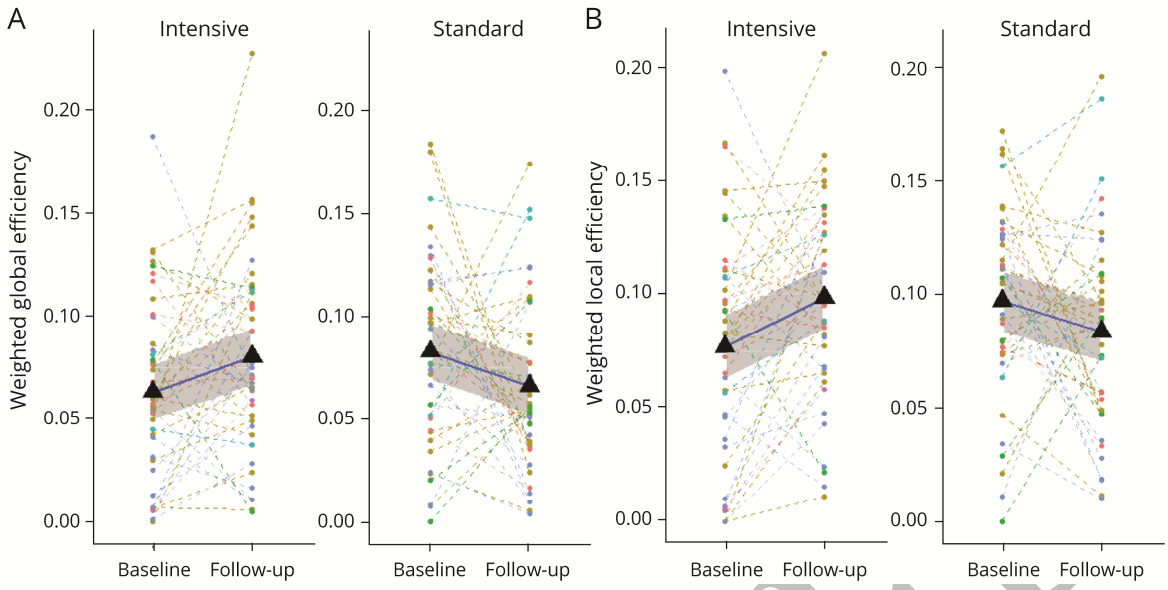
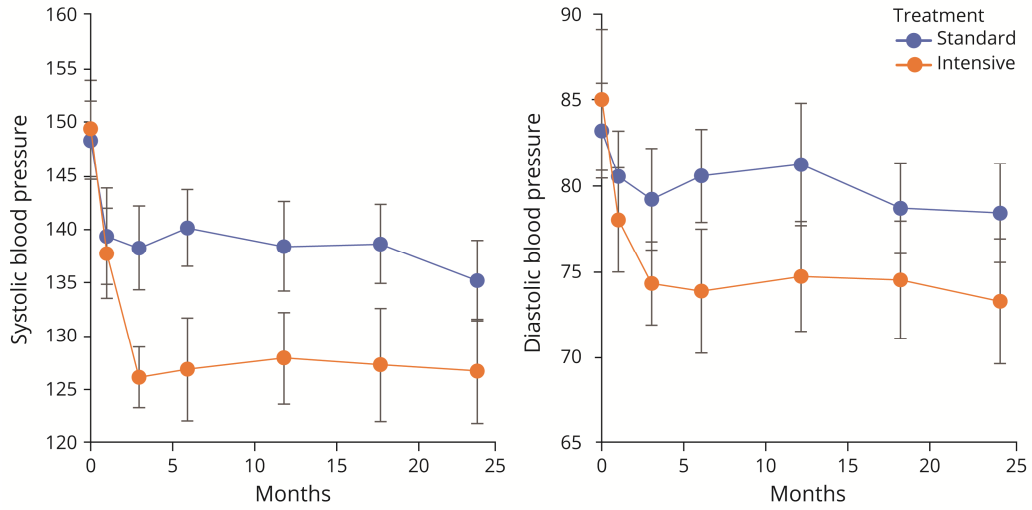


Figure 3. Blood pressure change across the study period

Reductions in blood pressure over the course of the clinical trial for the standard and the intensive treatment groups. The blue lines show the standard treatment group and the orange lines show the intensive treatment group. Error bars show the 95% confidence interval. Panel a shows the systolic blood pressure and panel b the diastolic.



Site	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6
3T Scanner (s)	**Philips Achieva TX**	**Philips Achieva, Philips Achieva TX**	**Siemens Verio, Siemens Magnetom Prisma[fit]**	**Philips Achieva TX**	**Philips Ingenia**	**Siemens Prisma**
Axial DTI (32 diffusion weighted gradient directions at b-value = 1000 s mm^{-2}, Isotropic voxel resolution $2mm^3$)	DwiSE TR = 6850ms TE = 75ms 60 slices, 8 b0	DwiSE TR = 6850ms TE = 75ms 60 slices, 8 b0	Twice-refocussed TR = 11500ms TE = 93ms 75 slices, 2 b0	DwiSE TR = 6850ms TE = 75ms 60 slices, 8 b0	DwiSE TR = 9100ms TE = 82ms 60 slices, 8 b0	Twice-refocussed TR = 9500ms TE = 93ms 81 slices, 2 b0
Sagittal 3D T1-weighted (Isotropic voxel resolution $1mm^3$)	Turbo Field Echo (TFE) TR = 8.27ms TE = 4.61ms	TFE TR = 9.81ms TE = 4.60ms	MP RAGE TR = 2200ms TE = 2.97ms Inversion Time = 900ms	TFE TR = 11ms TE = 4.61ms	TFE TR = 8.53ms TE = 4.61ms	MP RAGE TR = 2200ms TE = 2.94ms Inversion Time = 900ms
Axial T2*-weighted – Sequence type, TR/TE/Voxel Size	Fast Field Echo (FFE) 1800ms/20ms/ $0.5^2 \times 3mm^3$	FFE 1800ms/20ms/ $0.5^2 \times 3mm^3$	Spoiled Gradient Echo 1570ms/20ms /0.94^2x$3mm^3$	FFE 1800ms/20ms/ $0.5^2 \times 3mm^3$	FFE 1800ms/20ms/ $0.54^2 \times 3mm^3$	Spoiled Gradient Echo 1570ms/20.7 ms/0.94^2x$3mm^3$
Axial FLAIR (Inversion time = 2800ms) – TR/TE/Voxel Size	FLAIR 11000ms/120ms/$0.48^2 \times 3mm^3$	FLAIR 11000ms/120 ms/$0.48^2 \times 3mm^3$	Turbo Inversion Recovery 8000ms/124 ms/0.45^2x$3mm^3$	FLAIR 11000ms/120 ms/$0.48^2 \times 3mm^3$	FLAIR 11000ms/120 ms/$0.48^2 \times 3mm^3$	Turbo Inversion Recovery 8000ms/121ms/0.45^2x$3mm^3$

Table 1: MRI sequence details for the scanners used in the study.

	Standard group (N=40)	Intensive group (N=42)
BP target	systolic = 130-140 mmHg	systolic ≤ 125 mmHg
Mean systolic BP (± SD) at baseline	148 ± 12 mmHg	149 ± 15 mmHg
Mean diastolic BP (± SD) at baseline	83 ± 9 mmHg	85 ± 14 mmHg
Mean reduction in systolic BP (± SD)	-13 ± 14 mmHg	-23 ± 23 mmHg
Mean reduction in diastolic BP (± SD)	-5 ± 9 mmHg	-12 ± 16 mmHg
Mean (± SD) age	68.1 ± 8.5	69.6 ± 9.3
Sex	17 females	17 females

Table 2. Target, baseline and mean reduction blood pressure as well as age and sex in the standard and intensive treatment group.

Network Metric	Timepoint	Standard treatment group (N=40)				Intensive treatment group (N=42)				Permutational p-value
		Mean	Std. Deviation	95% Confidence interval		Mean	Std. Deviation	95% Confidence interval		
				Lower	Upper			Lower	Upper	
Weighted global efficiency	Baseline	0.083	0.046	0.068	0.098	0.063	0.044	0.049	0.077	
Weighted local efficiency		0.097	0.042	0.083	0.110	0.077	0.051	0.061	0.093	
Weighted global efficiency	Follow up	0.066	0.043	0.053	0.080	0.081	0.048	0.066	0.095	
Weighted local efficiency		0.083	0.045	0.069	0.098	0.098	0.043	0.85	0.112	
Weighted global efficiency	Difference between baseline and follow up	-0.017	0.063	-0.037	0.004	0.017	0.057	0.000	0.035	0.002 **
Weighted local efficiency		-0.013	0.060	-0.032	0.006	0.022	0.053	0.005	0.038	0.002 **

Table 3. Network metrics at baseline, follow-up, and the difference in network metrics between baseline and follow up in the standard and intensive treatment group from the intention-to-treat analysis.
P-values are permutational p-values from the non-parametric repeated measures ANCOVA with study site as covariate and treatment group as between-subjects factor.

Network Metric	Timepoint	Standard treatment group (N=34)				Intensive treatment group (N=26)				Permutational p-value
		Mean	Std. Deviation	95% Confidence interval		Mean	Std. Deviation	95% Confidence interval		
				Lower	Upper			Lower	Upper	
Weighted global efficiency	Baseline	0.085	0.049	0.068	0.102	0.066	0.048	0.047	0.086	
Weighted local efficiency		0.097	0.044	0.082	0.113	0.079	0.053	0.057	0.100	
Weighted global efficiency	Follow up	0.063	0.044	0.048	0.078	0.076	0.045	0.058	0.094	
Weighted local efficiency		0.081	0.046	0.065	0.097	0.092	0.042	0.075	0.109	
Weighted global efficiency	Difference between baseline and follow up	-0.022	0.065	-0.044	0.001	0.010	0.055	-0.013	0.032	0.0547
Weighted local efficiency		-0.017	0.062	-0.038	0.005	0.013	0.053	-0.009	0.034	0.0156 *

Table 4. Network metrics at baseline, follow-up, and the difference in network metrics between baseline and follow up in the standard and intensive treatment group from the per-protocol analysis that only included subjects reaching their blood pressure target.
P-values are permutational p-values from the non-parametric repeated measures ANCOVA with study site as covariate and treatment group as between-subjects factor.

Association of Blood Pressure Lowering Intensity With White Matter Network Integrity in Patients With Cerebral Small Vessel Disease

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