Effect of blood pressure-lowering agents on microvascular function in people with small vessel diseases (TREAT-SVDs)

Effect of blood pressure-lowering agents on microvascular function in people with small vessel diseases (TREAT-SVDs): a multicentre, open-label, randomised, crossover trial

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Summary

Background Hypertension is the leading risk factor for cerebral small vessel disease. We aimed to determine whether antihypertensive drug classes differentially affect microvascular function in people with small vessel disease.

Methods We did a multicentre, open-label, randomised crossover trial with blinded endpoint assessment at five specialist centres in Europe. We included participants aged 18 years or older with symptomatic sporadic small vessel disease or cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and an indication for antihypertensive treatment. Participants were randomly assigned (1:1:1) to one of three sequences of antihypertensive treatment using a computer-generated multiblock randomisation, stratified by study site and patient group. A 2-week washout period was followed by three 4-week periods of oral monotherapy with amlodipine, losartan, or atenolol at approved doses. The primary endpoint was change in cerebrovascular reactivity (CVR) determined by blood oxygen level-dependent MRI response to hypercapnic challenge in normal-appearing white matter from the end of washout to the end of each treatment period. Efficacy analyses were done by intention-to-treat principles in all randomly assigned participants who had at least one valid assessment for the primary endpoint, and analyses were done separately for participants with sporadic small vessel disease and CADASIL. This trial is registered at ClinicalTrials.gov, NCT03082014, and EudraCT, 2016-002920-10, and is terminated.

Findings Between Feb 22, 2018, and April 28, 2022, 75 participants with sporadic small vessel disease (mean age 64·9 years [SD 9·9]) and 26 with CADASIL (53·1 years [7·0]) were enrolled and randomly assigned to treatment. 79 participants (62 with sporadic small vessel disease and 17 with CADASIL) entered the primary efficacy analysis. Change in CVR did not differ between study drugs in participants with sporadic small vessel disease (mean change in CVR $1{\cdot}8\times10^{-4}$%/mm Hg [SE 20·1; 95% CI –37·6 to 41·2] for amlodipine; $16{\cdot}7\times10^{-4}$%/mm Hg [20·0; –22·3 to 55·8] for losartan; $-7{\cdot}1\times10^{-4}$%/mm Hg [19·6; –45·5 to 31·1] for atenolol; $p_{overall}=0{\cdot}39$) but did differ in patients with CADASIL ($15{\cdot}7\times10^{-4}$%/mm Hg [SE 27·5; 95% CI –38·3 to 69·7] for amlodipine; $19{\cdot}4\times10^{-4}$%/mm Hg [27·9; –35·3 to 74·2] for losartan; $-23{\cdot}9\times10^{-4}$%/mm Hg [27·5; –77·7 to 30·0] for atenolol; $p_{overall}=0{\cdot}019$). In patients with CADASIL, pairwise comparisons showed that CVR improved with amlodipine compared with atenolol ($-39{\cdot}6\times10^{-4}$%/mm Hg [95% CI –72·5 to –6·6; p=0·019) and with losartan compared with atenolol ($-43{\cdot}3\times10^{-4}$%/mm Hg [–74·3 to –12·3]; p=0·0061). No deaths occurred. Two serious adverse events were recorded, one while taking amlodipine (diarrhoea with dehydration) and one while taking atenolol (fall with fracture), neither of which was related to study drug intake.

Interpretation 4 weeks of treatment with amlodipine, losartan, or atenolol did not differ in their effects on cerebrovascular reactivity in people with sporadic small vessel disease but did result in differential treatment effects in patients with CADASIL. Whether antihypertensive drug classes differentially affect clinical outcomes in people with small vessel diseases requires further research.

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Introduction

Stroke and dementia rank among the most pressing health problems in Europe.[1,2] Small vessel diseases account for up to 30% of strokes and contribute to at least 40% of dementia cases,[3,4] but no treatment has specifically shown efficacy against small vessel disease in general, or for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)—the most frequent hereditary type of small vessel disease.[4,5]

Hypertension is considered to be the most important modifiable risk factor for small vessel diseases.[6] Current treatment guidelines recommend controlling blood pressure in people with covert small vessel disease and in

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed using the terms "cerebral small vessel disease", "CADASIL", "blood pressure", "antihypertensive", "cerebrovascular reactivity", "clinical trial", and "treatment" for articles published in English up to April 21, 2023. We also searched ClinicalTrials.gov to identify trials that are underway but have yet to be published. We identified no randomised controlled trials (RCTs) that directly compared individual antihypertensive agents to other antihypertensive agents or placebo in people with small vessel disease. We identified two trials that compared standard to intensive blood pressure lowering in people with small vessel disease (NCT00059306 and ISRCTN37694103). So far, there is no treatment with proven efficacy specifically against small vessel disease. Hypertension is considered the most important modifiable risk factor for small vessel disease, and current treatment guidelines recommend controlling blood pressure in people with covert small vessel disease and in those who have had a stroke. The results from RCTs in people with hypertension suggest that antihypertensive drug classes differ in their effects on stroke, but whether antihypertensive drug classes differ in their effects on microvascular function in people with small vessel disease is unknown.

Added value of this study

To our knowledge, this is the first RCT to compare different antihypertensive drug classes in people with small vessel disease, both sporadic small vessel disease and with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

Implications of all the available evidence

Current guidelines for the management of hypertension recommend restricting use of β blockers to people with comorbidities or compelling indications requiring their use. In our trial, no effect of any antihypertensive drug was noted on microvascular function in patients with sporadic small vessel disease. However, in patients with CADASIL, cerebrovascular reactivity improved with both amlodipine and losartan compared with atenolol. The findings in patients with CADASIL highlight the need for further studies that compare different antihypertensive drug classes in people with small vessel disease. The trial also illustrates the importance of including patients with rare hereditary subtypes of common diseases in clinical trials.

those who have had a stroke,[7,8] but there are few data from randomised controlled trials (RCTs) on the effects of lowering blood pressure in patients who have had lacunar stroke or with other clinical manifestations of small vessel disease,[9,10] or on the optimal antihypertensive drug class. The results from RCTs in people with hypertension suggest that drug classes differ in their effects on stroke risk,[11–13] possibly due to differences in effects on blood pressure variability that were independent of mean blood pressure level.[14,15] Blood pressure variability is an independent risk factor for stroke,[16,17] dementia,[18] and the presence or progression of white matter hyperintensities, which are markers of small vessel disease on brain MRI.[19] RCTs of antihypertensive drugs have shown that blood pressure variability is reduced by calcium channel blockers and increased by angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and β blockers.[16,20] However, no RCTs have compared different classes of antihypertensive drugs in patients who have had lacunar stroke or other manifestations of small vessel disease.

Results from experimental animal studies suggest a differential effect of antihypertensive drug classes on cerebral microvascular function. Amlodipine was shown to have a beneficial effect on functional hyperaemia in chronically hypertensive mice compared with losartan,[21] but whether antihypertensive drug classes have differential effects on microvascular function in people with small vessel diseases remains unknown. This knowledge is important, because drug classes that improve vascular function directly at the level of cerebral microvessels might affect the disease process in small vessel disease and, therefore, have additional benefits beyond the systemic effects on blood pressure.

Microvascular function can be measured non-invasively by measuring cerebrovascular reactivity (CVR),[22] which is determined by several factors, including endothelial function and the mechanical properties of cerebral microvessels, both of which are affected in small vessel diseases.[4] CVR can be quantified by blood oxygen level-dependent (BOLD) MRI during inhalation of 6% carbon dioxide in air compared with air alone,[23] and it has been shown to be impaired in people with CADASIL and following lacunar stroke.[5,24] In people with small vessel diseases, a lower CVR has been shown to be associated with both higher volume of white matter hyperintensities[25] and larger increase in white matter hyperintensity volume during follow-up,[26] suggesting a role for CVR in disease progression.

The Effects of Amlodipine and other Blood Pressure Lowering Agents on Microvascular Function in Small Vessel Diseases (TREAT-SVDs) trial was designed to test the hypothesis that there are differences in the effects of different antihypertensive drug classes on cerebral microvascular function in small vessel diseases. Specifically, we hypothesised that amlodipine has a beneficial effect compared with losartan or atenolol, and that losartan has a beneficial effect compared with atenolol. To account for the heterogeneity of small vessel diseases, we included people with both sporadic small vessel disease and CADASIL, but keeping the two groups separated for the analysis of drug effects.

Methods

Study design and participants

TREAT-SVDs was an open-label, randomised crossover trial with blinded endpoint assessment done at five specialist centres for diagnosis and treatment of small vessel diseases in Germany, Netherlands, and the UK (appendix). Eligible patients were aged 18 years or older, had symptomatic small vessel disease, had an indication for antihypertensive treatment, and had either sporadic small vessel disease or CADASIL (appendix p 8).

Patients with sporadic small vessel disease were eligible for study inclusion if they had a history of lacunar stroke or vascular cognitive impairment. Patients with sporadic disease with a history of lacunar stroke were required to have a subcortical infarct compatible with the clinical syndrome and visible as an acute diffusion-weighted imaging-positive lesion on MRI or as a new subcortical infarct on CT scan repeated within 3 weeks after stroke onset if not visible on the admission scan. Patients with sporadic disease with a history of vascular cognitive impairment were eligible if they were visiting a memory clinic with cognitive complaints and were diagnosed with cognitive impairment, as documented by a validated assessment tool. They further had to have a deep white matter hyperintensities score of 2 or higher on the Fazekas scale. Patients with CADASIL had to have a definite diagnosis by molecular genetic testing or skin biopsy (appendix p 8).

Study participants had to have an indication for antihypertensive treatment meeting previously published criteria (appendix p 8).[27] Patients with severe hypertension and those without the capacity to consent were excluded. The published protocol and appendix (pp 8–9) include the full list of the inclusion and exclusion criteria.[27]

Ethics approval for the study was obtained from the local ethics committees and relevant regulatory authorities at each trial site. All patients provided written informed consent.

Randomisation and masking

Eligible participants were enrolled by investigators and randomly assigned (1:1:1) to one of three treatment sequences starting with amlodipine, losartan, or atenolol (figure 1). Randomisation was done using computer-generated multiblock randomisation (with a block size of three) stratified by study site and patient group (sporadic small vessel disease *vs* CADASIL). Randomisation was performed centrally at the Münchner Studienzentrum (MSZ, Technical University Munich, Munich, Germany) by an independent biometrician for all study participants before study enrolment. If eligible, patients were randomly assigned by opening a sealed envelope containing their assigned sequence of treatment, which was kept in the investigator site file at each study site. Participants and investigators were informed of treatment assignment.

Procedures

Trial medications were amlodipine, losartan, and atenolol. Antihypertensive treatment was administered as open-label oral medication at approved doses (daily dose of 2·5–10 mg amlodipine, 25–100 mg losartan, and 25–100 mg atenolol). All study drugs used were approved for the treatment of hypertension, were recommended in national and international guidelines, and were not under patent protection. Local pharmacies purchased commercially available products.

The three sequences of medication are shown in figure 1. At the beginning of the trial, patients stopped their regular antihypertensive medication for a 2-week washout period. During this phase, participants were not allowed to take any antihypertensive medication except for thiazide or thiazide-like diuretics such as hydrochlorothiazide or bendroflumethiazide, which served as emergency medication. Study drugs were taken in the morning on rising, each one for 4 weeks of monotherapy according to the randomised sequence of drug intake. Blood pressure was assessed by daily telemetric monitoring.[27] Study physicians were responsible for adjusting the dosage of the study drug, aiming to lower systolic blood pressure (SBP) to less than 140 mm Hg and diastolic blood pressure (DBP) to less than 90 mm Hg. Emergency medication was taken as needed. Switching between blood pressure-lowering agents was done without washout. Antihypertensive agents other than the study

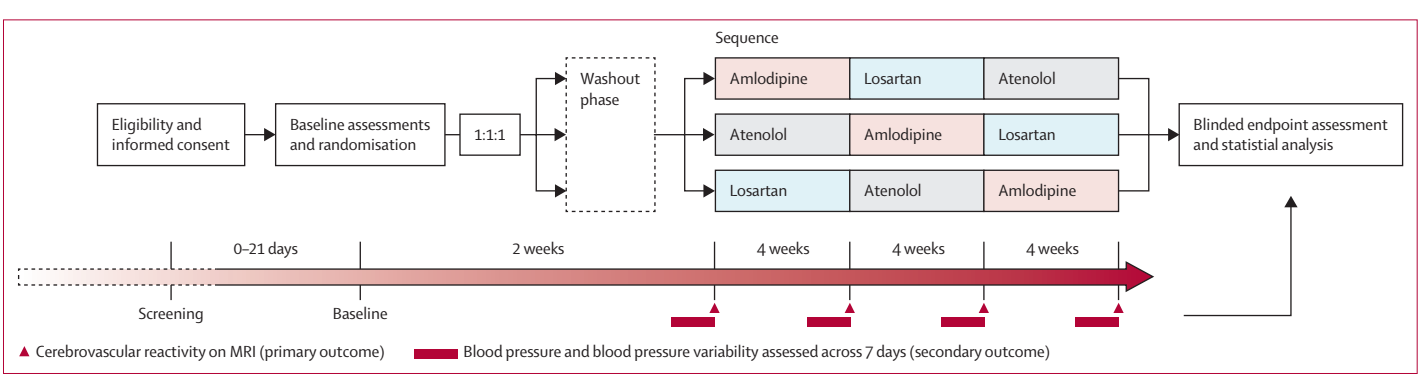


Figure 1: **Study design**

drugs were not allowed. Adherence to assigned therapy was assessed at each visit by pill counts. Patients returned for outpatient visits at 2 weeks after washout and then every 4 weeks for the assessment of outcome measures and adverse events. Data were collected on worksheets, entered into an electronic case report form, and managed centrally by the MSZ using MACRO software (version 4.2.3.3850). Monitoring at all study sites included a site-initiation visit, interim visits with frequency depending on the participant enrolment rate, and a close-out visit by the MSZ in Germany and in the UK. In the Netherlands, on-site monitoring was done by the clinical trial centre of the University of Maastricht (Maastricht). Additionally, there was regular remote monitoring by the MSZ. Adverse events were grouped according to Medical Dictionary for Regulatory Activities (MedDRA; version 25.1) organ classes. Adverse events were assessed by the study investigators and reported in the electronic case report form.

Outcomes

The primary endpoint was the change in CVR in normal-appearing white matter from the end of the washout to end of treatment. The outcome measure for the primary endpoint was CVR, as determined by BOLD brain MRI signal response to a hypercapnic challenge at the end of the 2-week washout phase and at the end of each 4-week period of drug treatment while still on medication.[27] CVR was chosen as the primary outcome measure because it provides a functional readout for brain microvessels and is, therefore, close to the primary pathology in small vessel diseases. Furthermore, lower CVR has been associated with a larger increase in white matter hyperintensity volume during follow-up,[26] suggesting a role for CVR in disease progression.

CVR was measured at 3T with two blocks of breathing 6% CO_2 in medical air for 3 min, alternating with medical air, delivered through a tightly fitting anaesthesia mask.[28] End-tidal CO_2 was continuously recorded using an open-ended circuit. BOLD MRI data were processed centrally at the University of Edinburgh (Edinburgh, UK) using Standard Operating Procedures and were matched with end-tidal CO_2 recordings (appendix pp 11–12). All MRI scans were performed according to a harmonised acquisition protocol.[27] CVR was assessed in prespecified brain regions, including normal-appearing white matter, white matter hyperintensities, and subcortical grey matter, as described.[27,28] We did not measure CVR in cortex due to contamination of the signal by overlying blood vessels, CSF, and white matter. The change in CVR from the end of the washout period to treatment (visits 2–4) was calculated for each study drug to compare drug effects (figure 1). Additional prespecified secondary analyses of the primary outcome included change in CVR in white matter hyperintensities and change in CVR in subcortical grey matter. Analyses were performed by raters from a world-leading institute for CVR measurements on MRI with many years of experience who were masked to clinical status and study medication.

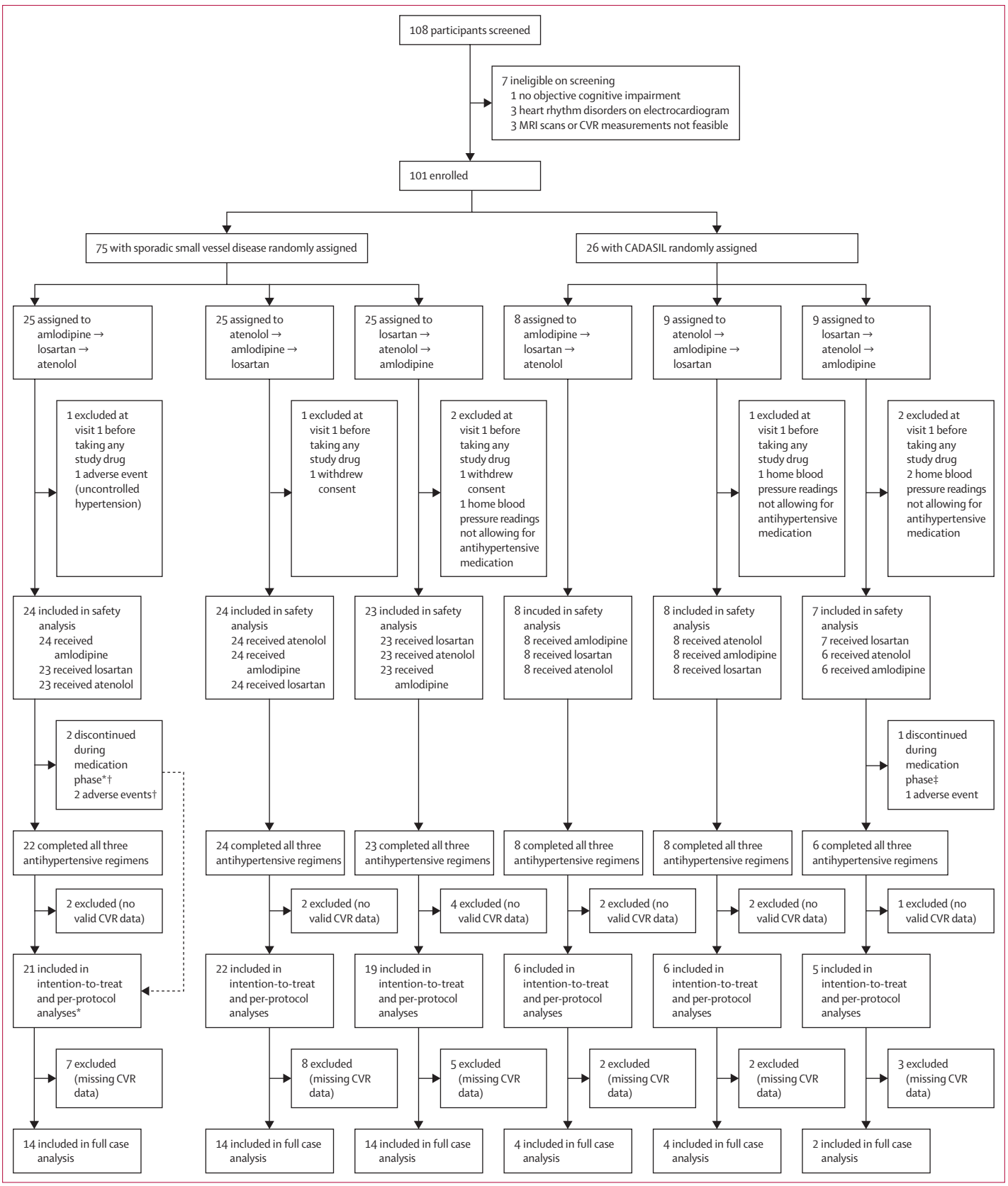
Secondary endpoints were change in mean central SBP and blood pressure variability from the end of washout to treatment. The outcome measure mean SBP was determined by daily telemetric monitoring in the last week of the washout phase and the last week of each treatment phase. The outcome measure for blood pressure variability was operationalised as coefficient of variation (100×SD/mean SBP).[27] The blood pressure monitoring device allowed for pulse wave analysis to derive pulse wave velocity and central blood pressure, so peripheral and central blood pressure data were assessed.

Statistical analysis

We planned to enrol 75 participants with sporadic small vessel disease and 30 with CADASIL. The sample size was calculated for participants with sporadic small vessel disease assuming an absolute mean change in CVR of 0·1% (SD 0·21), with power of 90% on a 5% significance level, using a two-sided one-sample *t* test and making the conservative assumption of a cross-correlation of 0.[27,28] For participants with CADASIL, the sample size was calculated assuming an absolute increase in CVR of 0·1% (SD 0·18), with a power of 80% on a 5% significance level using a two-sided one-sample *t* test (appendix p 12).[27] Changes to the original protocol and statistical analysis plan implemented after the first participant was enrolled are summarised in the appendix (pp 14–15). For the primary and secondary analyses, we used a linear mixed-effects model to assess sequence effects in crossover and corresponding treatment effects and likelihood ratio tests to compare models with interaction (time by treatment) and without interaction (time plus intervention). Following Jones and Kenward,[29] we tested the presence of sequence effects on a 10% significance level to reach a higher power (appendix pp 13–14). There was no evidence for the presence of carry-over effects (test of a model with interaction of time by treatment versus a model of a simple period effect of time plus treatment; appendix pp 13–14).

The primary analysis followed a hierarchical testing principle (closed testing)[30] by assessing an overall effect between amlodipine, losartan, and atenolol. The likelihood-ratio test was used to test the main effects model with time and treatment against a model with time only. In the case of a significant difference ($p<0·05$) in the test above, the analysis evaluated the three pairs of differences. Efficacy analyses were done in the intention-to-treat population, defined as all randomly assigned

Figure 2: **Trial profile**
CVR=cerebrovascular reactivity. *One study participant discontinued drug treatment after visit 3 because of an adverse event (low heart rate) related to atenolol but had valid CVR data and was therefore included in the intention-to-treat analysis for change in CVR. †One participant discontinued because of an adverse event during amlodipine treatment (uncontrolled hypertension). ‡One participant discontinued because of an adverse event during losartan treatment (heart rhythm disorder after stopping previous β blocker therapy).


108 participants screened
7 ineligible on screening
1 no objective cognitive impairment
3 heart rhythm disorders on electrocardiogram
3 MRI scans or CVR measurements not feasible
101 enrolled
75 with sporadic small vessel disease randomly assigned
26 with CADASIL randomly assigned
25 assigned to amlodipine → losartan → atenolol
25 assigned to atenolol → amlodipine → losartan
25 assigned to losartan → atenolol → amlodipine
8 assigned to amlodipine → losartan → atenolol
9 assigned to atenolol → amlodipine → losartan
9 assigned to losartan → atenolol → amlodipine
1 excluded at visit 1 before taking any study drug 1 adverse event (uncontrolled hypertension)
1 excluded at visit 1 before taking any study drug 1 withdrew consent
2 excluded at visit 1 before taking any study drug 1 withdrew consent 1 home blood pressure readings not allowing for antihypertensive medication
1 excluded at visit 1 before taking any study drug 1 home blood pressure readings not allowing for antihypertensive medication
2 excluded at visit 1 before taking any study drug 2 home blood pressure readings not allowing for antihypertensive medication
24 included in safety analysis 24 received amlodipine 23 received losartan 23 received atenolol
24 included in safety analysis 24 received atenolol 24 received amlodipine 24 received losartan
23 included in safety analysis 23 received losartan 23 received atenolol 23 received amlodipine
8 incuded in safety analysis 8 received amlodipine 8 received losartan 8 received atenolol
8 included in safety analysis 8 received atenolol 8 received amlodipine 8 received losartan
7 included in safety analysis 7 received losartan 6 received atenolol 6 received amlodipine
2 discontinued during medication phase*† 2 adverse events†
1 discontinued during medication phase‡ 1 adverse event
22 completed all three antihypertensive regimens
24 completed all three antihypertensive regimens
23 completed all three antihypertensive regimens
8 completed all three antihypertensive regimens
8 completed all three antihypertensive regimens
6 completed all three antihypertensive regimens
2 excluded (no valid CVR data)
2 excluded (no valid CVR data)
4 excluded (no valid CVR data)
2 excluded (no valid CVR data)
2 excluded (no valid CVR data)
1 excluded (no valid CVR data)
21 included in intention-to-treat and per-protocol analyses*
22 included in intention-to-treat and per-protocol analyses
19 included in intention-to-treat and per-protocol analyses
6 included in intention-to-treat and per-protocol analyses
6 included in intention-to-treat and per-protocol analyses
5 included in intention-to-treat and per-protocol analyses
7 excluded (missing CVR data)
8 excluded (missing CVR data)
5 excluded (missing CVR data)
2 excluded (missing CVR data)
2 excluded (missing CVR data)
3 excluded (missing CVR data)
14 included in full case analysis
14 included in full case analysis
14 included in full case analysis
4 included in full case analysis
4 included in full case analysis
2 included in full case analysis

participants who had at least one valid assessment for the endpoint (a valid assessment after washout and from at least one period of drug treatment). The per-protocol population was defined as all participants who were treated according to protocol and met all outcome measures allowing for data missing at random. We further added a sensitivity analysis restricting the per-protocol population to participants without missing values (full case analysis). Safety was assessed in all people who received at least one dose of study drug.

We are considering changes within individuals, and we report the mean of these intra-individual changes. Model parameters and their precision (SE and 95% CI) are presented. Linear mixed-effect models automatically handle missing values of the dependent outcome in the case of missingness at random.[31]

Analyses were split by diagnostic subgroups, as was prespecified in the protocol. This approach was chosen because there was no previous information on whether the two groups would behave similarly in terms of CVR while not on medication or while taking any of the three study drugs. We further reasoned that a parallel investigation of participants with sporadic small vessel disease and those with CADASIL could be informative (appendix p 10). Patients with sporadic small vessel disease formed the primary group for analysis and patients with CADASIL served as an additional study group that further allowed contrasting treatment effects in sporadic and hereditary small vessel diseases. Detailed analyses are described in a statistical analysis plan (available on request). An interim analysis was done after 50 patients had completed the trial, as detailed in the appendix (p 15). All analyses were done using the original assigned treatment sequence. A p value of less than 0·05 was judged significant (except in tests for carry over). All analyses were conducted using R (version 4.2.2). Effect analyses used the function lmer in the package lme4.[32]

This trial is registered at ClinicalTrials.gov, NCT03082014, and EudraCT, 2016-002920-10.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Feb 22, 2018, and April 28, 2022, 108 people were assessed for eligibility, of whom 101 (75 with sporadic small vessel disease and 26 with CADASIL) were enrolled and randomly assigned to one of the three treatment sequences starting with amlodipine, atenolol, or losartan (figure 2). The reasons for non-eligibility after obtaining informed consent were no objective cognitive impairment on detailed neuropsychological testing (n=1), heart rhythm disorders on ECG (n=3), contraindications for MRI (n=1), severe obesity that did not allow MRI scans (n=1), and withdrawal due to intolerance of CVR measurements after attempting to breathe CO_2-enriched gas with the anaesthesia mask (n=1). The trial was completed for participants with sporadic small vessel disease but halted prematurely for participants with CADASIL in December, 2022, after enrolment of 26 patients, because of slow recruitment.

Baseline characteristics of randomly assigned participants are shown in table 1. Patients with sporadic small vessel disease were older than those with CADASIL (mean 64·9 years [SD 9·9] *vs* 53·1 years [7·0]), more often male (55 [73%] *vs* ten [38%]), and had higher blood pressure values at baseline (mean SBP 139·1 mm Hg [SD 16·3] *vs* 130·0 mm Hg [13·9] and DBP 84·5 mm Hg [11·9] *vs* 78·4 mm Hg [8·4]). Markers of small vessel disease on MRI (white matter hyperintensity volume, lacune count, microbleed count, and diffusion tensor imaging metrics) were less prominent in patients with sporadic small vessel disease than in those with CADASIL.

Overall, 91 participants (69 with sporadic small vessel disease and 22 with CADASIL) completed all three antihypertensive regimens (figure 2). Seven patients were excluded at visit 1 before taking any study drug. Reasons for exclusion from the trial were home blood pressure readings during the washout phase not allowing for antihypertensive treatment (n=4), uncontrolled hypertension despite emergency medication (n=1), withdrawal of consent because of too demanding trial design (n=1), and refusal to perform further hypercapnic challenges on MRI (n=1). Furthermore, three patients discontinued the trial during the medication phase because of uncontrolled hypertension despite the highest dose of amlodipine and emergency medication (n=1), severe bradycardia while on atenolol (n=1), and cardiac arrhythmia after discontinuation of previous β blocker therapy (n=1). No patients were misrandomised, and all patients received the treatment to which they were assigned.

79 participants (62 with sporadic small vessel disease and 17 with CADASIL) had MRI data of sufficient quality for valid CVR assessments and were included in the primary efficacy analysis. For the primary endpoint, treatment effects between amlodipine, losartan, and atenolol were not significantly different in patients with sporadic small vessel disease (mean change in CVR $1·8\times10^{-4}$%/mm Hg [SE 20·1; 95% CI –37·6 to 41·2] for amlodipine; $16·7\times10^{-4}$%/mm Hg [20·0; –22·3 to 55·8] for losartan; $-7·1\times10^{-4}$%/mm Hg [19·6; –45·5 to 31·1] for atenolol; $p_{overall}=0·39$). However, a significant treatment effect was seen in patients with CADASIL ($15·7\times10^{-4}$%/mm Hg [SE 27·5; 95% CI –38·3 to 69·7] for amlodipine; $19·4\times10^{-4}$%/mm Hg [27·9; –35·3 to 74·2] for losartan; $-23·9\times10^{-4}$%/mm Hg [27·5; –77·7 to 30·0] for atenolol; $p_{overall}=0·019$; table 2). Pairwise comparisons showed that CVR in patients with CADASIL improved with amlodipine compared with atenolol ($-39·6\times10^{-4}$%/mm Hg [95% CI –72·5 to –6·6]; p=0·019), and with losartan compared with atenolol

	Sporadic small vessel disease				CADASIL			
	Total cohort (n=75)	Amlodipine→losartan →atenolol (n=25)	Atenolol→amlodipine →losartan (n=25)	Losartan→atenolol →amlodipine (n=25)	Total cohort (n=26)	Amlodipine→losartan →atenolol (n=8)	Atenolol→amlodipine →losartan (n=9)	Losartan→atenolol →amlodipine (n=9)
Age, years	64·9 (9·9)	62·2 (9·5)	65·6 (9·1)	66·9 (10·8)	53·1 (7·0)	54·4 (6·3)	54·3 (7·0)	50·7 (7·8)
Sex								
Female	20 (27%)	7 (28%)	6 (24%)	7 (28%)	16 (62%)	5 (63%)	6 (67%)	5 (56%)
Male	55 (73%)	18 (72%)	19 (76%)	18 (72%)	10 (38%)	3 (38%)	3 (33%)	4 (44%)
Ethnicity								
White	74 (99%)	24 (96%)	25 (100%)	25 (100%)	26 (100%)	8 (100%)	9 (100%)	9 (100%)
Asian	1 (1%)	1 (4%)	0	0	0	0	0	0
Hypertension	73 (97%)	24 (96%)	25 (100%)	24 (96%)	26 (100%)	8 (100%)	9 (100%)	9 (100%)
Systolic blood pressure at baseline, mm Hg	139·1 (16·3)	133·5 (15·3)	144·0 (19·2)	139·7 (12·8)	130·0 (13·9)	125·9 (13·8)	129·2 (9·7)	134·6 (17·3)
Diastolic blood pressure at baseline, mm Hg	84·5 (11·9)	82·4 (11·0)	88·2 (10·7)	82·7 (13·2)	78·4 (8·4)	76·2 (9·0)	79·9 (8·7)	78·8 (8·1)
Hypercholesterolaemia	57 (76%)	20 (80%)	20 (80%)	17 (68%)	16 (62%)	7 (88%)	5 (57%)	4 (44%)
LDL cholesterol, mmol/L*	2·0 (0·7)	2·1 (0·7)	2·2 (0·9)	1·7 (0·6)	2·8 (0·9)	2·5 (0·8)	2·6 (0·9)	3·4 (1·0)
Diabetes	15 (20%)	3 (12%)	7 (28%)	5 (20%)	1 (4%)	0	0	1 (11%)
HbA_{1c}, %†	6·0% (0·8)	5·9% (0·6)	6·1% (1·1)	5·8% (0·5)	5·4% (0·5)	5·7% (0·6)	5·3% (0·2)	5·2% (0·5)
HbA_{1c}, mmol/mol	42 (9)	41 (7)	43 (12)	40 (6)	36 (5)	39 (6)	35 (2)	34 (5)
BMI, kg/m²	27·8 (4·2)	27·6 (3·7)	28·3 (3·7)	27·4 (5·2)	30·1 (4·9)	31·3 (3·5)	28·3 (4·2)	30·8 (6·4)
Smoking status								
Never smoker	33 (44%)	12 (48%)	12 (48%)	9 (36%)	9 (35%)	4 (50%)	3 (33%)	2 (22%)
Current smoker	12 (16%)	3 (12%)	5 (20%)	4 (16%)	3 (12%)	2 (25%)	0	1 (11%)
Former smoker	30 (40%)	10 (40%)	8 (32%)	12 (48%)	14 (54%)	2 (25%)	6 (67%)	6 (67%)
Concomitant medication at baseline								
Antihypertensives‡	67 (89%)	23 (92%)	23 (92%)	21 (84%)	25 (96%)	8 (100%)	9 (100%)	8 (89%)
Statins	66 (88%)	22 (88%)	20 (80%)	24 (96%)	14 (54%)	5 (63%)	5 (56%)	4 (44%)
Oral antidiabetic drugs	10 (13%)	3 (12%)	3 (12%)	4 (16%)	2 (8%)	1 (13%)	0	1 (11%)
Insulin	5 (7%)	2 (8%)	2 (8%)	1 (4%)	0	0	0	0
Antiplatelet drugs	69 (92%)	22 (88%)	22 (88%)	25 (100%)	20 (77%)	5 (63%)	7 (78%)	8 (89%)
Oral anticoagulants	2 (3%)	1 (4%)	1 (4%)	0	0	0	0	0
History of stroke								
First ever stroke	52 (69%)	16 (64%)	18 (72%)	18 (72%)	7 (27%)	2 (25%)	2 (22%)	3 (33%)
Recurrent stroke	10 (13%)	3 (12%)	3 (12%)	4 (16%)	5 (19%)	2 (25%)	1 (11%)	2 (22%)
Time from last stroke to randomisation, years	0·7 (0·3–2·0)	0·7 (0·5–1·6)	0·4 (0·2–1·2)	1·0 (0·5–3·2)	3·2 (1·3–5)	3·4 (1·6–5·2)	1·5 (1·0–4·8)	4·0 (2·3–4·1)
Cognitive impairment	18 (24%)	7 (28%)	6 (24%)	5 (20%)	14 (54%)	4 (50%)	3 (33%)	7 (78%)
CADASIL confirmation								
Molecular genetic testing	..	..	..	..	24 (92%)	6 (75%)	9 (100%)	9 (100%)
Skin biopsy	..	..	..	..	4 (15%)	2 (25%)	0	2 (22%)

(Table 1 continues on next page)

	Sporadic small vessel disease				CADASIL			
	Total cohort (n=75)	Amlodipine→losartan →atenolol (n=25)	Atenolol→amlodipine →losartan (n=25)	Losartan→atenolol →amlodipine (n=25)	Total cohort (n=26)	Amlodipine→losartan →atenolol (n=8)	Atenolol→amlodipine →losartan (n=9)	Losartan→atenolol →amlodipine (n=9)
(Continued from previous page)								
NIHSS score§								
0	39 (52%)	12 (48%)	13 (52%)	14 (56%)	14 (54%)	4 (50%)	6 (67%)	4 (44%)
1	23 (31%)	10 (40%)	7 (28%)	6 (24%)	7 (27%)	2 (25%)	2 (22%)	3 (33%)
2	5 (7%)	1 (4%)	2 (8%)	2 (8%)	1 (4%)	0	0	1 (11%)
3	5 (7%)	2 (8%)	1 (4%)	2 (8%)	3 (12%)	1 (13%)	1 (11%)	1 (11%)
4	2 (3%)	0	0	0	1 (4%)	1 (13%)	0	0
Modified Rankin Scale grade								
0	22 (29%)	9 (36%)	6 (24%)	7 (28%)	11 (42%)	4 (50%)	5 (56%)	2 (22%)
1	43 (57%)	16 (64%)	16 (64%)	11 (44%)	10 (39%)	2 (25%)	3 (33%)	5 (56%)
2	8 (11%)	0 (%)	2 (8%)	6 (24%)	2 (8%)	0	1 (11%)	1 (11%)
3	1 (1%)	0 (%)	1 (4%)	0	1 (4%)	1 (13%)	0	0
4	1 (1%)	0 (%)	0	1 (4%)	2 (8%)	1 (13%)	0	1 (11%)
Neuropsychological examination								
Mini-Mental State Examination	29 (28–30)	29 (28–30)	29 (29–30)	29 (28–30)	29 (27–30)	29 (28–29)	29 (28–29)	29 (27–30)
Digit span forward	10 (8–12)	9 (8–11)	10 (8–11)	12 (8–12)	9·5 (7–10)	10 (8–10)	9 (7–10)	8 (6–12)
Digit span backward	7 (5–8)	6 (5–7)	6 (5–7)	8 (6–9)	6 (4–7)	6 (5–7)	6 (5–7)	5 (4–6)
Trail making test A, s¶	36 (28–47)	33 (28–42)	40 (24–57)	37 (29–46)	33 (29–48)	41 (30–57)	31 (23–36)	42 (31–48)
Trail making test B, s‖	74 (56–114)	85 (63–109)	68 (54–107)	78 (53–134)	67 (62–85)	71 (62–105)	64 (63–70)	66 (62–105)
Quantitative metrics on brain MRI**								
Fazekas score ≥2	58 (78%)	17 (71%)	21 (84%)	20 (80%)	26 (100%)	8 (100%)	9 (100%)	9 (100%)
Fazekas score	2 (2–3)	2·5 (1–3)	2 (2–3)	2 (2–3)	3 (3–3)	3 (3–3)	3 (3–3)	3 (3–3)
White matter hyperintensity volume, cm^3	17·2 (18·2)	23·1 (23·7)	13·3 (14·7)	15·4 (14·3)	84·4 (59·0)	106·9 (62·8)	79·4 (69·5)	69·3 (42·4)
Lacune count	2·2 (2·4)	1·5 (2·3)	2·2 (2·2)	2·8 (2·6)	9·2 (6·4)	11·9 (5·9)	5·6 (4·9)	10·4 (7·0)
Microbleed count	0 (0–1)	0 (0–1·25)	0 (0–1)	0 (0–2)	1 (0–2)	12 (8–31)	0 (0–7)	3 (0–6)
0	48 (65%)	13 (54%)	18 (72%)	17 (68%)	10 (39%)	2 (25%)	5 (56%)	3 (33%)
1–5	21 (28%)	9 (38%)	6 (24%)	6 (24%)	4 (15%)	0	1 (11%)	3 (33%)
6–10	4 (5%)	1 (4·2%)	1 (4%)	2 (8%)	4 (15%)	1 (13%)	1 (11%)	2 (22%)
>10	1 (1%)	1 (4·2%)	0	0	8 (31%)	5 (63%)	2 (22%)	1 (11%)
Mean diffusivity	$7{\cdot}86\times10^{-4}$ ($0{\cdot}33\times10^{-4}$)	$7{\cdot}85\times10^{-4}$ ($0{\cdot}38\times10^{-4}$)	$7{\cdot}86\times10^{-4}$ ($0{\cdot}28\times10^{-4}$)	$7{\cdot}87\times10^{-4}$ ($0{\cdot}35\times10^{-4}$)	$8{\cdot}81\times10^{-4}$ ($0{\cdot}77\times10^{-4}$)	$9{\cdot}05\times10^{-4}$ ($0{\cdot}89\times10^{-4}$)	$8{\cdot}64\times10^{-4}$ ($0{\cdot}62\times10^{-4}$)	$8{\cdot}75\times10^{-4}$ ($0{\cdot}74\times10^{-4}$)
Fractional anisotropy	0·481 (0·027)	0·480 (0·032)	0·482 (0·021)	0·482 (0·028)	0·426 (0·044)	0·414 (0·050)	0·438 (0·039)	0·424 (0·046)

Data are mean (SD), n (%), or median (IQR). The sum of the percentages might differ from 100% due to rounding. CADASIL=cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. HbA_{1c}=glycated haemoglobin. NIHSS=National Institutes of Health Stroke Scale. *Data on LDL cholesterol were missing for six participants with sporadic small vessel disease (one on sequence amlodipine→losartan→atenolol, three on sequence atenolol→amlodipine→losartan, and two on sequence losartan→atenolol→amlodipine), and for one participant with CADASIL on sequence losartan→atenolol→amlodipine. †Data on HbA_{1c} were missing for 14 participants with sporadic small vessel disease (four on sequence amlodipine→losartan→atenolol, four on sequence atenolol→amlodipine→losartan, and six on sequence losartan→atenolol→amlodipine) and for one participant with CADASIL on sequence losartan→atenolol→amlodipine. ‡Antihypertensive drugs were stopped after randomisation for the washout period. §Data on NIHSS were missing for one participant with sporadic small vessel disease on sequence losartan→atenolol→amlodipine. ¶Data on trail making test A were missing for two participants with sporadic small vessel disease (one on sequence amlodipine→losartan→atenolol and one on sequence losartan→atenolol→amlodipine). ‖Data on trail making test B were missing for 6 participants with sporadic small vessel disease (one on sequence amlodipine→losartan→atenolol, three on sequence atenolol→amlodipine→losartan and two on sequence losartan→atenolol→amlodipine) and for two participants with CADASIL (one on sequence amlodipine→losartan→atenolol, and one on sequence losartan→atenolol→amlodipine). **Data on quantitative MRI metrics were missing for one participant with sporadic small vessel disease on sequence amlodipine→losartan→atenolol.

Table 1: **Baseline characteristics**

	Without treatment	Amlodipine	Losartan	Atenolol	p value
Participants with sporadic small vessel disease					
Primary analysis					
Participants	62	54	56	57	..
Outcome measure: mean CVR in normal-appearing white matter (SD), 10^{-4}%/mm Hg	423·3 (120·0)	409·9 (165·8)	427·0 (110·1)	405·9 (134·2)	..
Endpoint: mean change in CVR in normal-appearing white matter (SE, 95% CI), 10^{-4}%/mm Hg	..	1·8 (20·1; −37·6 to 41·2)	16·7 (20·0; −22·3 to 55·8)	−7·1 (19·6; −45·5 to 31·1)	0·39
Secondary analysis					
Participants	68	67	67	67	..
Outcome measure: mean systolic blood pressure (SD), mm Hg	128·1 (9·8)	120·5 (8·0)	122·7 (10·2)	121·0 (10·6)	..
Outcome measure: mean blood pressure variability (SD)	7·1 (2·9)	6·3 (2·6)	7·2 (2·9)	8·2 (3·3)	..
Endpoint: mean change in systolic blood pressure (SE, 95% CI), mm Hg	..	−8·5 (1·2; −10·8 to −6·1)	−6·4 (1·2; −8·7 to −4·0)	−8·2 (1·2; −10·6 to −5·9)	0·075
Endpoint: mean change in blood pressure variability (SE, 95% CI)	..	−0·7 (0·4; −1·4 to 0·1)	0·3 (0·4; −0·4 to 1·0)	1·3 (0·4; 0·6 to 2·0)	<0·0001
Participants with CADASIL					
Primary analysis					
Participants	17	13	16	15	..
Outcome measure: mean CVR in normal-appearing white matter (SD), 10^{-4}%/mm Hg	356·9 (104·7)	377·0 (82·3)	386·2 (102·6)	325·2 (139·0)	..
Endpoint: mean change in CVR in normal-appearing white matter (SE, 95% CI), 10^{-4}%/mm Hg	..	15·7 (27·5; −38·3 to 69·7)	19·4 (27·9; −35·3 to 74·2)	−23·9 (27·5; −77·7 to 30·0)	0·019
Secondary analysis					
Participants	22	22	22	21	..
Outcome measure: mean systolic blood pressure (SD), mm Hg	122·4 (9·4)	116·2 (6·5)	116·0 (9·1)	116·5 (9·1)	..
Outcome measure: mean blood pressure variability (SD)	6·0 (1·7)	5·9 (2·2)	6·1 (1·9)	6·8 (1·9)	..
Endpoint: mean change in systolic blood pressure (SE, 95% CI), mm Hg	..	−7·8 (1·6; −11·0 to −4·6)	−8·2 (1·7; −11·5 to −4·9)	−7·3 (7·5; −10·5 to −4·0)	0·79
Endpoint: mean change in blood pressure variability (SE, 95% CI)	..	−0·04 (0·5; −1·0 to 0·9)	0·3 (0·5; −0·7 to 1·2)	0·8 (0·5; −0·1 to 1·8)	0·11

CADASIL=cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. CVR=cerebrovascular reactivity.

Table 2: **Outcome measures and endpoints in the intention-to-treat population**

(−43·3×10^{-4}%/mm Hg [−74·3 to −12·3]; p=0·0061; table 3; figure 3).

Because of the results in participants with CADASIL, and the noted lower mean age of participants with CADASIL compared with sporadic small vessel disease, we tested for an interaction between treatment effect and age in participants with sporadic small vessel disease and found evidence for an interaction (p<0·10). We therefore conducted an exploratory subgroup analysis in patients with sporadic small vessel disease using the median split of the study population (age 60 years) as a cutoff. Evidence of a treatment effect was seen among the 24 patients with sporadic small vessel disease who were younger than 60 years ($p_{overall}$=0·0037; appendix pp 17, 22). As in patients with CADASIL, change in CVR in participants younger than 60 years with sporadic small vessel disease improved with amlodipine compared with atenolol (p=0·022) and with losartan compared with atenolol (p=0·0004; appendix pp 17, 22).

The population for the per-protocol analysis was identical to the population for the primary efficacy analysis (62 patients with sporadic small vessel disease and 17 with CADASIL), but there were fewer observations due to protocol violations in patients with sporadic small vessel disease. As for the primary efficacy analysis, no significant difference was noted in the treatment effects between study drugs in patients with sporadic small vessel disease ($p_{overall}$=0·29), whereas there was a differential treatment effect in patients with CADASIL identical to the primary efficacy analysis ($p_{overall}$=0·019; appendix pp 18, 23). The

	Amlodipine *vs* losartan		Amlodipine *vs* atenolol		Losartan *vs* atenolol		$p_{overall}$
	Estimate (95% CI)	p value	Estimate (95% CI)	p value	Estimate (95% CI)	p value	
Participants with sporadic small vessel disease							
Mean change in CVR in normal-appearing white matter, 10^{-4}%/mm Hg	14·9 (–20·0 to 49·7)	0·42	–9·0 (–43·1 to 25·1)	0·61	–23·9 (–58·1 to 10·3)	0·17	0·39
Mean change in systolic blood pressure, mm Hg	2·1 (0·1 to 4·0)	0·037	0·2 (1·3 to 2·6)	0·83	–1·9 (–3·8 to 0·1)	0·061	0·075
Mean change in blood pressure variability	0·9 (0·3 to 1·6)	0·0059	1·3 (0·6 to 2·0)	<0·0001	1·0 (0·3 to 1·7)	0·0030	<0·0001
Participants with CADASIL							
Mean change in CVR in normal-appearing white matter, 10^{-4}%/mm Hg	3·8 (–29·4 to 36·9)	0·82	–39·6 (–72·5 to –6·6)	0·019	–43·3 (–74·3 to –12·3)	0·0061	0·019
Mean change in systolic blood pressure, mm Hg	–0·5 (–3·1 to 2·2)	0·74	0·5 (–2·2 to 3·2)	0·71	1·0 (–1·8 to 3·7)	0·49	0·79
Mean change in blood pressure variability	0·3 (–0·5 to 1·1)	0·47	0·9 (0·1 to 1·7)	0·033	0·6 (–0·2 to 1·4)	0·15	0·11

Shown are the p values for the global comparison as well as for pairwise comparisons of drug effects, reporting the estimate for intraindividual changes from the end of the washout period (without treatment) to treatment in the primary efficacy analysis. CADASIL=cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. CVR=cerebrovascular reactivity.

Table 3: **Pairwise comparisons of drug effects for the primary and secondary endpoints**

results in participants younger than 60 years with sporadic small vessel disease were likewise identical to the primary efficacy analysis ($p_{overall}$=0·0037; appendix p 24). The results of the primary efficacy and per-protocol analyses were confirmed by a sensitivity analysis restricting the per-protocol population to participants without missing values (42 patients with sporadic small vessel disease [$p_{overall}$=0·19] and ten with CADASIL [$p_{overall}$=0·025]; appendix pp 18, 23).

No difference was noted in the effects of study drugs on change in CVR in white matter hyperintensities in participants with sporadic small vessel disease ($p_{overall}$=0·080), whereas a treatment effect was seen in patients with CADASIL ($p_{overall}$=0·014; appendix p 19). For the change in CVR in subcortical grey matter, a differential treatment effect was reported in patients with sporadic small vessel disease ($p_{overall}$=0·033) but not in those with CADASIL ($p_{overall}$=0·25; appendix p 19). Across all analyses, change in CVR showed the lowest values with atenolol when compared with other study drugs (table 2; appendix p 19).

The absolute reduction in mean SBP obtained for patients with sporadic small vessel disease and those with CADASIL was similar between amlodipine, losartan, and atenolol (sporadic small vessel disease, $p_{overall}$=0·075; CADASIL $p_{overall}$=0·79; table 2; figure 3). Pairwise comparisons showed that mean SBP decreased with amlodipine compared with losartan (2·1 [95% CI 0·1 to 4·0]; p=0·037) but not for the other comparisons (table 3). For the change in blood pressure variability, a difference was noted in treatment effects between amlodipine, losartan, and atenolol in patients with sporadic small vessel disease ($p_{overall}$<0·0001), but not with CADASIL ($p_{overall}$=0·11). In pairwise analyses, blood pressure variability decreased with amlodipine compared with atenolol (1·3 [95% CI 0·6 to 2·0]; p<0·0001) and with losartan compared with atenolol (1·0 [0·3 to 1·7]; p=0·0030; table 3). The results for change in mean SBP and change in blood pressure variability remained stable after adjusting for the dose of the study drug (appendix pp 20–21).

Adverse events were reported by 79 of 94 participants in the safety population. 57 adverse events took place during the washout phase, 92 while taking amlodipine, 65 while taking losartan, and 118 while taking atenolol. Adverse events leading to discontinuation of trial treatment occurred during washout (n=1) and while taking study medication (n=3, one for each drug; figure 2). Two serious adverse events were reported (diarrhoea with reduced fluid intake while taking amlodipine and a fall with a fracture while taking atenolol), neither of which was related to study drug intake and neither of which led to discontinuation of trial treatment. The frequency of drug-related adverse events was 58 with amlodipine, 33 with losartan, and 87 with atenolol (detailed information on drug-related adverse events is provided in table 4). No strokes, myocardial infarctions, or deaths were documented during the trial period.

Discussion

In the TREAT-SVDs trial, which was a randomised, open-label, blinded-endpoint crossover trial in patients with either sporadic small vessel disease or CADASIL, 4 weeks of amlodipine, losartan, or atenolol did not differ in their effects on CVR in people with sporadic small vessel disease. However, differential treatment effects were noted in people with CADASIL. CVR in patients with CADASIL improved with both amlodipine and losartan compared with atenolol. Aside from showing

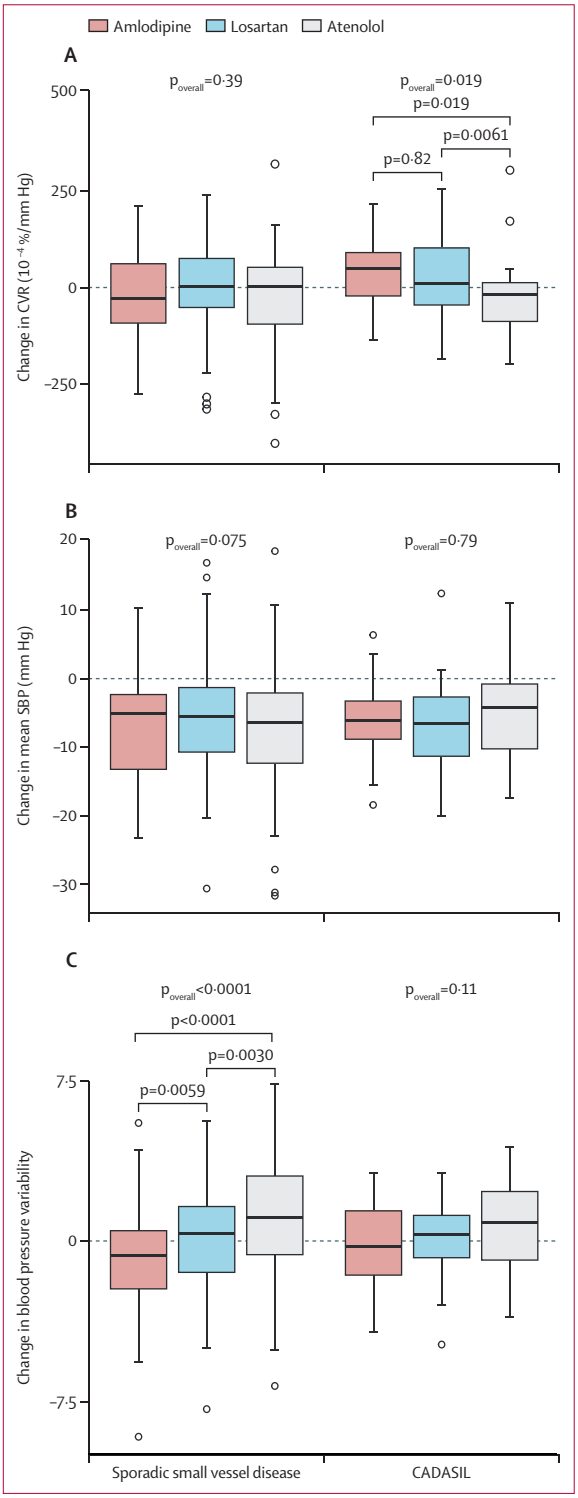


Figure 3: **Primary and secondary endpoints**
Mean change from the end of the washout period to treatment (visits 2–4) for CVR (A), mean SBP (B), and mean blood pressure variability (C). Shown are the results from the analyses presented in table 2. Boxes are drawn from the first to the third quartile with the horizontal line representing the median and circles representing outliers. CADASIL=cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. CVR=cerebrovascular reactivity. SBP=systolic blood pressure.

	Amlodipine	Losartan	Atenolol
All drug-related adverse events	67	37	91
System organ class			
Blood and lymphatic system disorders	1/1 (100%)	0	0
Cardiac disorder	6/13 (46%)	2/13 (15%)	5/13 (39%)
Ear and labyrinth disorders	2/7 (29%)	2/7 (29%)	3/7 (43%)
Eye disorders	0	1 (100%)	0
Gastrointestinal disorders	5/10 (50%)	0	5/10 (50%)
General disorders and administration site conditions	17/42 (40%)	8/42 (19%)	17/42 (40%)
Infections and infestations	3/3 (100%)	0	0
Injury, poisoning, and procedural complications	2/2 (100%)	0	0
Investigations	1/30 (3%)	2/30 (7%)	27/30 (90%)*
Metabolism and nutrition disorders	0	0	1/1 (100%)
Musculoskeletal and connective tissue disorders	5/6 (83%)	1/6 (17%)	0
Nervous system disorders	8/29 (28%)	12/29 (41%)	9/29 (31%)
Psychiatric disorders	5/16 (31%)	4/16 (25%)	7/16 (44%)
Renal and urinary disorders	1/4 (25%)	1/4 (25%)	2/4 (50%)
Reproductive system and breast disorders	0	1/2 (50%)	1/2 (50%)
Respiratory, thoracic, and mediastinal disorders	0	3/4 (75%)	1/4 (25%)
Skin and subcutaneous tissue disorders	6/13 (46%)	0	7/13 (54%)
Vascular disorders	5/11 (46%)	0	6/11 (55%)

Data are n/N (%). One drug-related adverse event might refer to more than one system of organ class. Percentage values are calculated as percentage of the respective system of organ class. The sum of the percentages might differ from 100% due to rounding. Drug-related adverse events were classified in the safety population (94 patients) by system organ classes in accordance with the Medical Dictionary for Regulatory Activities (version 25.1). *One drug-related adverse event led to discontinuation of the trial (low heart rate under atenolol).

Table 4: **Drug-related adverse events**

an antihypertensive drug class effect on cerebral microvascular function, the trial highlights the importance of including patients with rare hereditary subtypes of common diseases in clinical trials of sporadic disease and of performing separate analyses for these patients.

The blood pressure values achieved with antihypertensive treatment in this trial were in the range of those achieved in previous RCTs with intensive blood pressure lowering. In the PRESERVE trial,[10] intensive (target SBP of <125 mm Hg) compared with standard (target of 130–140 mm Hg) blood pressure lowering did not change resting cerebral blood flow in patients with severe small vessel disease, addressing concerns that intensive blood pressure lowering might cause cerebral hypoperfusion in this patient population. In the SPS3 trial,[9] blood pressure lowering in patients with recent lacunar stroke to a target SBP of less than 130 mm Hg was associated with a non-significant reduction in stroke rates compared with a target SBP of 130–149 mm Hg. The SPRINT-MIND trial showed that targeting an SBP of less than 120 mm Hg, compared with less than 140 mm Hg, among adults with hypertension was associated with a smaller increase in white matter hyperintensity volume.[33] A post-hoc analysis of SPRINT-MIND further found angiotensin-converting enzyme inhibitors and dihydropyridine calcium channel

blockers, but not selective β blockers, to be associated with reduced progression of white matter hyperintensities independent of blood pressure control and age.[34] However, the trial was not designed to compare different blood pressure-lowering drugs.

CVR declines with ageing.[35] Lower CVR is associated with an increased risk of stroke in patients with carotid artery stenosis[36] and with risk of death independent of stroke in the general population.[37] Reduced CVR was further found to precede the progression of normal-appearing white matter to white matter hyperintensities.[38] However, the mechanisms underlying the association between lower CVR and adverse outcomes remain to be determined. Blood pressure-lowering drugs from different drug classes differ in their effects on vascular remodelling and endothelial dysfunction. Long-term treatment with losartan has been shown to correct the altered structure and endothelial dysfunction of resistance arteries in people with hypertension, whereas treatment with atenolol had no effect.[39] In a substudy of the LIFE trial, long-term treatment with losartan was associated with less peripheral vascular hypertrophy than with atenolol.[40] Data from rodent models of hypertension likewise show drug class-specific effects of antihypertensive agents on vascular structure and function.[21,41] Hence, it seems possible that the differential effects of study drugs on change in CVR in patients with CADASIL observed in the TREAT-SVDs trial are related to differential effects on endothelial function or vascular remodelling. However, the period of intervention in our trial was short, and whether longer treatment would have similar results remains unknown. In any case, the differences in treatment effects on change in CVR in patients with CADASIL seem unrelated to the absolute reductions in blood pressure lowering, because amlodipine, losartan, and atenolol all reduced mean SBP to a similar extent. Current guidelines for the management of hypertension recommend restricting β blockers to people with comorbidities or compelling indications requiring their use.[42] The unfavourable effect of atenolol compared with both amlodipine and losartan on change in CVR in patients with CADASIL might be seen as an additional argument to adhere to current guidelines for blood pressure control in this patient population. The number of study participants with CADASIL entering the efficacy and per-protocol analyses was small, and only ten people had valid data for change in CVR for all four measurements (ie, after washout and at the end of each of the three treatment periods). Nevertheless, we detected a significant treatment effect, possibly due to the relative homogeneity of the CADASIL group and the crossover design.

To our knowledge, TREAT-SVDs is the first RCT to compare the treatment effects of different antihypertensive drugs in people with small vessel disease and on CVR. We chose an open-label study design because we anticipated that CVR, as assessed in the current study, would be independent of whether the patient or study personnel were aware of treatment allocation. After investigating the effects of the number of sequences in simulations, we further decided to use a three-sequence instead of a six-sequence model, because the three-sequence model was not inferior and because it limited the complexity of the study. The decision not to perform a washout between study drugs was motivated by the intention to limit the drug-free period in study participants, all of whom had an indication for antihypertensive treatment. Given the half-lives of the study drugs, this lack of a washout between treatments had no effect on the safety assessment (appendix p 13).

Overall, the study drugs were well tolerated. Our finding of significant differences in the treatment effects on the primary endpoint in participants with CADASIL but not in participants with sporadic small vessel disease was unexpected and shows the importance of including patients with rare hereditary subtypes of common diseases into clinical trials. Aside from the underlying genetic cause in participants with CADASIL, the two patient groups differed with respect to baseline characteristics. On average, participants with sporadic small vessel disease were almost 10 years older, had higher blood pressure values, were likely to have had long-standing hypertension, and had less severe manifestations of small vessel disease on MRI. Because of the lower blood pressure values in participants with CADASIL, the mean drug dose for the three study drugs was lower than in participants with sporadic small vessel disease. Still, the absolute effects on change in CVR seemed to be larger in participants with CADASIL than in those with sporadic small vessel disease. Motivated by these results, the lower mean age of participants with CADASIL than of those with sporadic small vessel disease, and previous data showing an overall reduction of CVR with ageing,[35] we conducted an exploratory subgroup analysis in young sporadic patients using the median split of the study population (age 60 years) as a cutoff. As in patients with CADASIL, change in CVR improved with both amlodipine and losartan compared with atenolol, suggesting that the effects of antihypertensive treatment on CVR might vary depending on age or duration of hypertension. However, this result should be interpreted with caution because this exploratory analysis was not prespecified.

Our trial has limitations. First, it was terminated prematurely for participants with CADASIL because of slow recruitment, and the overall sample size was small. Second, the proportion of participants with incomplete datasets for the primary outcome was relatively high. A reason for the incompleteness of data can be accounted for by the requirement for repeated MRIs with assessment of CVR, which is more challenging to obtain than a typical clinical outcome. Notably, there was no evidence for a sequence effect or bias originating from a selective loss of endpoints. The main reasons for incomplete datasets were premature termination of the CVR measurements

by study participants and movement artifacts raising concerns about the suitability of CVR measurements as an endpoint for future trials. Third, the treatment period for each drug was short, so no conclusions can be drawn about potential long-term effects of antihypertensive drugs on CVR. Finally, the results cannot be generalised to all people with small vessel disease and hypertension, because people with asymptomatic small vessel disease and people with severe hypertension taking more than two antihypertensive drugs at a maximum dose or equivalent were excluded from participation into the study.

Our trial has several strengths. TREAT-SVDs included people with sporadic small vessel disease as well as patients with CADASIL and, therefore, provides data for many people with symptomatic small vessel disease as well as a group of patients that is typically under-represented in clinical trials. Second, all endpoints were centrally assessed by experienced readers who were masked to clinical status and information related to study medication. Third, the primary endpoint measure related to cerebral microvascular function and, thus, was reflective of the primary pathology in small vessel diseases. Recent trials in Alzheimer's disease and other conditions have shown the importance of biomarkers that are close to the primary pathology as read-outs in clinical trials. Fourth, blood pressure was determined by daily telemetric monitoring, enabling close observation of drug treatment and the assessment of blood pressure variability as a secondary endpoint. Indeed, drug effects on blood pressure variability differed between study drugs, as expected from findings of previous blood pressure-lowering trials. Finally, study attrition was low, and 90% of participants completed all study visits despite the extensive study protocol with multiple MRIs, CVR measurements, telemetric blood pressure monitoring, four drug changes, and being conducted during the COVID-19 pandemic.

The TREAT-SVDs trial provides proof of concept for the feasibility of multicentre trials involving complex interventions and serial MRIs with dynamic tests of cerebral microvascular function in patients with symptomatic small vessel diseases. Whether antihypertensive drug classes differentially affect clinical outcomes in people with small vessel diseases requires further research.

Contributors

MD, JW, GJB, and UM designed the study, which was set up by MD, JW, GJB, RvO, PMR, AJSW, MDu, MJT, and MM. UM did the statistical analysis. JW, MSS, and AKa did the masked imaging analyses. AK, HvdB, DK, GWB, MvD, CAR, DJG, LO, KAW, JS, SLO, KM, and FND contributed to patient recruitment. MD was the principal clinical investigator and sponsor-delegated person of this trial, for which the Klinikum der Ludwig-Maximilians-Universität München was the sponsor. MD wrote the first draft of the report with help from AK. BN and MGB were members of the safety monitoring board. The paper was revised by all authors. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. AK and UM directly accessed and verified the underlying data reported in the manuscript.

Data sharing

The study protocol, statistical analysis plan, informed consent forms, and study data, including de-identified participant data and a data dictionary defining each field in the set, will be made available to others on formal request and receipt of a signed material transfer agreement. Requests should be directed to the corresponding author. Data will only be shared via individual secured network connections.

Declaration of interests

MD has received consultancy and advisory board fees from Bayer Vital, and speaker's fees from Bayer Vital. MDu reports no competing interests directly related to this work, but declares the following interests outside the submitted work: MIAC (employment), Roche (consultant), Biogen (scientific advisory board), Hovid Berhad (adjudication board), Bayer Vital, and Sanofi Genzyme (speaker honoraria). BN has received consultancy fees from Simbec-Orion for data monitoring committee work. KWM has received consultancy fees from Boehringer Ingelheim, Biogen, Abbvie, Lumosa, and Woolsey, advisory board fees from Boehringer Ingelheim, and speaker's fees from Boehringer Ingelheim. PMR has received consultancy and advisory board fees from Bayer, Bristol Myers Squibb, Sanofi, and Abbott, and speaker fees from Sanofi and Abbott. RvO reports financial support by the European Union's Horizon 2020 project 'CRUCIAL' (grant number 848109), and the Collaboration for New Treatments of Acute Stroke (CONTRAST) consortium (financed by the Netherlands Cardiovascular Research Initiative, an initiative of the Dutch Heart Foundation, the Netherlands Brain Foundation, Stryker, Medtronic, and Cerenovus). JMW is part funded by the UK Dementia Research Institute (funded by the Medical Research Council, Alzheimer's Society, and Alzheimer's Research UK) but has no competing interests. All other authors declare no competing interests.

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References

1 GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019; **18:** 459–80.

2 Pendlebury ST, Rothwell PM. Incidence and prevalence of dementia associated with transient ischaemic attack and stroke: analysis of the population-based Oxford Vascular Study. *Lancet Neurol* 2019; **18:** 248–58.

3 Gardener H, Wright CB, Rundek T, Sacco RL. Brain health and shared risk factors for dementia and stroke. *Nat Rev Neurol* 2015; **11:** 651–57.

4 Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. *Lancet Neurol* 2019; **18:** 684–96.

5 Chabriat H, Joutel A, Dichgans M, Tournier-Lasserve E, Bousser MG. Cadasil. *Lancet Neurol* 2009; **8:** 643–53.
6 Petrea RE, O'Donnell A, Beiser AS, et al. Mid to late life hypertension trends and cerebral small vessel disease in the Framingham heart study. *Hypertension* 2020; **76:** 707–14.
7 Dawson J, Béjot Y, Christensen LM, et al. European Stroke Organisation (ESO) guideline on pharmacological interventions for long-term secondary prevention after ischaemic stroke or transient ischaemic attack. *Eur Stroke J* 2022; **7:** I–II.
8 Wardlaw JM, Debette S, Jokinen H, et al. ESO Guideline on covert cerebral small vessel disease. *Eur Stroke J* 2021; **6:** CXI–XII.
9 Benavente OR, Coffey CS, Conwit R, et al. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet* 2013; **382:** 507–15.
10 Croall ID, Tozer DJ, Moynihan B, et al. Effect of standard vs intensive blood pressure control on cerebral blood flow in small vessel disease: the PRESERVE randomized clinical trial. *JAMA Neurol* 2018; **75:** 720–27.
11 Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009; **338:** b1665.
12 Lindholm LH, Carlberg B, Samuelsson O. Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet* 2005; **366:** 1545–53.
13 Verdecchia P, Reboldi G, Angeli F, et al. Angiotensin-converting enzyme inhibitors and calcium channel blockers for coronary heart disease and stroke prevention. *Hypertension* 2005; **46:** 386–92.
14 Dahlöf B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005; **366:** 895–906.
15 Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *Lancet* 2010; **375:** 938–48.
16 Rothwell PM, Howard SC, Dolan E, et al. Effects of β blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. *Lancet Neurol* 2010; **9:** 469–80.
17 Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet* 2010; **375:** 895–905.
18 Alpérovitch A, Blachier M, Soumaré A, et al. Blood pressure variability and risk of dementia in an elderly cohort, the Three-City Study. *Alzheimers Dement* 2014; **10** (suppl)**:** S330–37.
19 Ma Y, Song A, Viswanathan A, et al. Blood pressure variability and cerebral small vessel disease: a systematic review and meta-analysis of population-based cohorts. *Stroke* 2020; **51:** 82–89.
20 Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. *Lancet* 2010; **375:** 906–15.
21 Koide M, Harraz OF, Dabertrand F, et al. Differential restoration of functional hyperemia by antihypertensive drug classes in hypertension-related cerebral small vessel disease. *J Clin Invest* 2021; **131:** e149029.
22 Stevenson SF, Doubal FN, Shuler K, Wardlaw JM. A systematic review of dynamic cerebral and peripheral endothelial function in lacunar stroke versus controls. *Stroke* 2010; **41:** e434–42.
23 Sleight E, Stringer MS, Marshall I, Wardlaw JM, Thrippleton MJ. Cerebrovascular reactivity measurement using magnetic resonance imaging: a systematic review. *Front Physiol* 2021; **12:** 643468.
24 Knottnerus IL, Ten Cate H, Lodder J, Kessels F, van Oostenbrugge RJ. Endothelial dysfunction in lacunar stroke: a systematic review. *Cerebrovasc Dis* 2009; **27:** 519–26.
25 Blair GW, Thrippleton MJ, Shi Y, et al. Intracranial hemodynamic relationships in patients with cerebral small vessel disease. *Neurology* 2020; **94:** e2258–69.
26 Liem MK, Lesnik Oberstein SA, Haan J, et al. Cerebrovascular reactivity is a main determinant of white matter hyperintensity progression in CADASIL. *AJNR Am J Neuroradiol* 2009; **30:** 1244–47.
27 Kopczak A, Stringer MS, van den Brink H, et al. The EffecTs of Amlodipine and other Blood PREssure Lowering Agents on Microvascular FuncTion in Small Vessel Diseases (TREAT-SVDs) trial: study protocol for a randomised crossover trial. *Eur Stroke J* 2023; **8:** 387–97.
28 Blair GW, Stringer MS, Thrippleton MJ, et al. Imaging neurovascular, endothelial and structural integrity in preparation to treat small vessel diseases. The INVESTIGATE-SVDs study protocol. Part of the SVDs@Target project. *Cereb Circ Cogn Behav* 2021; **2:** 100020.
29 Jones B, Kenward MG. Design and analysis of cross-over trials. New York, NY: CRC Press, 2014.
30 Marcus R, Eric P, Gabriel KR. On closed testing procedures with special reference to ordered analysis of variance. *Biometrika* 1976; **63:** 655–60.
31 Peters SA, Bots ML, den Ruijter HM, et al. Multiple imputation of missing repeated outcome measurements did not add to linear mixed-effects models. *J Clin Epidemiol* 2012; **65:** 686–95.
32 Bates D, Mächler M, Bolker B, Walker SC. Fitting linear mixed-effects models using lme4. *J Stat Softw* 2015; **67:** 1–48.
33 Nasrallah IM, Pajewski NM, Auchus AP, et al. Association of intensive vs standard blood pressure control with cerebral white matter lesions. *JAMA* 2019; **322:** 524–34.
34 Goldstein ED, Wolcott Z, Garg G, et al. Effect of antihypertensives by class on cerebral small vessel disease: a post hoc analysis of SPRINT-MIND. *Stroke* 2022; **53:** 2435–40.
35 McKetton L, Sobczyk O, Duffin J, et al. The aging brain and cerebrovascular reactivity. *Neuroimage* 2018; **181:** 132–41.
36 King A, Serena J, Bornstein NM, Markus HS. Does impaired cerebrovascular reactivity predict stroke risk in asymptomatic carotid stenosis? A prospective substudy of the asymptomatic carotid emboli study. *Stroke* 2011; **42:** 1550–55.
37 Portegies ML, de Bruijn RFAG, Hofman A, Koudstaal PJ, Ikram MA. Cerebral vasomotor reactivity and risk of mortality: the Rotterdam Study. *Stroke* 2014; **45:** 42–47.
38 Sam K, Crawley AP, Conklin J, et al. Development of white matter hyperintensity is preceded by reduced cerebrovascular reactivity. *Ann Neurol* 2016; **80:** 277–85.
39 Schiffrin EL, Park JB, Intengan HD, Touyz RM. Correction of arterial structure and endothelial dysfunction in human essential hypertension by the angiotensin receptor antagonist losartan. *Circulation* 2000; **101:** 1653–59.
40 Olsen MH, Fossum E, Høieggen A, et al. Long-term treatment with losartan versus atenolol improves insulin sensitivity in hypertension: ICARUS, a LIFE substudy. *J Hypertens* 2005; **23:** 891–98.
41 Christensen KL, Mulvany MJ. Vasodilatation, not hypotension, improves resistance vessel design during treatment of essential hypertension: a literature survey. *J Hypertens* 2001; **19:** 1001–06.
42 Bakris G, Ali W, Parati G. ACC/AHA versus ESC/ESH on hypertension guidelines: JACC guideline comparison. *J Am Coll Cardiol* 2019; **73:** 3018–26.