Full Study Title: A Calcium channel or Angiotensin converting enzyme inhibitor/ Angiotensin receptor blocker Regime to reduce Blood pressure variability in acute ischaemic Stroke (CAARBS): A Feasibility Trial

Sponsor Reference No: 0611

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Sponsor:	University of Leicester
Funder:	British Heart Foundation/ Stroke Association (TSA BHF 2012/01)
Signatures:	The approved protocol should be signed by author(s) and/or person(s) authorised to sign the protocol

Confidentiality Statement

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(in cases of Multi-centre studies, this must be replicated for each site)

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1. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1 (pre-approval)	1.1	11 Sept 2017	Will Davison	Addition of ethics reference number. Removal of "participants who intend to donate blood during the study" from the exclusion criteria in response to REC review. Updated Safety Reporting section 10.3 in response to MHRA comments.
SA01	2.0	20 July 2018	Will Davison	Participant inclusion criteria amended to increase the window of eligibility from <72 hours from symptom onset to up to 7 days from symptom onset.

2. SYNOPSIS

Study Title	A Calcium channel or Angiotensin converting enzyme inhibitor/ Angiotensin receptor blocker Regime to reduce Blood pressure variability in acute ischaemic Stroke (CAARBS): A Feasibility Trial
Internal ref. no.	0611
Clinical Phase	Phase IV
Trial Design	Prospective Randomised Open-Label Blinded Endpoint Feasibility Study
Trial Participants	Mild to moderate acute ischaemic stroke (NIHSS <10) or clinically definite transient ischaemic attack (TIA) patients within 7 days of symptom onset and with blood pressure >130/80
Planned Sample Size	150
Follow-up duration	3 months
Planned Trial Period	15 months
Primary Objective	Feasibility: A screening log of all patients referred to the stroke services will be collected, and the reasons for non-inclusion in the study recorded.
Secondary Objectives	Feasibility Blood pressure variability: Changes in blood pressure variability from baseline to 21 (±7) days and 90 (±14) days by treatment arm. Compliance: Treatment compliance rates for each randomisation arm will be reported. Completion of and failure rates for BPV measurements at days 21 (±7) and 90 (±14) will be reported. Safety Serious adverse events, including recurrent TIA/ stroke, MI, other systemic embolic events, death and hospital re-admission will be recorded up to 3 months. Treatment discontinuation rates and reasons recorded.
Primary Endpoint	Day 90 modified Rankin score.
Secondary Endpoints	*Early (14 (±7) days)* Modified Rankin score National Institutes of Health Stroke Scale score Mean blood pressure Blood pressure variability *Late (90 (±14) days)* Montreal cognitive assessment score Mean blood pressure Blood pressure variability
Investigational Medicinal Products	Calcium channel blocker (e.g. Amlodipine 5-10mg od), at the discretion of the treating clinician Angiotensin converting enzyme inhibitor (e.g. Lisinopril 10-20mg od), at the discretion of the treating clinician Angiotensin receptor blocker (e.g. Candesartan 8-16mg od), at the discretion of the treating clinician
Form	Tablet

Dose	Amlodipine 5-10mg od, Lisinopril 10-20mg od, Candesartan 8-16mg od
Route	*Oral*

3. ABBREVIATIONS

ABPM	Ambulatory blood pressure monitoring
ACEI	Angiotensin converting enzyme inhibitor
AE	Adverse event
AR	Adverse reaction
ARB	Angiotensin receptor blocker
BB	Beta blocker
BP	Blood pressure
BPV	Blood pressure variability
BRS	Baroreceptor sensitivity
CCB	Calcium channel blocker
CI	Chief Investigator
CRA	Clinical Research Associate (Monitor)
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Clinical Trials
CTA	Clinical Trials Authorisation
DSMC	Data Safety Monitoring Committee
EC	Ethics Committee (see REC)
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
GP	General Practitioner
GTAC	Gene Therapy Advisory Committee
HRA	Health Research Authority
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
IMP	Investigational Medicinal Products
MoCA	Montreal Cognitive Assessment
MiND-B	Motor Neurone Disease Behaviour Scale
MHRA	Medicines and Healthcare products Regulatory Agency
mRS	Modified Rankin score
NHS	National Health Service
NIHSS	National Institutes of Health Stroke Scale
NRES	National Research Ethics Service
PI	Principal Investigator
PIL/S	Participant/ Patient Information Leaflet/Sheet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event

SAR	Serious Adverse Reaction
SBP	Systolic blood pressure
SmPC/SPC	Summary of Products Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TIA	Transient ischaemic attack
TMF	Trial Master File

4. BACKGROUND AND RATIONALE

Stroke and Hypertension Stroke is one of the leading causes of death and disability in the developed world. Hypertension is a major modifiable risk factor for stroke, and raised blood pressure (BP) is common after acute stroke with at least 75% of patients having a systolic BP (SBP) >130mmHg at hospital admission [1,2]; <130mmHg being the SBP target for secondary prevention following stroke [3]. Increased post-stroke BP is associated with poor prognosis [4,5], and might be caused by raised intracranial pressure [6], increased sympathetic nervous system activity [7], abnormal baroreceptor sensitivity (BRS) [8], haematoma expansion [9], cerebral oedema [10], and a white-coat response [11]. A spontaneous BP decrease usually occurs 4 to 10 days after stroke [12], but substantial BP reductions can be associated with cerebral hypoperfusion as a consequence of post-stroke dysautoregulation [13]. We have previously reported that both increased 24-hour [14] and beat-to-beat BP [15] levels following acute stroke are associated with a poor prognosis. Subsequently, data from the International Stroke Trial has suggested a U-shaped relation between baseline SBP (within 48 hours of stroke) and short- (14-day mortality) and long-term (6-month death and dependency) outcomes; the lowest risk of death and dependency was at SBP of 150mmHg [16]. In addition, neurological deterioration up to 3 weeks may be associated with early systolic hypertension; a study of 565 ischaemic stroke patients showing that SBP initially decreased over 6 hours in all patients, but those with neurological deterioration had higher SBP levels thereafter up to 36 hours post ictus [17]. There is limited and again conflicting evidence regarding acute stroke hypertension treatment per se. Data from RCTs suggest that BP can be safely reduced after the acute stroke period [18-23], and can improve long-term mortality [20] and reduce recurrent vascular events [18]. However, the recently published SCAST trial concluded that there was no indication that careful BP-lowering treatment with an angiotensin-receptor blocker (ARB) was beneficial in hypertensive acute stroke patients, and may be harmful with a non-significant increased risk of poor 6-month functional outcome (adjusted common odds ratio 1.17, 95% Confidence Intervals 1.00 to 1.38) [23]. However, this may reflect that only a small BP reduction was achieved (5/2mmHg), with treatment initiated too late after stroke onset (18 hours) in a mild stroke population (Scandinavian Stroke Scale score 41). Therefore, current Cochrane meta-analyses [24,25] and several international guidelines [26-30] state that optimal BP management in the context of hyperacute stroke remains uncertain.

Blood pressure variability and vascular risk There may be alternative explanations for the lack of a definite conclusion with regards to the prognostic implications of elevated BP and its therapeutic reduction following acute stroke. An attractive and topical hypothesis relates to BP variability (BPV), which is eloquently explored in a recent review article [31]. BPV can be defined in a number of ways. Typically, the standard deviation (SD) or coefficient of variation (CV: SD/ mean), which standardises for the absolute BP level, are reported. However, CV is often correlated with mean BP, and therefore variation independent of the mean (VIM: SD/ mean^{x}) can be derived. Furthermore, BPV is often reported over a period of time, particularly in the context of therapeutic interventions to reduce absolute BP, and therefore techniques, such as the average absolute difference between successive values (average successive variability, ASV), can be used to minimise the effect of trends [32]. Of course, to be of practical use in everyday clinical management, the definition of BPV used must be easily calculated, and of meaning to the clinician and patient.

Nonetheless, current guidelines for hypertension treatment predominantly focus on usual BP, defining a threshold for the initiation of therapy and target reduction to maximise the reduction in future stroke and other cardiovascular events. However, this does ignore the potential importance of BPV, which is dismissed as random and merely an obstacle to the reliable estimation of usual BP. Though guidelines recommend that 24-hour or home BP monitoring is used in patients with variable clinic BP, mean BP can still vary substantially even on repeated 24-hour BP monitoring [33,34]; the extent of which is associated with visit-to-visit variability in clinic BP [32]. Indeed, there are many examples to support the potential importance of BPV for vascular risk [32]. Firstly, the predictive value of estimated usual SBP and stroke risk falls with age [35], yet stroke incidence is well established to rise with age, and indeed the relative benefit of antihypertensive therapy is maintained in the elderly [36]. Secondly, the mid-morning surge in stroke risk transposes almost

exactly onto the diurnal BPV. However, whilst an increasing morning surge in BP is predictive of stroke, it is poorly associated with mean BP [37]. Thirdly, other causes of transient hypertension are recognised triggers of vascular events, including sympathetic overactivity and orthostatic hypertension [38]. Fourthly, in the majority of studies, there is no threshold of baseline SBP below which vascular risk stops falling [35,39]; with antihypertensive therapy reducing risk even at 'normal' baseline systolic BP [40]. Fifthly, 'white-coat' hypertension, a common example of situational BPV, is associated with long-term target organ damage independent of mean BP [41]. Sixthly, though hypertension is a recognised risk factor for vascular dementia, there is limited evidence of reduced dementia risk in trials of antihypertensive therapy. However, a trial of calcium channel blockers (CCB), which have the most consistent effect on reducing BPV [42,43], has shown a substantial reduction in the incidence of dementia [44]. Finally, specific group differences in stroke risk are not accounted for by mean BP alone, for example in black individuals [45].

Blood pressure variability and stroke In a retrospective analysis of RCTs in a TIA population, which included the UK-TIA, ESPS-1, Dutch TIA and ASCOT-BPLA trials, visit-to-visit intra-individual BPV was a risk factor for stroke independent of the mean 'absolute' BP level, and perhaps of greater significance [32]. Rothwell and colleagues also reported that within-visit SBPV, based on casual BP measurements, was correlated with visit-to-visit SBPV, but was a weak predictor of future vascular events [32]. Importantly, in a separate analysis of the UK-TIA data, as well as the European Carotid Surgery Trial, Howard and Rothwell reported that BPV was reproducible (i.e. those patients with the highest and lowest variability was consistent over time) and independent of confounding factors, including seasonal variation, randomisation to therapeutic intervention, and variation according to day and time of measurement [46]. Increased BPV may also be an important predictor of short-term outcome following acute stroke, though the data are limited. Robinson and colleagues have shown that beat-to-beat SBPV was greater in acute stroke compared to controls [47], and that high mean arterial and diastolic beat-to-beat BPV was associated with a worse prognosis [15]. Furthermore, in a post hoc analysis of the TAIST study, high SBPV using casual BP readings was associated with an increase in death or early neurological deterioration at day 10 [48]. In addition, a post hoc analysis of the INTERACT2 study demonstrated that increased systolic BPV, defined as maximum systolic BP in the hyperacute period or by standard deviation in the acute period, was associated with increased 90-day death and disability (modified Rankin score $\geq$3) [49]. However, a retrospective analysis of nearly 1,000 patients in the COSSACS and CHHIPS trials did not demonstrate a significant association between SBPV based on 2 sets of 3 casual BP readings within 48 hours of ischaemic or haemorrhagic stroke onset and 2-week death and dependency [50]. Overall, a recent systematic review and meta-analysis reported that increased SBPV, measured early from ischaemic and haemorrhagic stroke onset, was associated with poor long-term functional outcome [51]. Nonetheless, there is further scope to explore the relationship between BPV and outcome following acute stroke, and in particular the applicability of different techniques of measuring BPV and its definition, as well as the natural history of BPV after acute stroke, and this forms the basis of an on-going work programme by the principal investigators of the proposed trial.

Importantly, would a further understanding of BPV following acute stroke have implications for therapeutic management, particularly in the immediate post-stroke period? Rothwell's group have explored the differential effects of BP-lowering therapies on BPV in a hypertensive population [42,43]. Though clinical benefits with reduction in risk of stroke and coronary events were seen for all classes of antihypertensive agent, class-specific effects existed; CCBs reduce stroke risk to a greater extent than expected from mean SBP reduction alone, and beta-blockers (BB) to a smaller extent. A detailed analysis of the ASCOT-BPLA, comparing an amlodipine- versus atenolol-based regime, and the MRC trial, comparing an atenolol- versus diuretic-based regime, reported opposite effects of CCB and BB on SBPV. In addition, this differential effect accounted for the disparity in observed effects on stroke risk and observed effects on mean SBP [43]. This was confirmed in a systematic review and meta-analysis of 389 RCTs; Webb and colleagues reporting that SBPV was significantly reduced by CCB and non-loop diuretic drugs, but increased by angiotensin-converting enzyme inhibitors (ACEI), ARB and BB [42]. Again, the effects on SBPV were correlated with effects on stroke risk independent of differences in mean SBP [42]. The potential differential effect of antihypertensive drug classes on BPV is possibly important after acute stroke, where normal cardiovascular autonomic and cerebrovascular autoregulatory pathways are impaired. BRS is

important in the short-term regulation of the cardiovascular system, including BP, and is known to be impaired following acute ischaemic stroke [52], and associated with poor short- and long-term prognosis [53]. In addition, it is well established that cerebral autoregulation (CA) is impaired, particularly following moderate to severe stroke [13]. As a consequence, cerebral perfusion is pressure-dependent, and therefore hypertensive episodes related to increased BPV may contribute to reperfusion injuries, for example post-ischaemic oedema and/ or intracerebral haemorrhage (ICH). Conversely, hypotensive episodes associated with increased BPV in the presence of impaired CA may lead to secondary ischaemia, particularly in the absence of a good collateral circulation. Indeed, further information about the effect of different classes of antihypertensive therapy on acute stroke BPV may inform current guidelines. For example, labetalol, a combined beta- and alpha-blocker, is recommended in a number of guidelines for emergency acute stroke BP management, particularly in the context of thrombolysis. Therefore, there may be concerns regarding its use, particularly its potential adverse effect on BPV, though a post hoc analysis of the CHHIPS trial did not report an increase in SBPV with labetalol compared to lisinopril or placebo in antihypertensive-naive patients treated within 36 hours of stroke onset [54].

Summary In conclusion, increased BPV is associated with vascular risk independent of mean BP, and commonly used antihypertensive agents have different class effects on BPV which may in part explain the overall differential effects on stroke risk for similar absolute reductions in mean BP in a hypertensive population. A practical method of defining and monitoring BPV in routine clinical practice needs to be derived, so that a strategy of reducing BPV as well as absolute BP level to reduce recurrent stroke and other cardiovascular events in a high risk stroke and TIA population can be assessed in an RCT of a CCB versus ACEI/ ARB-based regime.

5. OBJECTIVES

5.1 Primary Objective

In this feasibility study, patient recruitment and reasons for non-eligibility will be recorded. Accordingly, a screening log of all patients referred to the stroke services will be collected, and the reasons for non-inclusion in the study recorded.

5.2 Secondary Objectives

In this feasibility study, the following secondary feasibility and safety objectives will be recorded:

Feasibility

Blood pressure variability: Changes in blood pressure variability from baseline to 21 (±7) days and 90 (±14) days by treatment arm.

Compliance: Treatment compliance rates for each randomisation arm will be reported. Completion of and failure rates for BPV measurements at days 21 (±7) and 90 (±14) will be reported.

Safety

Serious adverse events, including recurrent TIA/ stroke, MI, other systemic embolic events, death and hospital re-admission will be recorded up to 3 months.

Treatment discontinuation rates and reasons recorded.

5.3 Exploratory End Point (where applicable)

In a future definitive randomised controlled trial, the proposed primary outcome will be day 90 modified Rankin score. Therefore, this exploratory end point will be justified to support a future powers analysis for a definitive RCT.

6. STUDY DESIGN

6.1 Summary of Trial Design

Prospective Randomised Open-Label Blinded Endpoint Feasibility Study.
An estimated 150 first-ever clinically definite TIA and ischaemic stroke patients (mild to moderate severity with NIHSS <10) referred to and assessed by the in- and/ or out-patients stroke services in Leicester, Norwich and Oxford within 7 days of symptom onset will be randomised by a computer-based system to a CCB- or ACEI/ ARB-based treatment regime, with baseline, 3-week and 3-month post-randomisation visits.

6.2 Primary and Secondary Endpoints/Outcome Measures

In this feasibility study, the proposed primary and secondary feasibility and safety outcomes have been previously described. In addition, the proposed primary and secondary endpoints for a future definitive RCT will be assessed. These include:

The proposed primary endpoint is 90-day modified Rankin score.

The proposed secondary endpoints are:

Early (21 (±7) days)
Modified Rankin score
National Institutes of Health Stroke Scale score
Mean blood pressure
Blood pressure variability

Late (90 (±14) days)
Montreal cognitive assessment score
Mean blood pressure
Blood pressure variability

7. TRIAL PARTICIPANTS

7.1 Overall Description of Trial Participants

An estimated 150 first-ever clinically definite TIA and ischaemic stroke patients (mild to moderate severity with NIHSS <10) referred to and assessed by the in- and/ or out-patients stroke services in Leicester, Norwich and Oxford within 7 days of symptom onset.

7.2 Inclusion Criteria

Age >18 years;
First-ever clinically definite TIA and ischaemic stroke patients (NIHSS <10);
Within 7 days of symptom onset;
BP >130/80;
Ability to comply with randomly assigned BP-lowering regime and BP measurements;
Able to understand written and verbal English;
Able to give informed consent;
Willing to allow his or her General Practitioner and consultant, if appropriate, to be notified of participation in the study.

7.3 Exclusion Criteria

The participant may not enter the study if ANY of the following apply:
Known definite contra-indication to BP-lowering regime or therapeutic agents;
Swallowing difficulties which would preclude the taking of oral medication;
Definite indication for BB, CCB, ACEI or ARB therapy;
Significant pre-stroke dependency (mRS >3);
Co-existing life-threatening condition with life expectancy <3 months;
Previous participation in this trial or current participation in another investigational drug trial;
Atrial fibrillation;
Female participants who are pregnant, lactating or planning pregnancy during the course of the study;
Unable to understand written and verbal English;
Cannot give informed consent.

8. STUDY PROCEDURES

8.1 Informed Consent

The participant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed.

Written and verbal versions of the participant information and Informed consent will be presented to the participants detailing no less than: the exact nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

Once they have received the PIS the participant will be allowed up to 4 hours to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator as detailed on the Delegation of Authority and Signature log for the study. The original signed form will be retained at the study site within the Trial Master File (TMF) or Investigator Site File (ISF). A copy of the signed Informed Consent will be given to participants and a copy retained in the participant medical notes.

8.2 Screening and Eligibility Assessment

First-ever TIA and minor ischaemic stroke patients referred to and assessed by the in- and/ or out-patients stroke services in Leicester, Norwich and Oxford within 7 days of symptom onset will be identified by the treating clinician and/ or the research team. If the patient provides verbal consent to be considered for the study then their medical records will then be assessed against the study inclusion and exclusion criteria. Where the potential participant is eligible then research staff will approach the individual to discuss the study in more detail and seek written consent, as described in Section 8.1.

8.3 Baseline Assessments

Following written consent, the following baseline details will be documented from the medical notes and by participant interview:

Demographics

The date of birth, sex, ethnicity, smoking and drinking habits will be recorded.

Medical History

Details of any history of the following diseases will be recorded: hypertension, hypercholesterolaemia, ischaemic heart disease, peripheral vascular disease, diabetes. Participants with prior stroke and atrial fibrillation are excluded from the study. Details of any family history of ischaemic heart disease, stroke, hypertension, and hypercholesterolaemia will also be recorded.

Concomitant Medication

All over-the-counter or prescription medication will be recorded on the study CRF.

Physical Examination

Height and weight will be recorded.

Baseline casual BP and heart rate will be calculated in all patients as a mean of two sets of three supine brachial BP readings taken 10 minutes apart, using a UA767 BP

monitor (enhanced casual BP). Patients with BP <130/80 will be excluded.
Additional blood pressure measurements will include beat-to-beat measurement and daytime ABPM. Three consecutive periods of 10-min beat-to-beat non-invasive BP monitoring in the supine position using the middle finger of the non-hemiparetic hand will be recorded with a Finometer device. The servo adjust mechanism of the Finometer will be switched off during the recording period, but applied at 10-minute intervals during the monitoring period. Daytime ABPM will be performed using a Spacelabs-90207 recorder, programmed to record BP at 20-minute intervals. Daytime is defined as between 0700-2200 hours.
Baseline NIHSS, mRS (including premorbid), MoCA, Albert's line test, MiND-B and GDS assessments will be recorded.
In addition, on the basis of clinical examination and/ or investigation, all participants will be classified according to the Oxfordshire Community Stroke and TOAST classifications.

ECG Test
A 12-lead ECG, undertaken as part of routine clinical care, will be reviewed, and recorded in the CRF. This will include the results of a 24-hour ECG, if undertaken as part of the stroke work-up.

Laboratory Tests
The results of all laboratory investigations, undertaken as part of routine clinical care, will be reviewed, and recorded in the CRF. These will include haematology (full blood count, clotting), and biochemistry (urea, electrolytes, creatinine, estimated glomerular filtration rate, total cholesterol, random glucose).

Radiology / Imaging Procedures
The results of all imaging investigations, undertaken as part of routine clinical care, will be reviewed, and recorded in the CRF. These will include neuroimaging (CT or MRI), vascular ultrasound (carotid ultrasound) and cardiac imaging (transthoracic, or transoesophageal echocardiography, 'bubble' test).

8.4 Randomisation and Codebreaking (if applicable)

After the baseline assessments eligible patients will be randomised at the baseline visit to a CCB (e.g. Amlodipine 5mg) or ACEI/ ARB-based (e.g. Lisinopril 10mg, Candesartan 8mg) regime by a computer-based system. The study treatment will be dispensed at the baseline visit, with the actual therapeutic agent used being at the discretion of the treating clinician, but dictated by the class of therapy that the participant is assigned to. Prescription of the medication will be done by the treating clinician and the initial supply will be dispensed by the treating hospital or community pharmacy in accordance with the hospital's policy for providing discharge or out-patient medication. Further supplies will be provided by the participant's GP. Randomisation will be stratified by Centre and by diagnosis; with other potential factors influencing treatment outcome, including Age ($\leq$80 years, >80 years) and baseline BP included in the statistical analysis. Subject numbers will be assigned sequentially as each subject enters the study. Unblinding will not be necessary as this is a prospective, randomised, open-label study design.

8.5 Subsequent Assessments

Follow-up assessments will be undertaken at the following time-points in the trial centre or where the patient is resident at the time (including the hospital ward, rehabilitation facility, or their own home):

Day 21 ($\pm$ 7 days)
Specific baseline assessments will be repeated, including casual BP and beat-to-beat BP measurements, NIHSS and mRS scores, and recording of concomitant medications. In addition, treatment compliance will be recorded. Serious Adverse

Events, including recurrent TIA/ stroke, MI, other systemic embolic events, death and hospital re-admission will be recorded up to 3 weeks. In those patients failing to reach BP target of <130/ 80mmHg, the medical assessor at the follow-up visit will advise about altering BP-lowering treatment and this will be communicated to the participant's GP. The first-line change will be to increase the study regime medication (i.e. CCB or ACEI/ARB) to twice the starting dose: e.g. to amlodipine 10mg (CCB group) or Lisinopril 20mg/ candesartan 16mg (ACEI/ ARB group). If the patient is on the maximum dose of the study regime medication already, then the second-line change will be to add a thiazide-like diuretic. If a third-line change is required then Spironolactone or an alpha-blocker will be added to the combination of study medication and thiazide-like diuretic. Renal function (urea, electrolytes and creatinine) will be repeated in the ACEI/ ARB group prior to treatment continuation and/ or dose adjustment.

Day 90 (± 14 days)
Specific baseline assessments will be repeated, including casual BP measurements, beat-to-beat BP measurements, daytime ABPM, NIHSS and mRS score, MoCA, Albert's line test, MiND-B, GDS, and recording of concomitant medications. This will be recorded by a member of the research team blinded to the patient's treatment group. Treatment compliance will again be recorded. Serious Adverse Events, including recurrent TIA/ stroke, MI, other systemic embolic events, death and hospital re-admission will be recorded up to 3 months. Subsequently, BP-lowering therapy will be at the discretion of the treating clinician, but it is anticipated that this will conform to national guidelines.

8.6 Definition of End of Trial

The end of trial is the date of the last visit of the last participant.

8.7 Discontinuation/Withdrawal of Participants from Study Treatment

Each participant has the right to withdraw from the study at any time. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:
Ineligibility (either arising during the study or retrospective having been overlooked at screening);
Significant protocol deviation;
Significant non-compliance with treatment regimen or study requirements;
An adverse event which requires discontinuation of the study medication or results in inability to continue to comply with study procedures;
Specified outcome event (i.e. recurrent TIA, stroke, myocardial infarction, or other systemic embolic event);
Disease progression which requires discontinuation of the study medication or results in inability to continue to comply with study procedures;
Loss of capacity preventing ongoing compliance with the study procedures or follow-up;
Consent withdrawn;
Lost to follow up.

The reason for withdrawal will be recorded in the CRF.

If the participant is withdrawn due to an adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

8.8 Source Data

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised

into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

9. TREATMENT OF TRIAL PARTICIPANTS

9.1 Description of Study Treatment & Pharmacy Process

Study treatment will be at the discretion of the treating clinician within the drug class that the participant has been randomised to, i.e. CCB or ACEI/ ARB.

9.2 Storage of Study Treatment

Study treatment will be stored under SmPC recommended conditions in the hospital or community pharmacy, in the participant's locker (for hospitalised patients) and at the participant's home (for discharged patients).

9.3 Compliance with Study Treatment

The participants will be instructed to return all unused or part-used medication at each visit. The Investigator may withdraw the participants if they consider dose compliance is unsatisfactory. Compliance will be assessed by tablet count undertaken by study research staff.

9.4 Accountability of the Study Treatment

The study medication will be supplied by the hospital or community pharmacy. The Investigator will use a standard prescription form. The participant will be asked to bring all unused medication back to the clinic at each visit where it will be returned to pharmacy.

9.5 Concomitant Medication

Throughout the study Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in the exclusion criteria. If these are required, the participant will be withdrawn. Any medication, other than the study medication taken during the study will be recorded in the CRF.

10. SAFETY REPORTING

10.1 Definitions

10.1.1 Adverse Event (AE)

An AE or adverse experience is:

Any untoward medical occurrence in a patient or clinical investigation participants administered a medicinal product, which does not necessarily have to have a causal relationship with this treatment (the study medication).

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the study medication, whether or not considered related to the study medication.

10.1.2 Adverse Reaction (AR)

All untoward and unintended responses to a medicinal product related to any dose.

The phrase "responses to a medicinal product" means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions.

10.1.3 Severe Adverse Events

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

10.1.4 Serious Adverse Event or Serious Adverse Reaction

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events*

*Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

10.1.5 Expected Serious Adverse Events/Reactions

A list of expected serious adverse events/ reactions following acute ischaemic stroke/ TIA is listed in appendix B. A list of expected serious adverse events/

reactions from study medication will be listed in the summary of product characteristics.

10.1.6 Suspected Unexpected Serious Adverse Reactions
A serious adverse reaction, the nature or severity of which is not consistent with the applicable product.

10.2 Reporting Procedures for All Adverse Events
AEs will not be recorded during this feasibility study.

10.3 Reporting Procedures for Serious Adverse Events
All SAEs will be recorded in keeping with GCP recommendations and must be reported to the sponsor within 24 hours of discovery or notification of the event. The Sponsor will perform an initial check of the information and ensure that it is reviewed at the next R&I Management meeting. All SAE information must be recorded on an SAE form and sent to the Sponsor. Additional information received for a case (follow-up or corrections to the original case) needs to be detailed on a new SAE form and sent to the Sponsor. SAE's that are expected, as defined in section 10.1.5, do not require expedited reporting. However, where an SAE listed in appendix B is suspected to be related to the IMP and is not listed in the SmPC, this will be treated as a SUSAR and will be subject to expedited reporting.
The Sponsor will report all SUSARs to the Competent Authorities (MHRA in the UK) and the Research Ethics Committee concerned. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days. The CI will inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.
In addition to the expedited reporting above, the CI shall submit once a year throughout the clinical trial or on request a Developmental Safety Update Report to the Competent Authority (MHRA in the UK) and Ethics Committee.

11. STATISTICS

11.1 Description of Statistical Methods

Assessment of feasibility will focus on recruitment and retention rates. The total numbers of patients screened and the proportion recruited will be determined. Reasons for ineligibility and non-inclusion will be analysed. The proportion of participants completing follow-up will also be determined and reasons for withdrawal will be analysed.

The feasibility of determining BPV will be assessed by the proportion of participants having all BP measurements recorded successfully. Inter-individual systolic, mean and diastolic BPV will be expressed as the SD, CV, VIM, and ASV calculated from all BP measurements: enhanced casual, beat-to-beat measurements (each 10 minute recording and the total 30 minute recording), and daytime ABPM measurements. Changes in BPV from baseline to the follow-up time-points will be analysed.

Treatment effect will be analysed by changes in BPV stratified according to treatment arm. Comparison of BPV according to baseline diagnosis (stroke vs. TIA) will also be compared. Mean BP will also be calculated from enhanced casual measures. Differences in mean BP at each time-point will be analysed and stratified according to treatment arm. Effect on stroke outcome will be assessed by changes in mRS, NIHSS, MoCA, Albert's line test, MiND-B questionnaire and GDS at each time-point.

11.2 The Number of Participants

A feasibility study of 150 patients (64 patients per group with a 15% drop-out rate) will have an 80% power at the 5% significance level of detecting an 8mmHg difference in SBPV between the CCB and ACEI/ ARB-based regimes, assuming a mean SBPV SD of 14.97mmHg in the CCB arm and 16.95mmHg in the ACEI arm [42].

11.3 The Level of Statistical Significance

The standard level of statistical significance, at 5%, will be used for statistical analyses undertaken in this study.

11.4 Criteria for the Termination of the Trial.

The study will be terminated after the recruitment of 150 patients or the current end period of funding by the British Heart Foundation/ Stroke Association (November 2018), though consideration will be given for application for a no-cost extension, if required.

11.5 Procedure for Accounting for Missing, Unused, and Spurious Data.

No interpolation will be used for missing data.

11.6 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan will be described and justified in protocol in the final report.

11.7 Inclusion in Analysis

All randomised patients will be included in the statistical analysis, on an intention-to-treat basis. Additional statistical analyses will be undertaken on the per protocol population.

12. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

13. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

Regular monitoring will be performed according to ICH GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

The Trial Management Group will meet on a monthly basis by teleconference, and include Professor Robinson (CI), Professors Potter and Rothwell (Co-CIs) and Dr Davison (Clinical Research Fellow).

Details of the Trial Steering, and Data and Safety Monitoring Committees are provided in Section 16.

14. CODES OF PRACTICE AND REGULATIONS

14.1 Ethics

Participant consent must be in place before the undertaking of any research project-specific assessments, using the current version of the information sheet and consent form approved by the National Research Ethics Service and local Research Departments. Due to the nature of acute stroke some patients who are admitted during the study period will be too unwell to consent, or may have specific difficulties such as speech disturbance which prevents them from providing consent, We have specified that we will only recruit patients with mild to moderate severity stroke (NIHSS <10) and we will not use relative assent or proxy consent to recruit patients who cannot consent for themselves.

The proposed study medications are antihypertensives and are expected to lower BP of participants. In line with accepted stroke guidelines we will only recruit patients with uncontrolled BP (>130/ 80) who would otherwise require antihypertensive treatment for secondary stroke prevention. Medications that inhibit the renin-angiotensin system are known to potentially cause kidney dysfunction in patients with unrecognised renal artery stenosis. To ensure the safety of patients commenced on these medications a blood test for kidney function will be done at the 2 to 4-week follow-up which is in keeping with standard practice.

Multiple BP measurements are required to establish BPV. To minimise any disturbance to participants we will use enhanced casual measurements (multiple measurements using a standard BP cuff and machine) and beat-to-beat measurements, which are more acceptable than some other methods.

14.2 Sponsor Standard Operating Procedures

All relevant Sponsor SOPs will be followed to ensure that this study complies with all relevant legislation and guidelines

14.3 Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004).

14.4 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

14.5 Approvals

Once Sponsor authorisation has been confirmed, the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities (MHRA and HRA in the UK), and host institution(s) for written approval. The Investigator will comply with the requirements of annual and end-of-trial reports to the REC.

Once Sponsor authorisation has been confirmed, the Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

14.6 Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF

and any electronic database. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

14.7 Other Ethical Considerations

Only participants able to provide written consent will be included in this feasibility study.

15. DATA HANDLING AND RECORD KEEPING

All Investigators and staff involved with this study will comply with the requirements of the General Data Protection Regulation (2018)/Data Protection Act (2018) with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles

Study data will initially be entered onto a standardised paper CRF and will only be collected once informed consent has been obtained from the participant. All documents will be stored in a secure location. Study data will subsequently be transferred onto a password protected, computer-based data management system at each centre. With the exception of the signed consent form the participant will be identified by a study specific participant's number and/ or code on any paperwork and in any database. The name and any other identifying detail will NOT be included in any study data files. Anonymised data will be subsequently entered on a dedicated and secure database held at the University of East Anglia.

Statistical analysis will be undertaken by the Project Statistician using appropriate statistical software in conjunction with input from the research team. Only anonymised data in encrypted format will be transferred from study centres to the Project Statistician.

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

Study data will be retained and stored at the University of Leicester for 15 years from study completion in accordance with standard requirements

16. STUDY GOVERNANCE

16.1 Trial Steering Committee (TSC)

The Trial Steering Committee (TSC) will meet prior to study start-up and then at a minimum of 6-monthly intervals during the course of the study, either by face-to-face or teleconference meetings.

Membership will comprise: TBC (Chair; voting member); Professor David Werring, Professor of Clinical Neurology, University College London (Independent Clinician; voting member); TBC (Independent Clinician; voting member); TBC (statistican); TBC (Sponsor representative); Dr Kate Holmes, Assistant Director of Research, Stroke Association (Funder representative); TBC (PCPIE representative); Professor Tom Robinson, Professor of Stroke Medicine, University of Leicester (Chief Investigator); Professor John Potter, Professor of Ageing and Stroke Medicine, University of East Anglia (Co-Chief Investigator); Professor Peter Rothwell, Professor of Clinical Neurology, University of Oxford (Co-Investigator); Dr Will Davison, Clinical Research Fellow, University of East Anglia (Clinical Research Fellow).

The TSC Charter, including Terms of Reference, will be approved at the initial TSC meeting, but the key items will include:

- To provide advice, through its Chair, to the Trial Management Group (TMG), the Sponsor and the Trial Funder on all aspects of the trial.
- To monitor and supervise the progress of the trial towards its overall objectives, review accrual and results of the trial, adherence to the protocol, patient safety and the consideration of new information of relevance to the trial and the research question.
- To ensure that the rights, safety and wellbeing of the trial participants are the most important considerations and should prevail over the interests of science and society.
- To ensure that all relevant approvals are obtained before a project begins.
- To agree proposals for substantial protocol amendments and provide advice to the TMG regarding approvals of such amendments.
- To consider the recommendations of Ethics committees, the trial DSMC and/or other trial committees where appropriate.
- The TSC (in conjunction with recommendations from the DSMC where appropriate) should inform the TMG if:
    - There are concerns about the safety of participants
    - Accrual is too low to provide meaningful results
    - It is evident that if the study continues it would fail to provide a clear benefit
    - To recommend whether to continue or terminate the study or further adapt it based on safety and efficacy considerations.

16.2 Data Safety Monitoring Committee (DSMC)

The Data Safety Monitoring Committee (DSMC) will meet prior to study start-up and then at a minimum of 12-monthly intervals during the course of the study, either by face-to-face or teleconference meetings.

Membership will comprise: Professor Richard McManus, Professor of Primary Care, University of Oxford (Chair); Professor Christine Roffe, Professor of Stroke Medicine, University of Keele (Independent Clinician); TBC (Independent Statistician).

The DSMC Charter, including Terms of Reference, will be approved at the initial

DSMC meeting, but the key role of the DSMC will be to monitor data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue. The safety, rights and well-being of the trial participants are paramount.

17. FINANCING AND INSURANCE

The trial is funded by a joint Stroke Association and British Heart Foundation programme grant entitled 'Blood Pressure Variability – definition, natural history, prognosis and treatment following acute stroke'.

The current remaining funding from this five year programme grant is as follows:

Leicester £87,000
The participant recruitment and follow-up will be undertaken by a PhD student who has completed GCP and consent training.
There are no other current commitments to this funding. Therefore, there is clearly sufficient resource to cover monitoring costs from the budget.

Norwich £150,000
The participant recruitment and follow-up will be undertaken by a Clinical Research Fellow, supported by a Research Nurse. An extension of the Clinical Research Fellow's post would cost an additional £28,625 on that budget line.
This leaves £75,000 for the Research Nurse salary for the remaining grant period.

Oxford £83,000
The remaining monies will support continued funding to the Research Nurse to support participant recruitment and follow-up, and for statistical support to the overall programme.

18. PUBLICATION POLICY

All publications will be approved by the Trial Management Group, in consultation with the Trial Steering Committee, and include all BHF/ TSA grant applicants as co-authors, together with the Clinical Research Fellow undertaking the feasibility study, as the minimum authorship list. Other researchers who fulfill the criteria for authorship will be included on any study publications.

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20. APPENDIX A: SCHEDULE OF PROCEDURES

Procedures	Visits			
	Screening	**Baseline**	**21 (±7) days**	**90 (±14) days**
Informed consent		**X**		
Demographics		**X**		
Medical history		**X**		
Concomitant medications		**X**	**X**	**X**
Physical examination		**X**		
ECG		**X**		
Clinical investigation results (bloods tests, CT/MRI scan results)		**X**		
Eligibility assessment	**X**			
Randomisation		**X**		
Dispensing of study drugs		**X**		
Treatment compliance			**X**	**X**
Blood test for renal function in ACEI/ARB group			**X**	
NIHSS		**X**	**X**	**X**
mRS		**X**[1]	**X**	**X**
MoCA		**X**		**X**
Albert's line test		**X**		**X**
MiND-B		**X**		**X**
GDS		**X**		**X**
BP measurements[2]		**X**	**X**	**X**
Beat-to-beat BP measurements		**X**	**X**	**X**
Daytime ABPM		**X**		**X**
SAEs			**X**	**X**[2]

[1] Including Premorbid mRS
[2] SAEs at Day 90 followed-up until resolution

21. APPENDIX B: EXPECTED SAES FOLLOWING ACUTE ISCHAEMIC STROKE/ TIA

After stroke the following events are expected and therefore not subject to expedited reporting:

== Cardiovascular ==

Acute coronary syndrome (ACS)

Atrial fibrillation (AF)

Bradycardia

Cardiac arrest

Cardiac failure

Cardiac dysrhythmia

Carotid endarterectomy

Chest pain

Collapse

Deep vein thrombosis (DVT)

Hypertension

Hypotension

Myocardial infarction (MI)

Pulmonary embolism (PE)

Sudden cardiac death

Systemic embolism

Tachycardia

Unstable angina

== Central nervous system ==

Agitation

Anxiety

Cerebral oedema

Complication of initial stroke

Dementia

Depression

Dysphagia

Extension of initial haemorrhagic stroke – haematoma expansion

Extension of initial ischaemic stroke –infarct expansion

Haemorrhagic transformation of infarct (HTI)

Headache

Intracerebral bleed

Recurrent stroke - ischaemic

Sedation

Seizure

Sensory loss

Transient ischaemic attack (TIA)

Vertigo

Visual loss

Weakness

== Gastro-intestinal ==

Abdominal pain

Cholecystitis

Constipation

Diarrhoea

Dysphagia

Feeding tube insertion and/or complication

Gall Stones

Gastrointestinal bleed

Gastrointestinal disturbance

Incontinence, faecal

Heartburn

Hepatitis

Malaena

Nausea

Oral ulceration

Pancreatitis

Vomiting

Weight loss

== Genito-urinary ==

Sexual dysfunction

Incontinence, urinary

Renal impairment

Urinary retention

Urinary tract infection (UTI)

== Haematological ==

Anaemia

Leukopenia

Thrombocytopenia

== Miscellaneous ==

Acid base disturbance

Bacteraemia

Diaphoresis

Electrolyte disturbance

Fall

Fatigue

Hyperglycaemia

Hyperuricaemia

Hypoglycaemia

Lymphadenopathy

Malignancy/Cancer –new diagnosis

Muscle twitching

Osteoarthritis

== Respiratory ==

Asthma

Bronchitis

Bronchospasm

Chest infection

Chronic obstructive pulmonary disease (COPD)

Emphysema

Exacerbation of COPD

Hypoxia

Pleural effusions

Pneumonia

Pulmonary embolism (PE)

Shortness of breath