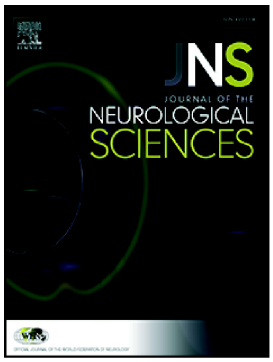
Journal Pre-proof



A calcium channel or angiotensin converting enzyme inhibitor/ angiotensin receptor blocker regime to reduced blood pressure variability in acute ischaemic stroke (CAARBS): A feasibility trial

William J. Davison, Karen Appiah, Thompson G. Robinson, Iain J. McGurgan, Peter M. Rothwell, John F. Potter

PII: S0022-510X(20)30089-7

DOI: https://doi.org/10.1016/j.jns.2020.116753

Reference: JNS 116753

To appear in: *Journal of the Neurological Sciences*

Received date: 3 October 2019

Revised date: 2 February 2020

Accepted date: 18 February 2020

Please cite this article as: W.J. Davison, K. Appiah, T.G. Robinson, et al., A calcium channel or angiotensin converting enzyme inhibitor/angiotensin receptor blocker regime to reduced blood pressure variability in acute ischaemic stroke (CAARBS): A feasibility trial, *Journal of the Neurological Sciences* (2020), https://doi.org/10.1016/j.jns.2020.116753

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

William J Davison[1,*] willdavison@doctors.org.uk, Karen Appiah[2],Thompson G Robinson[2,3], Iain J McGurgan[4], Peter M Rothwell[4], John F Potter[1]

[1]Ageing and Stroke Medicine, Norwich Medical School, University of East Anglia, Norwich, UK.

[2]Department of Cardiovascular Sciences, University of Leicester, Leicester, UK.

[3]NIHR Biomedical Research Centre, Leicester, UK.

[4]Centre for Prevention of Stroke and Dementia, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK.

[*]Corresponding author at: Dr William J Davison, Ageing and Stroke Medicine, University of East Anglia, Bob Champion Research and Education Building, James Watson Rd, Norwich NR4 7UY

Abstract

Background

Trials of lowering blood pressure in patients with acute ischaemic stroke not undergoing thrombolysis have not demonstrated improved outcomes with intervention. Rather than absolute levels, it may be that blood pressure variability is important. However, there are no prospective randomised trials investigating the benefit of reducing blood pressure variability in this patient group.

Aims

The primary aim of this trial was to determine the feasibility of recruitment to a randomised trial investigating the effect of different antihypertensive medications on blood pressure variability.

Methods

CAARBS was a multi-centre, open-label, randomised parallel group controlled feasibility trial. Adults with a first mild-moderate ischaemic stroke or transient ischaemic attack, requiring antihypertensive therapy for secondary prevention, were randomised to a calcium channel blocker or angiotensin-converting enzyme inhibitor/angiotensin receptor blocker. Blood pressure and variability were measured at baseline, three weeks, and three months. Compliance with measurements and treatment was monitored.

Results

Fourteen patients were recruited to the trial (0.6% of those screened), nine of whom completed follow-up. The majority of patients screened (98.1%) were ineligible. Compliance with the

intervention was good, as were measurement completion rates (88.9% or higher in all cases except ambulatory measurements). No major adverse events were recorded.

Conclusions

Recruitment to the trial was difficult due to patient ineligibility, suggesting that the current protocol is unlikely to be successful if scaled for a definitive trial. However, the intervention was safe, and compliance was good, suggesting a future trial with modified eligibility criteria could be successful.

Trial registration: ISRCTN10853487

Keywords: blood pressure variability, hypertension, stroke.

Introduction

Following an acute ischaemic stroke, blood pressure (BP) levels are frequently raised, even in the absence of known prior hypertension.[1] Reasons for increased BP are multifactorial, but may relate to the maintenance of blood flow to the ischaemic penumbra in the context of dysfunctional cerebral autoregulation.[2] Data from major stroke trials indicate that raised BP in the acute period is associated with a poor prognosis,[3] yet trials investigating the treatment of raised BP in these patients have not shown any benefit from intervention,[1] even if administered within 1-2 hours of symptom onset.[4] Indeed, one trial has suggested intervention may be harmful.[5] Furthermore, low BP is probably also detrimental, with data demonstrating a "U" shaped relationship between BP in the acute period, and both short- and long-term mortality.[6] Consequently, the management of raised BP in acute stroke remains uncertain, with guidelines suggesting that it is unlikely to be beneficial to start or continue treatment in the first few days unless there are adverse features of accelerated hypertension or the patient has had thrombolytic therapy.[7]

An alternative consideration is that it may be BP variability (BPV), not absolute BP level, which is important in the acute phase of ischaemic stroke,[8] as evidence indicates that BPV is an independent cardiovascular risk factor.[9] BP fluctuations may damage the vulnerable ischaemic penumbra, with dips causing hypoperfusion and infarct expansion, and rises causing oedema and haemorrhagic transformation. This may at least partly explain the "U" shaped relationship between BP and stroke outcome. Furthermore, research has demonstrated that BPV is increased in acute ischaemic stroke,[10] is associated with adverse outcomes,[11, 12] and is associated with the risk of recurrent stroke.[13] Whether BPV is a potential target for therapeutic intervention has not been investigated in acute stroke. However, it has been shown that routinely used antihypertensive medications

influence BPV.[14, 15] Calcium channel blockers (CCB) and thiazide-like diuretics are consistently reported to lower BPV, whereas beta blockers increase it as possibly do renin-angiotensin inhibitors.[14-16] There is a need for prospective randomised trials to investigate whether lowering BPV conveys any benefit in terms of morbidity and mortality after ischaemic stroke.

Aims

The primary aim of this study was to determine the feasibility of recruiting patients with an acute ischaemic cerebrovascular event to a randomised trial investigating the effect of different antihypertensive medications on BPV. Secondary feasibility aims were assessment of the viability of measuring a change in BPV at 90 day follow-up, assessment of compliance with treatment and trial measurements, and safety.

Methods

The Calcium channel (CCB) or Angiotensin converting enzyme inhibitor (ACEI)/Angiotensin receptor blocker (ARB) Regime to reduced Blood pressure variability in acute ischaemic Stroke (CAARBS) study was a multi-centre, open-label, randomised parallel group controlled feasibility trial. The protocol has previously been published.[17] In brief, eligible patients were aged ≥18 years with a first-episode transient ischaemic attack (TIA) or mild/moderate ischaemic stroke (NIHSS <10), presenting within 72 hours of symptom onset, and requiring antihypertensive therapy for secondary stroke prevention (defined as repeated clinic BP >130/80mmHg). Where symptom onset time was unclear it was taken to be the last time the patient was seen well. Patients were excluded if they had a known contraindication to the proposed investigational medicinal products, clinically required treatment with a specific class of antihypertensive, had a pre-event modified Rankin score (mRS) >3, life expectancy <3 months or atrial fibrillation (AF). Due to higher than expected rates of patient ineligibility, the eligibility criteria were substantially amended during the trial, following discussion with the Trial Steering Committee. Specifically, the allowed time from symptom onset was increased from <72 hours to <7 days. It was hoped this would improve recruitment and further help inform protocol design for any subsequent definitive trial.

Patients presenting to inpatient and outpatient stroke services were screened for eligibility. In accordance with local protocols, pre-existing antihypertensive therapy was stopped at admission and antihypertensive therapy was not commenced until at least 48 hours after symptom onset unless clinically indicated. All diagnoses were reviewed by two experienced stroke physicians. Eligible patients willing to participate provided written informed consent prior to being randomised

in a 1:1 ratio using a computer generated protocol in blocks of four, to treatment with either a dihydropyridine CCB or an ACEI/ ARB. Intervention groups were defined by antihypertensive class, with the choice of medication from the randomly allocated class at the discretion of the treating clinician. Ethical approval for the trial was granted by the London – Central Research Ethics Committee (REC No. 17/LO/1427).

At baseline, demographic and clinical details were recorded with BP from enhanced clinic monitoring, beat-to-beat monitoring, and daytime ambulatory BP monitoring (ABPM), and a cognitive battery (Montreal Cognitive Assessment (MoCA), Albert's line test, and Motor Neuron Disease Behavioural Instrument (MiND-B)). Enhanced clinic monitoring was defined as two sets of three BP measurements taken using an appropriately sized cuff with the patient seated, after a period of five minutes rest, with at least one minute between readings and 10 minutes between sets. Measurements were taken using a semi-automated oscillometric BP monitor (Omron 705IT, Omron Healthcare UK Ltd., Milton Keynes, UK). Three 10 minute recordings of non-invasive beat-to-beat BP were taken using the Finapres® MIDI device (Finapres Medical Systems, Enschede, The Netherlands) fitted to the middle finger of the unaffected hand with the patient in the supine position. The servo adjust mechanism was disabled during recording and re-applied prior to each 10 minute period. Daytime ABPM was conducted using a Spacelabs 90207 monitor (Spacelabs Healthcare Ltd. (UK), Hertford, UK) programmed to measure BP at 20 minute intervals. BPV was derived as the standard deviation (SD) and coefficient of variation (CV) using all BP measurements from a set. Interim follow-up was completed after 21 ± 7 days to assess treatment compliance with a tablet count and a self-rating scale,[18] and repeat enhanced clinic and beat-to-beat BP measurements. Participants were questioned about treatment side effects and the ACEI/ARB group had blood renal function testing as a safety measure, as per routine clinical practice. Final follow-up was completed after 90 ± 14 days, at which time treatment compliance assessment, all baseline BP measurements, assessment of stroke severity and functional recovery, and the cognitive battery were repeated.

The primary outcome measure for the trial was the assessment of rates of recruitment and retention, including reasons for exclusion. Secondary feasibility outcomes were (i) change in BPV from baseline to follow-up by intervention arm; (ii) rates of treatment compliance and discontinuation; (iii) completion rates of BPV measurements; (iv) serious adverse events. Secondary exploratory outcomes were (i) difference in mean BP and BPV at day 21 and day 90 by intervention arm; (ii) mRS at day 21 and day 90 by intervention arm; (iii) difference in MoCA score at day 90 by

intervention arm. Although the primary objective was the assessment of feasibility, a sample size calculation was performed to estimate the number of participants required to detect a potential difference in BPV between intervention arms. Assuming a mean systolic BPV SD of 14.97mmHg in the CCB arm and 16.95mmHg in the ACEI/ARB arm,[15] a sample of 150 patients (64 per group allowing for a 15% drop-out rate) was estimated to be required to detect an 8mmHg difference in systolic BPV with 80% power at the 5% significance level.

Statistical analysis

Data were analysed using SPSS (version 25.0). Only descriptive analyses were undertaken, in keeping with the CONSORT recommendations for reporting feasibility trials.[14] The proportion of patients screened that were eligible for the trial, the proportion of eligible patients that were recruited, and the proportion of participants that completed follow-up were determined from screening and management logs. Reasons for ineligibility were assessed. Where known, reasons for eligible patients declining to participate and reasons for participants withdrawing from the trial were assessed. All exploratory variables were assessed for normality. Normally distributed variables are presented as mean (SD) and non-normally distributed variables are presented as median (IQR). For change in BP and BPV from baseline to follow-up the absolute change for each intervention arm is presented.

Results

Recruitment commenced on 3rd January 2018 and continued until 31st December 2018 (the pre-specified end date), with all follow-up completed three months post-randomisation. A total of 2321 patients were screened, 14 (0.6%) of whom were eligible and consented to participate (**Figure 1**). Of those screened, 2264 (98.1%) were ineligible, with 1858 (81.7%) having a single reason for exclusion recorded and 463 (18.3%) having multiple reasons recorded. The most common reasons for ineligibility were recurrent stroke/TIA (N=496 [21.4%]), non-stroke diagnosis (N=453 [19.5%]), and concurrent AF (N=431 [18.5%] **Supplementary Table I**). Late presentation beyond the 72 hour window of eligibility was also a prominent reason for exclusion (N=314 [19.4%]), but became less frequent following the substantial amendment to the eligibility criteria (N=46 [6.6%]).

In addition to the excluded patients, 43 (1.9%) met the eligibility criteria but declined to participate. These patients were not obliged to provide a reason for their decision, but some stated that they could not commit the time to attend trial visits (N=7) or did not wish to attend hospital for additional

appointments (N=3), despite the offer of reimbursement for travel costs. Two patients did not like the idea of being randomly assigned to a medical treatment.

Randomised participants were evenly split between the two intervention groups, allowing for the small sample size. Baseline characteristics are displayed in **Table 1**. Two participants were withdrawn as "screening failures" as their initial BP was >130/80mmHg, but repeated measurements at the baseline consultation were below the threshold value making them ineligible. One participant withdrew from the CCB arm of their own choice, one participant was withdrawn from the ACEI/ARB arm by the trial team due to concomitant treatment with a CCB commenced by clinicians outside of the trial team, and one participant from the ACEI/ARB arm discontinued treatment due to side effects. There were no other major side effects reported and no serious adverse events recorded in either intervention arm.

Figure 1: CAARBS CONSORT flow diagram. CCB denotes calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; GP, general practitioner.

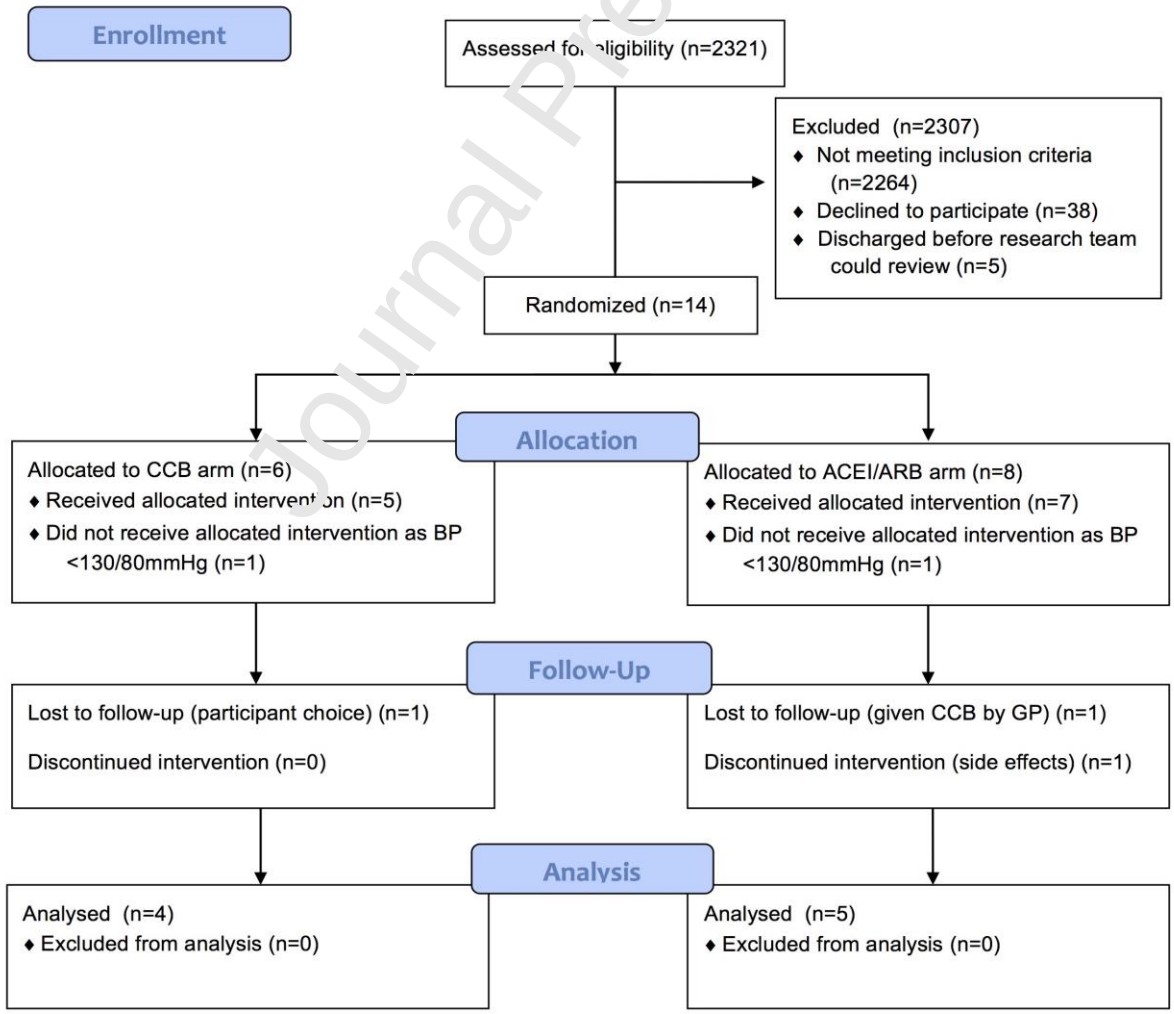


Table 1: Baseline characteristics of randomised participants. Data presented are mean (SD), frequency (%), or median (IQR).

		CCB	ACEI/ARB
N		5	7
Age (years)		74.8 (4.2)	64.9 (9.1)
Gender	**Male**	4 (80.0%)	4 (57.1%)
Ethnicity	**White-British**	4 (80.0%)	6 (85.7%)
BMI (kg/m^2)		28.2 (4.6)	27.1 (5.8)
Smoking	**Never smoked**	2 (40.0%)	2 (28.6%)
	Ex-smoker	3 (60.0%)	2 (28.6%)
	Current smoker	0 (0.0%)	3 (42.8%)
Alcohol (units/wk)		5 (0-17)	14 (12-38)
Diagnosis	**TIA**	3 (60.0%)	3 (42.9%)
	Stroke	2 (40.0%)	4 (57.1%)
Past medical history	**Hypertension**	3 (60.0%)	1 (14.3%)
	Diabetes	1 (20.0%)	0 (0.0%)
	Ischaemic heart disease	0 (0.0%)	0 (0.0%)
Mean enhanced clinic BP (mmHg)	**SBP**	163.6 (17.3)	152.7 (14.5)
	DBP	81.8 (5.9)	83.1 (6.5)
SD enhanced clinic BP (mmHg)	**SBP**	8.4 (5.2)	6.8 (5.3)
	DBP	5.6 (3.0)	6.0 (3.4)
CV enhanced clinic	**SBP**	4.9 (2.6)	4.5 (3.4)

BP (%)	**DBP**	7.0 (3.9)	7.2 (4.0)
Mean beat-to-beat BP (mmHg)	**SBP**	156.6 (5.7)	151.0 (11.9)
	DBP	79.8 (7.1)	82.6 (6.1)
SD beat-to-beat BP (mmHg)	**SBP**	9.9 (3.9)	9.2 (5.5)
	DBP	5.2 (2.2)	5.1 (2.4)
CV beat-to-beat BP (%)	**SBP**	6.3 (2.5)	6.0 (2.6)
	DBP	6.6 (2.6)	6.3 (3.0)

CCB denotes calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; TIA, transient ischaemic attack; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation; CV, coefficient of variation.

Completion rates of clinic and beat-to-beat BP measurements were good across all study visits, with all completed readings judged to be valid (**Table 2**). Completion rates of daytime ABPM measurements were lower, partly because of a software failure at one trial site, and partly because of participant refusal (N=2). Furthermore, only 6/13 (46.2%) daytime ABPM measurements provided ≥14 readings and were considered valid for analysis. Compliance with trial treatment according to the self-rating questionnaire was good, with 8/9 (88.9%) participants who completed the trial indicating compliance ≥80%. However, tablet count was unsuccessful as participants often failed to bring their medication to follow-up visits, being completed in only 5/18 (27.7%) consultations.

Table 2: Completion rates of blood pressure measurements.

	Enhanced clinic BP	**Beat-to-beat BP**	**Daytime ABPM**
Baseline	12/12 (100.0%)	11/12 (91.7%)	7/12 (58.3%)
21 days	9/10 (90.0%)	9/10 (90.0%)	-
90 days	9/9 (100.0%)	8/9 (88.9%)	6/9 (66.6%)

BP denotes blood pressure; ABPM, ambulatory blood pressure measurement.

Enhanced clinic BP was possibly reduced to a greater degree at 90 days with CCB compared to ACEI/ARB (-35/-9mmHg vs. -22/-8mmHg), but clinic BPV reduction was similar (SD -3/-1mmHg vs. -3/-3mmHg, CV -1/-1% vs. -1/-3% [**Supplementary Table II**]). Reductions in beat-to-beat BP and BPV were possibly greater with CCB (mean BP -20/-8mmHg vs. -14/-7mmHg, SD -4/-2mmHg vs. -1/-1mmHg, CV -2/-2% vs. 0/-1%[**Supplementary Table III**]). There were no apparent differences in functional or cognitive outcome between the intervention arms.

Discussion

Recruitment to this trial was difficult owing to high rates of patient ineligibility. Recruitment targets were not met and it seems unlikely that it would be feasible to scale up the current protocol to attempt a definitive trial. However, despite the proportion of eligible patients recruited being low, this is not necessarily unusual for randomised controlled trials.[20] Furthermore, retention in this trial was reasonable, with 9/14 (64.3%) randomised participants completing three-month follow-up. The main reasons for patient ineligibility were having a previous cerebrovascular event, non-stroke diagnosis, presenting beyond the window of eligibility, and having concurrent AF. A proportion of patients presenting with a stroke mimic must be accepted, but other criteria could potentially be altered to improve recruitment. Firstly, although extending the eligibility window did not translate into a significant increase in recruitment in this trial, retaining the extension could be helpful. It would increase the likelihood of eligibility at the point of presentation to stroke services and it may also allow time for patients initially too unwell to participate (e.g. if they are nil by mouth) to recover sufficiently for inclusion. Secondly, although increased BPV may persist chronically post-stroke,[21] large gains could be achieved by including patients with a previous stroke . Employing minimisation criteria to balance first and recurrent stroke patients in each trial arm, or pre-specified statistical techniques, such as planned subgroup analysis of patients with first episode stroke or adjustment for previous stroke in statistical testing, could safeguard their inclusion. Thirdly, as most patients require multiple agents to achieve BP control,[22] it may be necessary to include patients taking antihypertensive medications other than the intervention products. Again, techniques such as pre-specified subgroup analysis or adjustment in statistical testing could control for their inclusion. A treatment escalation algorithm would minimise unintentional intervention group crossover during follow-up, whilst allowing for treatment intensification. Finally, as beat-to-beat BPV is increased in patients with AF compared to control,[23] and beta blockers are frequently used as part of a rate control treatment strategy for AF,[24] it may be difficult to justify including patients with AF. However, automated oscillometric BP measurement devices are reliable in AF provided multiple

measurements are taken.[25] Therefore, if BPV from clinic or ambulatory monitoring rather than beat-to-beat measurements was used, it may be possible to include them. Further safeguarding could be achieved with specified data validation criteria for patients with AF, such as an acceptable range for heart rate variability across BP measurements used to derive BPV.

There are no directly comparable trials to this one and so its novelty should be noted. The major strength of the trial is in its feasibility design, with accomplishment of the primary objective and analysis allowing for recommendations to be made which could improve recruitment in a future trial. The trial also met its secondary feasibility objectives, although these findings must be interpreted in the context of the small sample size, demonstrating good compliance with the intervention and trial measurements (ABPM measurements being largely limited by a technical issue), and raising no safety concerns. Furthermore, it was demonstrated that it is possible to measure a change in BPV over a three-month follow-up period in this patient group, indicating that if sufficient numbers of participants could be recruited, it should be possible to detect a differential effect of different antihypertensive medication classes on BPV if one exists.

The trial also has limitations that require consideration. Firstly, not all eligible patients who declined to participate offered a reason for their decision and this represents a missed opportunity for improving the trial design. Secondly, owing to the small sample size limited data regarding participant retention and reasons for withdrawal were obtained. Obtaining more data in both of these areas would have been useful for judging the feasibility of any similar future trial. Thirdly, it was not possible to demonstrate a differential effect on BPV between the two intervention arms. In part this was due to the small sample size, but it cannot be excluded that the use of antihypertensive agents in some participants prior to their recruitment could have influenced their BPV as recorded in the trial. Unfortunately, as it is accepted standard care to treat raised BP for secondary stroke prevention it would not be ethical to incorporate a complete washout period into the trial design. Therefore, follow-up in any further trials may need to be prolonged, or previous antihypertensive use adjusted for in the statistical analysis.

In summary, CAARBS was hindered by insufficient recruitment, but did achieve its pre-specified feasibility objectives and demonstrate the possibility of measuring a change in BPV following an ischaemic stroke or TIA. With the application of modified eligibility criteria, such as retaining a longer window of eligibility and including patients with previous stroke, it is possible that a future trial to investigate BPV reduction in this patient group could be successful.

Declaration of conflicting interests: The authors declare that there is no conflict of interest.

Funding acknowledgements: This work was supported by a programme grant awarded jointly by The Stroke Association and The British Heart Foundation (Ref: TSA BHF 2012/01).

References

1. Bath PM and Krishnan K. Interventions for deliberately altering blood pressure in acute stroke. *Cochrane Database Syst Rev* 2014: CD000039. DOI: 10.1002/14651858.CD000039.pub3.
2. Qureshi AI. Acute hypertensive response in patients with stroke: pathophysiology and management. *Circulation* 2008; 118: 176-187. DOI: 10.1161/CIRCULATIONAHA.107.723874.
3. Willmot M, Leonardi-Bee J and Bath PM. High blood pressure in acute stroke and subsequent outcome: a systematic review. *Hypertension* 2004; 43: 18-24. DOI: 10.1161/01.HYP.0000105052.65787.35.
4. Right-Investigators. Prehospital transdermal glyceryl trinitrate in patients with ultra-acute presumed stroke (RIGHT-2): an ambulance-based, randomised, sham-controlled, blinded, phase 3 trial. *Lancet* 2019; 393: 1009-1020. 2019/02/11. DOI: 10.1016/S0140-6736(19)30194-1.
5. Sandset EC, Bath PM, Boysen G, et al. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. *Lancet* 2011; 377: 741-750. DOI: 10.1016/S0140-6736(11)60104-9.
6. Leonardi-Bee J, Bath PM, Phillips SJ, et al. Blood pressure and clinical outcomes in the International Stroke Trial. *Stroke* 2002; 33: 1315-1320.
7. Intercollegiate Stroke Working Party. National Clinical Guideline for Stroke 5th ed., https://www.rcplondon.ac.uk/guidelines-policy/stroke-guidelines (2016, accessed 17th July 2017 2017).
8. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *Lancet* 2010; 375: 938-948. DOI: 10.1016/S0140-6736(10)60309-1.
9. Stevens SL, Wood S, Koshiaris C, et al. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. *BMJ* 2016; 354: i4098. DOI: 10.1136/bmj.i4098.
10. Robinson T, Ward-Close S and Potter J. A Comparison of beat-to-beat blood pressure variability in acute and subacute stroke patients with cerebral infarction. *Cerebrovasc Dis* 1997; 7: 214-219.
11. Dawson SL, Manktelow BN, Robinson TG, et al. Which parameters of beat-to-beat blood pressure and variability best predict early outcome after acute ischemic stroke? *Stroke* 2000; 31: 463-468.
12. de Havenon A, Bennett A, Stoddard GJ, et al. Increased Blood Pressure Variability Is Associated with Worse Neurologic Outcome in Acute Anterior Circulation Ischemic Stroke. *Stroke Res Treat* 2016; 2016: 7670161. DOI: 10.1155/2016/7670161.
13. Webb AJS, Mazzucco S, Li L, et al. Prognostic Significance of Blood Pressure Variability on Beat-to-Beat Monitoring After Transient Ischemic Attack and Stroke. *Stroke* 2018; 49: 62-67. DOI: 10.1161/STROKEAHA.117.019107.
14. Rothwell PM, Howard SC, Dolan E, et al. Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. *Lancet Neurol* 2010; 9: 469-480. DOI: 10.1016/S1474-4422(10)70066-1.

15. Webb AJ, Fischer U, Mehta Z, et al. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. *Lancet* 2010; 375: 906-915. DOI: 10.1016/S0140-6736(10)60235-8.
16. Levi-Marpillat N, Macquin-Mavier I, Tropeano AI, et al. Antihypertensive drug classes have different effects on short-term blood pressure variability in essential hypertension. *Hypertens Res* 2014; 37: 585-590. DOI: 10.1038/hr.2014.33.
17. Robinson TG, Davison WJ, Rothwell PM, et al. Randomised controlled trial of a Calcium Channel or Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker Regime to Reduce Blood Pressure Variability following Ischaemic Stroke (CAARBS): a protocol for a feasibility study. *BMJ Open* 2019; 9: e025301. 2019/02/21. DOI: 10.1136/bmjopen-2018-025301.
18. Schroeder K, Fahey T, Hay AD, et al. Adherence to antihypertensive medication assessed by self-report was associated with electronic monitoring compliance. *J Clin Epidemiol* 2006; 59: 650-651. 2006/05/23. DOI: 10.1016/j.jclinepi.2005.10.013.
19. Eldridge SM, Chan CL, Campbell MJ, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *BMJ* 2016; 355: i5239. 2016/10/26. DOI: 10.1136/bmj.i5239.
20. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". *Lancet* 2005; 365: 82-93. DOI: 10.1016/S0140-6736(04)17670-8.
21. Grilletti JVF, Scapini KB, Bernardes N, et al. Impaired baroreflex sensitivity and increased systolic blood pressure variability in chronic post-ischemic stroke. *Clinics (Sao Paulo)* 2018; 73: e253. DOI: 10.6061/clinics/2018/e253.
22. Fretheim A, Odgaard-Jensen J, Brors O, et al. Comparative effectiveness of antihypertensive medication for primary prevention of cardiovascular disease: systematic review and multiple treatments meta-analysis. *BMC Med* 2012; 10: 33. DOI: 10.1186/1741-7015-10-33.
23. Olbers J, Gille A, Ljungman P, et al. High beat-to-beat blood pressure variability in atrial fibrillation compared to sinus rhythm. *Blood Press* 2018; 27: 249-255. 2018/02/09. DOI: 10.1080/08037051.2018.1436400.
24. National Institute for Health and Care Excellence. Atrial fibrillation: management, https://www.nice.org.uk/guidance/cg180/resources/atrial-fibrillation-management-pdf-35109805981381 (2014, accessed 14th March 2019 2019).
25. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018; 39: 3021-3104. DOI: 10.1093/eurheartj/ehy339.

Highlights

- Lowering blood pressure variability (BPV) after ischaemic stroke may be beneficial.
- This feasibility trial investigating BPV reduction did not meet recruitment targets.
- Potential changes to eligibility criteria for possible future trials were identified.
- Measuring change in BPV over a follow-up period of three months was possible.
- Intervention to reduce BPV in the subacute phase of ischaemic stroke was safe.