SELF-MANAGEMENT OF POSTNATAL HYPERTENSION:

THE SNAP-HT TRIAL

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Abstract

Hypertension affects one in ten pregnancies, often persisting postpartum, when antihypertensive requirements may vary substantially. This unmasked, randomized controlled trial evaluated the feasibility and effects on blood pressure of self-management of postpartum hypertension. Women with gestational hypertension or pre-eclampsia, requiring postnatal antihypertensive treatment, were randomized to self-management or usual care. Self-management entailed daily home blood pressure monitoring and automated medication reduction via telemonitoring. Women attended five follow-up visits over six months. The primary outcome was feasibility: specifically recruitment, retention and compliance with follow-up rates. Secondary outcomes included blood pressure control and safety, analyzed on an intention to treat basis. Forty-nine percent (91/186) of those women approached were randomized (45 intervention, 46 control), and 90% (82/91) finished follow-up. The groups had similar baseline characteristics. Following randomization, blood pressure was lower in the intervention group, most markedly at six weeks: intervention group mean (SD) 121.6 (8.7) / 80.5 (6.6) mmHg, control group 126.6 (11.0) / 86.0 (9.7) mmHg, adjusted differences (95% confidence interval) -5.2 (-9.3 to -1.2) / -5.8 (-9.1 to -2.5) mmHg. Diastolic blood pressure remained significantly lower in those self-managing to six months: adjusted difference at -4.5 (-8.1 to -0.8) mmHg. This is the first randomized evaluation of blood pressure self-management postpartum, and indicates it would be feasible to trial this intervention in larger studies. Self-management resulted in better diastolic blood pressure control to six months, even beyond medication cessation.

Keywords

Preeclampsia; postpartum; self-management; telemedicine; antihypertensive agent

Introduction

Hypertensive disorders of pregnancy (HDP), which include gestational hypertension and pre-eclampsia, are common and may lead to significant morbidity and mortality.[1, 2] HDP may persist postpartum, and complications can occur, although for most women blood pressure (BP) subsequently returns to normal.[3] BP can change rapidly and unpredictably postpartum,[3, 4] with shifting medication requirements, posing a challenge to both physicians and patients. American data from 1,179,719 deliveries (2005-9) showed that hypertension was the commonest indication for postnatal hospital readmission.[5] Emerging evidence suggests that the degree of hypertension in the months following a hypertensive pregnancy may correlate with the severity of later hypertension[6] and hence long term cardiovascular risk.[7] National Institute of Health and Care Excellence (NICE) guidelines,[8] a Cochrane review (2013)[9] and a recently published systematic review,[10] highlight that few studies have addressed postnatal BP management.

Home BP monitoring (HBPM) appears to be more strongly related to indices of target organ damage[11] and has better prognostic value in essential hypertension than office BP measurement.[12] Previous work in the non-pregnant population has shown that HBPM accompanied by self-titration of antihypertensive medications in essential hypertension was more effective than usual care, with better BP control.[13, 14] Small, non-randomized evaluations of remote monitoring of HDP during pregnancy and postpartum have suggested this approach might be feasible and acceptable.[15, 16] Postnatal self-management could lead to better BP control, a reduced burden of healthcare visits and might improve women's long-term cardiovascular health.[7]

A novel self-management intervention was developed from the TASMIN self-management trials,[13, 14] for use by women, with medicated HDP, postpartum. This trial aimed to evaluate the feasibility of this intervention, and to perform an initial assessment of effectiveness with regard to BP control. This randomized controlled trial (RCT) is reported in line with the CONSORT 2010 statement (Appendix S1).[17]

Methods

This was a prospective, randomized, unmasked trial, prospectively registered with ClinicalTrials.gov (NCT02333240) and approved by a National Research Ethics Service (NRES) Committee (reference 14/SC/1316), with research governance approval at each site. The study protocol can be found online (https://www.phc.ox.ac.uk/files/research/snap-ht-protocol-v5-1.pdf). This study is a member of the BP-SMART Collaborative in terms of prospective meta-analyses.[18] The data that support the findings of this study are available from the corresponding author upon reasonable request.

Participants were recruited from five NHS hospital sites in England. Women aged ≥18 years, with gestational hypertension or pre-eclampsia (according to NICE definitions[8]), requiring antihypertensive treatment, were eligible. Exclusions included: prescription of more than three antihypertensive medications, self-report of hypertension diagnosed outside of pregnancy, inability to speak English. Women were approached during pregnancy, after identification by their direct care team, and provided with written information. Those wishing to participate gave written informed consent.

Eligible women that consented underwent a screening visit during pregnancy, when baseline demographic and clinical data were collected. Women were randomized at a baseline visit following delivery and were excluded prior to randomization if they withdrew consent, lost capacity to consent, or became ineligible due to cessation of antihypertensive treatment. Women were randomized (block sizes 2 or 4) in a 1:1 ratio, to self-management or usual postnatal care, stratified by recruitment center. The randomization sequence was computer-generated, and secure web-based randomization software was used to ensure allocation concealment. Neither participants nor investigators were masked. Outcome measurement was not blinded but used automated validated BP monitors to minimize investigator bias.

Women allocated to usual care had their BP monitored by their community midwife, and their antihypertensive medication adjusted by their general practitioner. Women allocated to self-management commenced this following discharge from hospital after birth. Self-management entailed daily self-monitoring, at approximately the same time each morning using a validated device (Microlife WatchBP Home®),[19] whilst taking antihypertensive treatment and for five days after treatment cessation. If BP remained normal for five consecutive days off treatment, participants continued with weekly self-monitoring for the remainder of the trial. Participants typed BP readings into their mobile phone or smartphone. These were then automatically transmitted to the study server (via text message or the internet by the smartphone app), which provided immediate responses. The telemonitoring service sent reminders when BP readings were overdue (dependent on the most recent BP, between 24 and 96 hours since the

missing reading), and incorporated an individualized medication reduction schedule: this was set by the chief investigator, in collaboration with the participant's direct care team, in line with a set of predefined rules, which automatically instructed women how to down-titrate their medications in response to their BP readings (see Appendix S2 for further details).

Women from both groups had five follow-up visits at home over six months (day 10, four weeks, six weeks, three months, six months). BP was measured six times at each visit, after five minutes rest, at one minute intervals using the same monitor as used for HBPM by the intervention group.[19] All participants had their arm circumference measured, and the appropriate cuff size was used. All researchers were trained to use the monitor. The mean arterial pressure (MAP) was calculated using the formula: $MAP = \frac{[(2 \times DBP)+SBP]}{3}$. Additionally current medications, side effects, serious adverse events and quality of life (QOL) scores (EQ-5D-5L) were recorded.[20]

This was the first trial of self-management of postnatal hypertension, hence the primary outcome was feasibility: specifically recruitment, retention and compliance with follow-up rates. The pre-defined success criteria were: attrition rate <10%; compliance with follow-up visits rate >90%; recruitment rate of three participants per week across the sites; no site was to contribute <5% of participants.

Secondary outcomes included mean systolic BP (SBP), diastolic BP (DBP) and MAP, postnatal readmission rates, safety data, side effects and QOL scores (EQ-5D-5L).

Exploratory outcomes included compliance with, and accuracy of HBPM reporting in the intervention group.

The target sample size for consent was 100 women, following guidelines for feasibility studies.[21] A formal sample size calculation was not performed. All analyses were performed in Stata version 14.2. An intention-to-treat approach was taken using all data available from randomized patients without replacement of missing data. Continuous variables were summarized as means with standard deviations (SD) (or medians with interquartile ranges (IQR) if skewed), and categorical variables as counts and percentages. Differences between groups were reported with 95% confidence intervals (95% CI) and did not include significance tests. No interim analyses were performed. A Data Monitoring and Ethics Committee oversaw the pilot trial.

The mean of the second and third BP readings was used for the main analysis, with the mean of the second to sixth readings in a sensitivity analysis. Differences in SBP, DBP and MAP were estimated using mixed effects regression models. These models included the outcome with treatment group, time and an interaction between time and randomized group as fixed effects, adjusting for recruitment site and baseline BP, fitted as fixed effects with an unstructured covariance pattern. Differences in adjusted means between groups at each time point were calculated. For the combined mean BP across follow-up, a linear regression model was fitted with treatment group as the independent variable, adjusting for recruitment center and baseline BP. Follow-up BP readings were classified according to target range, and safety thresholds (Appendix S2).

These binary outcomes were compared at each follow-up time point, using a logistic regression model, with treatment group and recruitment center fitted as covariates.

Results

Between 01/04/2015 and 30/04/2016, 186 women were approached. Of these, 154 (83%) were eligible, of whom 101 (66%) gave written consent (target 100). Ten women withdrew postpartum: five withdrew consent, and five became ineligible between screening and the baseline visit. Of these, three were randomized in error but withdrawn immediately without becoming aware of their allocation. 91 women were correctly randomized: 45 to self-management, 46 to usual care (see Figure 1). 9/91 (10%) withdrew during follow-up: five intervention, and four control. 82/91 participants (90%) finished follow-up. 86/91 women contributed data for analysis of secondary outcomes (Figure 1). 75/86 provided complete follow-up data (i.e. no missed follow-up visits), 7/86 finished follow-up but missed one interim visit and 4/86 withdrew but contributed some data. The trial finished on 25/11/2016 when the last participant completed follow-up.

Baseline characteristics were similar in the two groups although the mean SBP and DBP, and median protein:creatinine ratio tended to be higher in the intervention group (Table 1). There were no maternal deaths, and no fetal or neonatal deaths amongst those randomized.

The recruitment rate for the study was 91/186 (49%) of all approached potential participants, and 91/154 (59%) of those eligible (Table 2 including definitions). The

randomization rate was 1.5 participants per site per month. Amongst the 82 participants who finished follow-up, 403/410 (98%) of follow-up visits were completed (Table 2).

Overall, women who self-managed had a lower mean BP at follow-up (Table 3). The adjusted difference in the mean BP readings was greatest at six weeks postpartum: intervention group mean (SD) 121.6 (8.7) / 80.5 (6.6) mmHg, control group 126.6 (11.0) / 86.0 (9.7) mmHg, adjusted differences -5.2 (95% CI -9.3 to -1.2) / -5.8 (95% CI -9.1 to -2.5) mmHg. Mean DBP was consistently lower in the intervention group from four weeks to six months; with 95% CI around adjusted mean differences that did not cross zero (Table 3). In a sensitivity analysis, at all time points, the adjusted mean between-group differences for the mean of the second to sixth readings (Appendix S3) were similar to those for the mean of the second and third readings (Table 3).

The adjusted between-group difference for the mean DBP (mean of second and third readings) across all follow-up visits was -3.7mmHg (95% CI -6.3 to -1.1). No between-group difference was seen in the mean SBP across visits; however, the MAP was consistently lower in the intervention group (Appendix S4). Participants in the intervention group were more likely to have SBP and DBP readings inside the target range at six weeks postpartum (Table 4): adjusted odds ratio 8.0 (95% CI 2.1 to 30.6). Only a very small number of readings from both groups were outside the safety ranges (intervention group 2/203 (1%); control group 4/209 (2%)) (Appendix S5).

The profiles (Table 3) and duration (Appendix S6) of postnatal antihypertensive treatment were calculated. The median World Health Organisation (WHO) defined daily

doses were similar at all visits, and by six months, only one woman (3%) self-managing and two (5%) from the control group remained on treatment (Table 3). Median treatment duration was 29 days (IQR 17 to 49) in the intervention group and 41 days (IQR 23 to 58) in the control group; adjusted mean difference -12 days (95% CI -30 to 6).

No between-group differences were seen at screening, six weeks or six months, in participants' mean self–reported EQ5D-5L overall QOL score, or in any of five QOL domains (Appendix S7).

Eleven serious adverse events were reported (Appendix S8): all were readmissions to hospital with no serious maternal morbidity, or mortality. Three were unrelated to BP. Eight women were readmitted to hospital with high or low BP, all within the first two weeks postpartum, five from the self-management group. All were still taking their antihypertensive medications from discharge, and none had yet begun to down-titrate. Reported side effects were similar between both groups, with the most commonly reported being dizziness, (14% intervention group; 11% control group (Appendix S8)). Other side effects reported included headaches, fatigue, dry mouth and weakness.

Self-monitored BP data, from the telemonitoring website and home BP monitors, were evaluated for complete cases in the intervention group (n=40). The median participant compliance with submission of daily readings, whilst on treatment, was 85% (IQR 66 to 98). 7/40 (17.5%) participants had overdue readings (Appendix S2) whilst on treatment. Only 4/40 (10%) participants had more than one overdue reading.

Comparison of BP readings from the telemonitoring website, with readings downloaded from home BP monitors, revealed the median participant accuracy for reporting readings via the SMS service or app was 94% (IQR 84 to 100). 87% (926/1061) submitted daily readings were accurate (where data was available for comparison – duplicate readings and lost downloaded data from the home BP monitors were excluded). 6% (68/1061) readings were inaccurate (non-identical SBP, DBP or both), however only 14 of these (1% of total) were submitted at a different BP threshold (Appendix S2), such that they had the potential to influence down-titration. A further 6% (67/1061) appeared fictitious: no corresponding reading was downloaded from the monitor.

Discussion

This RCT, for the first time, has shown that self-management of BP after pregnancy is feasible and appears to result in better BP control than usual care. The reduction in DBP persisted from four weeks until six months; well after cessation of antihypertensive medication. Whilst this trial was not powered to detect a difference in BP control, women who self-managed had lower DBP throughout follow-up to six months, lower SBP at six weeks and were significantly more likely to have BP readings inside the target range at six weeks. This consistency of finding mitigates against the play of chance. Reassuringly, very few participants in either group had BP readings outside the safety thresholds. Randomization rates, attrition and compliance with follow-up were all around the norms for UK randomised trials.[22]

The persisting differences in DBP, even off treatment, are what would be expected from an antihypertensive intervention in a younger population and may reflect a long lasting effect of stricter early BP control: during hypertensive pregnancies, adverse cardiac and vascular remodeling occurs, which then partially resolves in the first six weeks postpartum.[23] Early tighter BP control may have a beneficial impact on this remodeling, potentially resulting in some reversal of the isolated diastolic hypertension seen classically developing in 30-50 year olds.[24] Observational data have shown that higher BP at six weeks postpartum correlates with a greater risk of hypertension up to ten years later, which may underpin the increased long-term cardiovascular risk and points to a potential mechanism for benefit should these results be reproducible in a larger study.[7, 25, 26]

In contrast to recent data from a severely pre-eclamptic cohort,[27] almost all women in both groups were normotensive and off antihypertensive treatment by six months, and the intervention group showed a tendency towards a shorter overall duration of antihypertensive treatment. Therefore it appears that the observed treatment effect was not mediated through increased antihypertensive prescription, but perhaps through more appropriately targeted utilization of medication mediated through improved adherence, or taking more medication early on but stopping appropriately once no longer needed.

A previous individual patient data meta-analysis outside of pregnancy has shown that self-monitoring alone has limited impact on BP control, when compared to self-

management.[28] It therefore seems likely that in this trial the main treatment effect resulted from self-management, i.e. the whole package of information and telemonitoring support provided to participants in addition to HBPM.

As for hypertension outside pregnancy,[13, 14] this trial produced no evidence that self-management was associated with an increase in adverse events and where serious adverse events occurred they all related to readmission soon after initial discharge before medication titration had commenced precluding problems with self-management. In a larger study an increase in readmission might be anticipated due to more frequent monitoring and would need to be carefully monitored.

Most women self-monitored regularly and reported the results accurately. The automatic BP monitoring reminder strategy (Appendix S2) used may have contributed to good compliance, and perhaps improved medication adherence. The accuracy level (87%) for reporting readings was not as high as has previously been described for HBPM in pregnancy: Waugh *et al.* reported an accuracy level of 97% (n=72).[29] However their study period was only 5-7 days, compared to this population who submitted daily readings for a mean of almost six weeks.

This trial benefited from being run across five NHS hospitals, with recruitment from a relatively wide geographic area. No limitations were placed upon prescribing choices – so participants were taking a range of different antihypertensive medications, reflecting usual clinical care. In contrast to the previously published intervention trials in postpartum hypertension, the follow-up data extend to six months postpartum.[10]

Randomization with robust allocation concealment limited selection bias, and produced two study groups with similar baseline characteristics.

The conclusions are limited because this trial was not powered to detect a difference in secondary outcomes. Whilst the pre-defined criteria for success of an attrition rate of <10% and a compliance rate of >90% were achieved, the randomization rate over time fell short of our initial target. However, the randomization rate per site per month (1.5 participants) exceeded the median rate reported in a review of UK clinical trials (0.92 participants).[22]

The trial population was largely white (>80%) and middle-class (59% had Index of Multiple Deprivation scores in the first or second quintile), and the majority of participants had fairly mild, later-onset hypertensive disorders of pregnancy, which may limit the generalizability of the findings. The trial was unmasked, as the nature of self-management precluded blinding. However, BP outcome data were collected using the automated mode of a validated, oscillometric monitor, to limit detection bias. The intensive schedule of home follow-up visits, intended for the collection of research data, might not be necessary in clinical practice or in a future larger trial, but this would require further study.

No previous trials have evaluated self-management of postnatal hypertension and only three identified studies report follow-up periods of six months or longer.[10] Two trials evaluated indapamide versus methyldopa, in open label-RCTs, in small study populations (both n=30) and showed no difference between groups in BP control at 6-12

months.[30, 31] The third open-label RCT compared labetalol with nifedipine (n=50): no difference was seen in BP control. The long-term follow-up data were limited by significant missing data (only 20% collected at 6 weeks), and it is unclear how many women provided data about total treatment duration at 6 months.[32] Therefore this, to our knowledge, is the first time any intervention has been reported to reduce DBP on an on-going basis in the medium-term following birth.

Perspectives

Self-management of hypertension following birth appears to be feasible. Given the caveat of sample size, the improvements in BP observed and in the case of DBP, the persistence of the differences well after the initial intervention, suggest that self-management may have a significant place in the postpartum management of HDP. A large-scale RCT with BP as the primary outcome is warranted to confirm these findings and further explore the hypothesis that improved short-term BP control in the puerperium can positively modulate long-term BP and potentially cardiovascular risk.

Contributors

RJM gained funding for the study. AEC led the study, drafted the report and undertook the analyses, with statistical advice from SM and JM. All authors participated in design, execution, and oversight of the study. All authors had access to the data, commented on subsequent drafts, and approved the final submitted version. RJM will act as guarantor and with AEC made the final decision to submit for publication.

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Novelty and Significance

What's new?

- No studies have previously evaluated self-management of hypertension postpartum;
- First evaluation of a comprehensive management strategy that suggests improved postpartum BP control;
- First postpartum hypertension trial to demonstrate a potential treatment effect between groups in the medium term.

What's relevant?

- The puerperium often falls into the shadow of pregnancy and childbirth, but in view of the proportion of complications that occur after delivery, and readmissions attributable to hypertension, it should not be overlooked.

Summary of conclusions

- Self-management appears to be a feasible and promising management strategy for postpartum women with HDP, and large-scale evaluation is justified.

Figures

Figure 1: Consort Flowchart

Tables

Abbreviations: Adj. OR = adjusted odds ratio; AHT = antihypertensive; BMI = body mass index; BP = blood pressure; C = control; CI = confidence interval; DBP = diastolic blood pressure; I = intervention; IMD = Index of multiple deprivation; IQR = interquartile range; MAP = mean arterial pressure; PCR = protein:creatinine ratio; PN = postnatal; SBP = systolic blood pressure; SD = standard deviation; WHO DDD = World Health Organisation defined daily dose

Table 1: Baseline characteristics (n=91)

Variable	Intervention (n=45)	Control (n=46)
Mean age (SD) /years	31.7 (5.3)	31.7 (5.3)
Mean BMI (SD) /kg/m^2	29.0 (7.5)	28.0 (8.3)
Parity (n (%))		
0	32 (71%)	31 (67%)
≥1	13 (29%)	15 (33%)
Ethnicity (n (%))		
White (British)	38 (84%)	37 (80%)
White (other)	3 (7%)	6 (13%)
Black	1 (2%)	1 (2%)
Asian	3 (7%)	2 (4%)
IMD quintile (n (%))		
1st	16 (36%)	22 (48%)
2nd	9 (20%)	7 (15%)
3rd	14 (31%)	9 (20%)
4th	4 (9%)	7 (15%)
5th	2 (4%)	1 (2%)
Diagnosis (n (%))		
Gestational hypertension	20 (44%)	22 (48%)
Pre-eclampsia	25 (56%)	24 (52%)

Median PCR (IQR) *(pre-eclampsia)* /mg/mmol	109.2 (55 to 152.9)	55.4 (41.4 to 114.5)
Median gestation at diagnosis (IQR) /weeks	35.9 (31.9 to 37.7)	34.7 (31.7 to 36.9)
Median gestation at delivery (IQR) /weeks	37.6 (36.2 to 39.2)	37.2 (36.3 to 39.1)
In-utero growth restriction (n (%))	12 (27%)	15 (33%)
Special Care Baby Unit admission (n (%))	10 (22%)	14 (30%)
Median duration antenatal AHT treatment (IQR) /days	10 (4 to 19)	9 (5 to 22)
Median dose AHT at baseline visit (IQR) (WHO DDD)	1 (0.7 to 1.5)	1 (0.7 to 1.7)
Mean SBP / DBP at antenatal booking visit (SD) /mmHg	119.2 (14.1) / 72.7 (9.3)	116.8 (12.6) / 73.0 (9.4)*
Mean SBP / DBP (readings 2+3) at baseline† **(SD)** /mmHg	135.2 (15.5) / 87.1 (9.2)	130.8 (13.0) / 85.4 (10.5)

* n=44 (missing data for n=2)

† Baseline visit day 1-6 after birth

Table 2: Feasibility measures

Recruitment*			
Recruitment rate	49% (*91 randomized, 186 approached*) 59% (*91 randomized, 154 eligible approached*)		
Recruitment rate per site per month	1.5 participants randomized per site per month (*91 randomized, cumulative 59.1 months recruitment period*)		
Consent rate	66% (*101 consented, 154 eligible approached*)		
Conversion rate	90% (*91 randomized, 101 consented*)		
Retention rate	***Whole population (n=91)***	***Intervention (n=45)***	***Control (n=46)***
6-months	90% (82)	89% (40)	91% (42)
6-weeks	92% (84)	91% (41)	94% (43)
Trial fidelity	***Whole population (n=91)***	***Population that finished follow-up (n=82)***	
Study follow-up visits attended within pre-defined window	85% (388/455)	93% (380/410)	
Study follow-up visits attended	91% (412/455)	98% (403/410)	

* The majority of patients were consented pre-delivery (two consented after birth) and randomised if they remained eligible and willing post-delivery

Table 3: Mean blood pressure at follow-up

Variable		Baseline (1-6d PN)	Day 10 (8-14d PN)	4 weeks (21-35d PN)	6 weeks (36-49d PN)	12 weeks (77-91d PN)	26 weeks (168-196d PN)
Number of observations (I/C)		45 / 46	41 / 42	41 / 42	41 / 42	40 / 41	40 / 42
AHT treatment (n (%)) (I/C)		45 (100%) / 45 (100%)	38 (93%) / 38 (91%)	22 (54%) / 30 (71%)	14 (34%) / 19 (45%)	5 (13%) / 8 (20%)	1 (3%) / 2 (5%)
Median WHO DDD AHT treatment (IQR) (I/C)		1 (0.7 to 1.5) / 1 (0.7 to 1.7)	1 (0.4 to 1.4) / 1 (0.7 to 1.5)	0.3 (0 to 0.7) / 0.4 (0 to 1)	0.2 (0.5) / 0.4 (0.8)	0 (0 to 0.4) / 0 (0 to 0.7)	0 (0 to 0) / 0 (0 to 0)
SBP	**I** (*Mean (SD)) /mmHg*[*]	135.2 (15.5)	127.5 (10.9)	123.3 (10.4)	121.6 (8.7)	126.7 (13.1)	125.8 (12.9)
	C (*Mean (SD)) /mmHg*	130.8 (13.0)	125.5 (16.0)	124.9 (10.7)	126.6 (11.0)	126.6 (10.9)	126.8 (14.0)
	Adj. ΔI–C *(95% CI) /mmHg*[†,‡]	4.5 (-1.2 to 10.3)	1.6 (-3.9 to 7.1)	-1.8 (-6.1 to 2.6)	**-5.2 (-9.3 to -1.2)**	-0.1 (-5.1 to 4.9)	-1.0 (-6.3 to 4.4)

Bold denotes where 95% CI around adjusted difference does not cross zero

[*] 6 readings taken at 1-minute intervals: first reading discarded, mean of second and third readings used

[†] For differences between BP readings at baseline, a linear regression model was fitted, with treatment group as the independent variable, adjusting for recruitment centre.

Variable		Baseline (1-6d PN)	Day 10 (8-14d PN)	4 weeks (21-35d PN)	6 weeks (36-49d PN)	12 weeks (77-91d PN)	26 weeks (168-196d PN)
DBP	**I** (*Mean (SD)) /mmHg*	87.1 (9.2)	83.7 (8.6)	82.0 (6.5)	80.5 (6.6)	81.7 (8.4)	81.0 (8.2)
	C (*Mean (SD)) /mmHg*	85.4 (10.5)	85.2 (10.9)	84.8 (7.4)	86.0 (9.7)	85.8 (8.2)	85.5 (9.9)
	Adj. ΔI–C *(95% CI)* /mmHg	1.7 (-2.4 to 5.9)	-1.7 (-5.7 to 2.3)	**-3.0 (-5.8 to -0.1)**	**-5.8 (-9.1 to -2.5)**	**-4.3 (-7.7 to -0.8)**	**-4.5 (-8.1 to -0.8)**

ǂ For differences between BP readings at follow-up, a repeated measures mixed effects regression model was used, with randomised group, time and an interaction between time and randomised group as fixed effects, adjusting for recruitment site and baseline BP, fitted as fixed effects with an unstructured covariance pattern.

Table 4: Proportion of BP readings inside target range at follow-up

Variable			Day 10 (8-14d PN)		4 weeks (21-35d PN)		6 weeks (36-49d PN)		12 weeks (77-91d PN)		26 weeks (168-196d PN)	
			I	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**
Number of observations			41	42	41	42	41	42	40	41	40	42*
SBP <140 ≥100mmHg & DBP <90 ≥60mmHg *(on treatment)* OR **SBP <140mmHg & DBP <90mmHg** *(off treatment)*	**Mean of readings 2&3**	**n (%)**	27 (66%)	26 (62%)	37 (90%)	30 (71%)	38 (93%)	26 (62%)	30 (75%)	30 (73%)	32 (80%)	26 (62%)
		Adj. OR (95% CI)	1.2 (0.4 to 3.2)		**3.7 (1.0 to 13.1)**		**8.0 (2.1 to 30.6)**		1.2 (0.4 to 3.3)		2.3 (0.8 to 6.3)	
	Mean of readings 2-6	**n (%)**	33 (81%)	26 (62%)	36 (88%)	31 (74%)	36 (88%)	25 (60%)	32 (80%)	31 (76%)	30 (75%)	28 (67%)
		Adj. OR (95% CI)	**3.3 (1.0 to 10.6)**		2.5 (0.8 to 8.3)		**5.4 (1.7 to 17.6)**		1.3 (0.5 to 3.9)		1.4 (0.5 to 3.7)	

Bold denotes where 95% CI around adjusted odds ratio does not cross zero

* n=41 for mean of readings 2-6