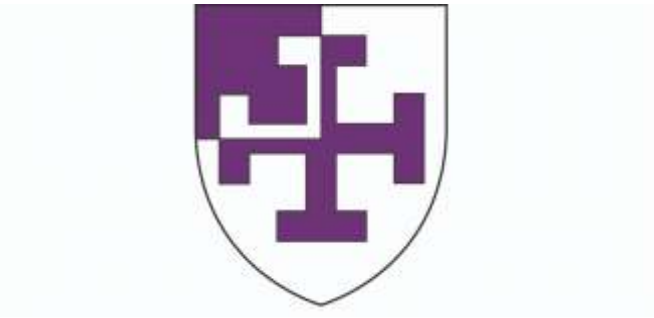
Cardiovascular remodelling after hypertensive pregnancy: the impact of postpartum blood pressure control

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Thesis presented for degree of Doctor of Philosophy

Trinity Term 2022



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Word count: 48,288 words

ACKNOWLEDGEMENTS

This thesis would not have been possible without the support of so many. I hope along the way I have ensured that they have realised my gratitude for the role they have played. Kirsten, my wife, has been with me every step of the way through this work and her guidance, encouragement and support has been immeasurable. My supervisors, Paul Leeson, Richard McManus and Adam Lewandowski have been instrumental in helping me develop and perform this research and have guided me throughout, I have learnt much from them all and enjoyed working together. My predecessors Alexandra Cairns and Harry Boardman paved much of the way for my project to happen, and although we have not worked much together directly I feel that I have shared history with this research area. I am grateful to Alexandra Cairns who recruited the initial 101 patients to the SNAP-HT trial that enabled me to then perform the SNAP-HT Extension study in due course. In SNAP-HT Extension, I recruited and performed the assessments and analysis on the 63 participants who agreed to partake in the SNAP-HT Extension study. Harry Boardman helped develop many of the MRI based imaging protocols used in POP-HT during his D Phil, to which I am hugely indebted. POP-HT visits were all led/overseen by me aside from two weeks of annual leave during which Adam Lewandowski, Annabelle McCourt, Annabelle Frost, William Woodward and Yvonne Kenworthy graciously covered the self-management process, and continued recruitment and V4 visits for this period. Yvonne and Annabelle also performed most of the remote V2 and V3 (week 1 and week 6) ZOOM® based BP follow up visits too to allow me to focus on the baseline and V4 visits.

Yvonne Kenworthy, the research midwife on the study, Annabelle McCourt and William Woodward, research scientists have all worked so hard to make this project a success and they have been an immense pleasure to work with. Annabelle Frost, my successor in the group as a BHF CRT-F has also been a beacon of light. Winok Lapaidare (brain analysis lead), Aiden Doherty and Shing Chang Chang (accelerometer analysis), Mauro Santos and Cristian Roman (OIBME app design and implementation), Katherine Tucker (moral support throughout), Miriam Khan (OCMR radiographer and assistant in CMR analysis) have all been of invaluable assistance and very patient with my demands. Polly and Kate your smooth running of CCRF has helped my study and also made it a fun place to work. Rachael Fox helped my statistical cross-checking for the SNAP-HT Extension study and Holger Burchert helped cross-check my statistical work for POP-HT, both of whom have been irreplaceable for their assistance in this area. Similarly, all my other research colleagues have helped to steer me in the right direction and keep it fun on the journey, Maryam, Cheryl, Affifa, Andy, Natalie and Hannah – thank you. I am also grateful for assistance from colleagues in OCMR to allow me the odd short-break in a rather hectic scanning schedule: Joanna, Rebecca, Vimbae and Miriam – thank you. My thanks also go to Lucy MacKillop and

Christina Aye who helped with access to patients and the study's day to day running. I would also like to thank my Trial Steering committee and the insight provided by my external collaborators Lucy Chappell and Basky Thilangathan. Henner Hansen and Lukas Streese are analysing the retinal data to be added to this body of work in due course. Finally, I am grateful for the financial support from the British Heart Foundation and NIHR without which this work would not have been possible.

All the statistical analysis in this thesis, and the conclusions made within are my own work. The primary outcome analysis was cross-checked by the respective study statistician for each study to ensure consistency of results. Rachael Fox also helped me cross-check my statistical findings for the SNAP-HT Extension study and POP-HT trial and Holger Burchert helped in Graph Pad Prism® in the production of the box-plot figures, for which I thank him.

DEDICATIONS

To Kirsten, Constance and William with all my love

ABBREVIATIONS

ACEI	Angiotensin Converting Enzyme inhibitor
AE	Adverse event
ABPM	Ambulatory Blood pressure monitoring
AHA	American Heart Association
AHT	Anti-hypertensive
AI	Augmentation index
AR	Adverse reaction
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
CAD	Coronary artery disease
CONSORT	Consolidated Standards of Reporting Trials i.e. a flow diagram of the process through the phases of a parallel randomised trial of two groups
CI	Chief Investigator
CCRF	Cardiovascular Clinical Research Facility
CMR	Cardiovascular magnetic resonance
COVID-19	Coronavirus disease caused by SARS-COV-2 that emerged in December 2019
CPET	Cardiopulmonary exercise test
CRF	Case Report Form
CT	Clinical Trials
CTRG	Clinical Trials and Research Governance
DBP	Diastolic Blood pressure
DDD	Defined daily dose (WHO)
DIC	Disseminated intravascular coagulation
DMC/DMSC	Data Monitoring Committee / Data Monitoring and Safety Committee
DSUR	Development Safety Update Report
ECV	Extra-cellular volume
EDV	End-diastolic volume
EDVi	End-diastolic volume indexed (to either BSA or height (H)
EQ-VAS	EuroQOL Visual Analogue Scale
ESV	End-systolic volume
ESVi	End-diastolic volume indexed (to either BSA or height (H)
ESC	European Society of Cardiology
GCP	Good Clinical Practice

GH	Gestational Hypertension
GP	General Practitioner
HDP	Hypertensive disorder of pregnancy
HDL	High density lipoprotein
HELLP	Haemolysis Elevated Liver Enzymes Low Platelet Syndrome (severe complication of pre-eclampsia)
HRA	Health Research Authority
IBM®	International Business Machines
ICF	Informed Consent Form
IMD	Index of Multiple Deprivation
ITT	Intention to Treat
IUGR	Intra-Uterine growth restriction
JCMR	Journal of Cardiovascular Magnetic Resonance
LDL	Low density Lipoprotein
LV	Left ventricle
LVH	Left ventricular hypertrophy
LTF	Lost to Follow-up
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
NICE	National institute for clinical excellence
NHS	National Health Service
NIHR	National Institute for Health Research
OCMR	Oxford Centre for Clinical Magnetic Resonance
OIBME	Oxford Institute for Biomedical Engineering
OR	Odds Ratio
PCR	Protein-Creatinine ratio
PE/PET	Pre-eclampsia
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
PN	Postnatal
POP-HT	Physician Optimised Postpartum Hypertension Treatment
PPE	Personal Protective Equipment
PPI	Patient and Participant Involvement
PWV	Pulse wave velocity
R&D	NHS Trust R&D Department
RES	Research Ethics Service

REC	Research Ethics Committee
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
ShMOLLI	Shortened Modified Look-Locker Inversion recovery (ShMOLLI) sequence for clinical myocardial T1-mapping
SMS	Short message service
SNAP-HT	Self-Management of Postnatal Hypertension
SOP	Standard Operating Procedure
SPSS	Statistical Packaged for the Social Sciences
SV	Stroke Volume
SVR	Systemic Vascular Resistance
TSC	Trial Steering Committee
WHO	World Health Organisation

ABSTRACT

Hypertensive disorders of pregnancy (HDP) are associated with an increased risk of later cardiovascular disease. Whether this relates to how HDP are managed or because HDP merely identify women predisposed to disease is debated. HDP induce significant cardiac remodelling and, several years ago, the researchers I work with proposed a novel hypothesis: that failure of cardiovascular recovery postpartum permanently alters blood pressure (BP) trajectory. In support of this, persistent BP elevation six weeks postpartum, and/or adverse cardiac remodelling predict future hypertensive risk. Furthermore, in a randomised trial [SNAP-HT] investigating feasibility of BP self-management postpartum, diastolic BP was lower 6 months postpartum in the intervention group. I have now tested this hypothesis further using two clinical trials. Firstly, by performing long-term follow up of the SNAP-HT cohort I found that BP differences were sustained for up to four years postpartum, consistent with a permanent alteration in blood pressure trajectory. I then undertook the Physician Optimised Post-partum Hypertension Treatment trial (POP-HT), a prospectively randomised open blinded endpoint study of >200 women, with pre-eclampsia or gestational hypertension, who required anti-hypertensive medication on discharge. The trial was appropriately powered for blood pressure differences with randomisation 1:1 to either physician-optimised postpartum BP self-management or usual care. The trial demonstrated the intervention significantly reduced systolic and diastolic BP 6-9 months postpartum, measured by both clinic and 24hr ambulatory BP. Differences were evident by one week postpartum and the intervention was associated with reduced postnatal readmissions. Echocardiography and cardiovascular magnetic resonance demonstrated BP reductions associated with improved left ventricular systolic and diastolic function, beneficial atrial and ventricular remodelling, and increased aortic compliance. These findings provide significant evidence supporting the hypothesis that effective puerperal BP control has long-term benefits for the mother, including reduced readmission rates, improved BP for up to 4 years after, and beneficial cardiovascular remodelling.

Figure 1. Cardiac changes in pregnancies complicated by hypertensive disorders of pregnancy (HDP)

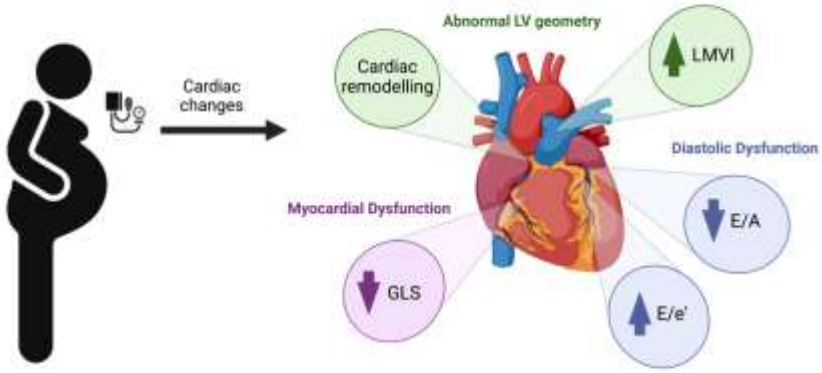
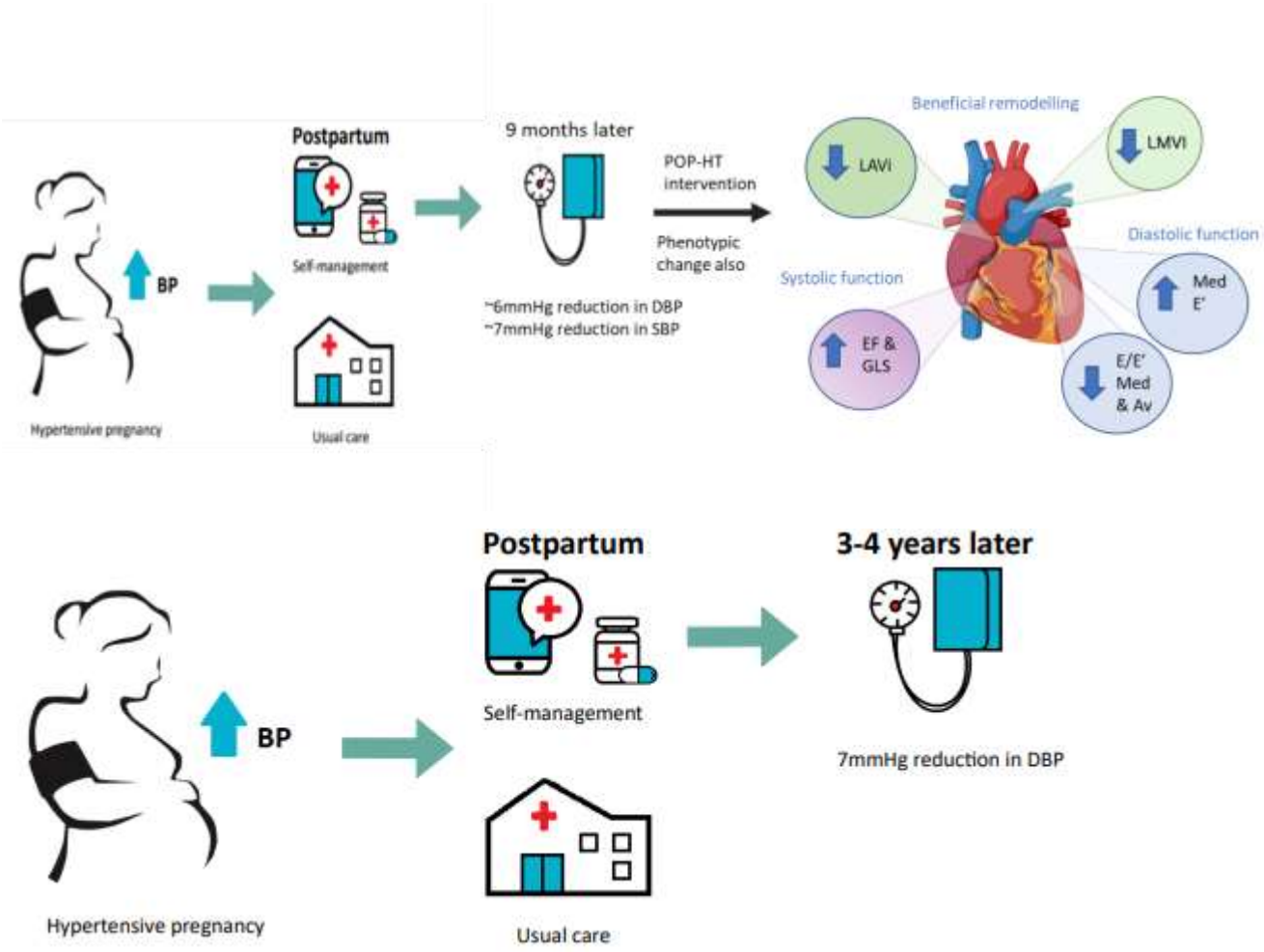


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LIST OF PUBLICATIONS PUBLISHED DURING MY D PHIL

1. **Kitt J**, Fox R, Tucker KL, McManus RJ. New Approaches in Hypertension Management: a Review of Current and Developing Technologies and Their Potential Impact on Hypertension Care. *Curr Hypertens Rep.* 2019; 21(6):44. doi: 10.1007/s11906-019-0949-4.

2. Fox R, **Kitt J**, Leeson P, Aye CL, Lewandowski A. Preeclampsia: Risk Factors, Diagnosis, Management, and the Cardiovascular Impact on the Offspring *J Clin Med* 2019; 8(10):1625. https://doi.org/10.3390/jcm8101625

3. **Kitt J**, Fox R, Tucker KL. Digital Health: New Approaches in Hypertension Management. *J Cardiol and Cardiovasc Sciences.* 2020;4(1):18-23

4. **Kitt J**, Frost A, Leeson P. Preeclampsia and the Brain—A Long-term View. *JAMA Netw Open.* 2021;4(4):e215364. doi:10.1001/jamanetworkopen.2021.5364

5. **Kitt J**, Fox RL, Cairns AE, Mollison J, Burchert HH, Kenworthy Y, McCourt A, Suriano K, Lewandowski AJ, Mackillop L, Tucker KL, McManus RJ, Leeson P. Short-Term Postpartum Blood Pressure Self-Management and Long-Term Blood Pressure Control: A Randomised Controlled Trial. *Hypertension*. 2021;78:469–479. doi.org/10.1161/HYPERTENSIONAHA.120.17101

6. **Kitt J,** Frost A, Mollison J, Tucker KL, Suriano K, Kenworthy Y, McCourt A, Woodward W, Tan C, Lapidaire W, Mills R, Lacharie M, Tunnicliffe EM, Raman B, Santos M, Roman C, Hanssen H, Mackillop L, Cairns A, Thilaganathan B, Chappell L, Aye C, Lewandowski AJ, McManus RJ, Leeson P. Postpartum blood pressure self-management following hypertensive pregnancy: protocol of the Physician Optimised Postpartum Hypertension Treatment (POP-HT) trial. *BMJ Open* 2022; 12:e051180. doi:10.1136/ bmjopen-2021-051180

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CHAPTER 1 – INTRODUCTION

I. Risk of hypertensive pregnancy on long-term cardiovascular risk in the mother

Hypertensive disorders of pregnancy (HDP) are a common problem effecting up to 20% of mothers. This umbrella term covers both worsening hypertension in those with chronic hypertension, as well as new onset hypertension after 20 weeks gestation, either as pregnancy induced hypertension, or the syndrome of preeclampsia. Preeclampsia accounts for 3-5% of pregnancy complications and 10% of preterm deliveries [1] and is a multisystem disorder [2] defined by the International Society for the Study of Hypertension in Pregnancy (ISSHP) as new onset hypertension accompanied by evidence of uteroplacental dysfunction and/or maternal measures of organ dysfunction [2]. The onset of hypertension during pregnancy has significant impacts on maternal and foetal health during pregnancy and this is a worldwide problem, accounting for 50% of maternal mortality, with the majority of patients found in low- and middle-income countries [3, 4].

The postpartum period has traditionally been considered a lower risk period as blood pressure has often returned to the normal range within 6 months postpartum [5]. However, this period can be accompanied by rapid and often unpredictable changes in blood pressure. One study showed that 50% of women with pre-eclampsia have persistent significant hypertension on day 5 following delivery [6], with blood pressure control remaining an issue for up to six weeks after childbirth, often requiring multiple medications and careful titration. At the same time, competing postnatal demands on mothers, not least from the new baby, can be associated with poor adherence and/or poor levels of clinical contact. Drug titration can therefore be sporadic exacerbating poorly controlled hypertension. There may also be longer term implications from poor blood pressure control in the postpartum period. Risk of higher blood pressure 5 to 10 years after a hypertensive pregnancy is related to blood pressures levels during the first few months postpartum [7] and a recent publication highlighted that one third of women after hypertensive pregnancy represent with chronic (i.e. essential) hypertension within 10 years [8]. Consistent with these findings, HDP are associated with a two-fold increase in the risk of subsequent cardiovascular disease [9] [10] and, as a result, recent ESC [11] and AHA guidance

[12] advise that women should be informed of this increased risk after pregnancy, advocating annual blood pressure monitoring. However, beyond routine risk factor management, no specific additional interventions are currently available to reduce long-term risk as outlined further in section VI and VII of this chapter.

The latest NICE guidance in the UK [13] has attempted to quantify the risks for the first time (see figure 3 below) and a recent publication by Honigberg et al also demonstrates these risks extend well beyond coronary artery disease [14], albeit some of this is mediated by chronic hypertension. As well as a 1.8 fold increase in the risk of coronary artery disease, there is also a 1.7 fold increase in the risk of heart failure by the 6^{th} decade of life. The impact on valvular heart disease is even more alarming with a 2.9 fold increase in the risk of aortic stenosis and a 5 fold increase in the risk of mitral regurgitation. In this study Cox proportional hazards models began follow-up at study enrolment and were adjusted for age at enrolment and race. Whilst other co-morbidities were not adjusted for in the primary published data, in a sensitivity analyses excluding 12,121 women in the cohort with any prevalent cardiovascular disease diagnosis, there were still significant associations between HDP and incident coronary artery disease (HR: 1.7; 95% CI: 1.1 to 2.5; p = 0.01), aortic stenosis (HR: 2.2; 95% CI: 1.0 to 5.0; p = 0.04), and mitral regurgitation [14].

Figure 3: Adapted from NICE guideline NG133 [13]: Long-terms risk associated with HDP

Future risk [a,b]	Pre-eclampsia	Gestational hypertension
Any hypertension	~ 20% (1 in 5 women)	~ 22% (1 in 5 women)
Pre-eclampsia	Up to approximately 16% (1 in 6 women) If birth was at 28–34 weeks: approximately 33% (1 in 3 women) If birth was at 34–37 weeks: approximately 23% (1 in 4 women)	~ 7% (1 in 14 women)
Gestational hypertension	Between approximately 6 and 12% (up to 1 in 8 women)	Between approximately 11 and 15% (up to 1 in 7 women)
Major adverse cardiovascular event	Risk increased 1.5–3 fold	Risk increased 1.5–3 fold
Cardiovascular mortality	Risk increased 2 fold	(no data)
Stroke	Risk increased 2–3 fold	Risk may be increased
Hypertension	Risk increased (approximately 2–5 fold)	Risk increased (approx. 2–4 fold)

[a] Risks described are overall estimates, summarised from risk ratios, odds ratios and hazard ratios [13]. [b] Increased risk is compared to the background risk in women who did not have hypertensive disorders during pregnancy. Absolute risks are not reported, because these will vary considerably, depending on the follow-up time (range from 1 to 40 years postpartum) [13]

II. Does long-term risk of hypertensive pregnancy represent pre-existing cardiovascular risk or relate to the pathophysiology of the hypertensive disorder?

The mechanisms responsible for HDP are not fully understood though an increasing number of contributory mechanisms are being brought to light. One of the earliest manifestations, which is widely supported to be important in the process, is the impaired implantation of the placenta [15]. It has long been presumed by researchers interested in preeclampsia that defects of trophoblast development, motility, invasion and function are intrinsic defects which influence the persistence of a high-resistance uterine artery circulation as a result of inadequate spiral (uterine) artery invasion. Rodriguez et al [16] demonstrated that, in women with late onset pre-eclampsia, uterine artery doppler indices can be used in the classification of clinical disease, and these doppler indices also correlate with placental histological findings[17]. Histological specimens from these women show the presence of acute atheroma, in some of the placental vessels, characterised by vascular necrosis and foam cell infiltration [18]. These vascular findings often relate to areas of placental infarct [19] and resemble early atherosclerosis [20]. The ischaemic placenta is thought to result in release of soluble placental factors into the maternal circulation which promote anti-angiogenesis and inflammation and lead to widespread endothelial dysfunction [21, 22]. Angiogenic factors have been shown to be altered 5-10 weeks prior to the onset of hypertension, with increased soluble fms-like tyrosine kinase 1 (sFLT-1) and reduced placental growth factor (PlGF) [23]. In fact, this correlation is so strong that the ratio of sFLT-1:PlGF is now used alongside clinical practice to help predict the onset of pre-eclampsia in women between 20 and 34 weeks plus 6 days of gestation, and has been endorsed in the updated NICE NG133 guidance[13] . The case for an important role of sFLT-1 and sEng (a related angiogenic factor) is supported by findings that exposure to pregnant rats with adenovirus expressing sFLT-1 and sEng causes a syndrome very similar to preeclampsia [24]. sFLT-1 and sEng impair the binding of pro-angiogenic factors to their receptors, vascular endothelial growth factor (VEGF) and PlGF to the former and TGF-β to the latter [25].

The triad of inadequate placentation, placental insufficiency, and widespread endothelial activation is the most recognised justification of the pathology underlying preeclampsia. However, clinical findings supporting this triad are only found in a minority of all pre-eclamptic pregnancies, and many women with pre-eclampsia have histologically normal placentas [26]. As already described in section I, the link between cardiovascular disease and pre-eclampsia is ever more evident. Given that in other vascular disorders e.g. chronic kidney disease, and vascular dementia, it is the disruption in vascular perfusion that leads to end-organ damage, rather than the organ itself (the placenta in this case) causing the upstream damage, it is more plausible that this classically described triad is a consequence rather than the cause of pre-eclampsia. This is supported by the increasing body of evidence that demonstrates cardiovascular problems associated with preeclampsia are seen before as well as after the index pregnancy. The HUNT studies [27], described in more detail below, suggest that the cardiovascular system is not a downstream target of poor placentation, but rather that it plays a vital role in the pathogenesis of the disorder itself. This proposition is reinforced by a systematic review from Kalafat *et al [28]*, which reveals that Doppler assessment of two unrelated maternal vessels (ophthalmic and uterine arteries) can be used to predict the onset of pre-eclampsia. The finding of such a relationship between ophthalmic Doppler indices and pre-eclampsia cannot be a consequence of impaired trophoblast invasion alone. Based on work such as Kalafat's demonstrating the involvement of extra-uterine vessels in pre-eclampsia, there are now several models proposed to explain the pathophysiology of future hypertensive and cardiovascular disease risk in the mother [29] (and offspring [30]).

Figure 4 below proposes three possible models. Firstly, that the hypertensive disorder of pregnancy induces a vascular dysfunction that increases future risk (Panel B). Secondly, that a pre-existing difference in vascular and cardiac function increases risk of pregnancy hypertension and the pre-existing risk explains the later increased cardiovascular risk (Panel C – dotted line). Thirdly, that later risk is a combination of both pre-existing risk and further subclinical endothelial or cardiac 'injury' at the time of pregnancy (Panel C – solid line). In support of the third model, studies and recent meta-analyses have demonstrated both endothelial dysfunction and macrovascular dysfunction e.g.

increased arterial stiffness and sub-clinical atherosclerosis, before and after hypertensive pregnancy, the latter evident from just 3 months postpartum [22, 31].

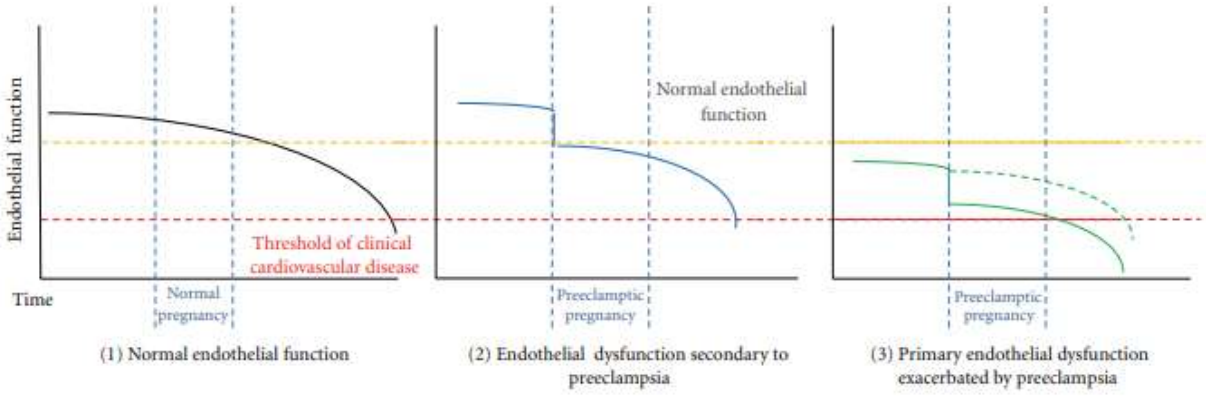


Figure 4 reproduced with permission from Lazdam et al [29]: Theoretical timelines of impairment of endothelial function and development of cardiovascular disease following pre-eclamptic pregnancy. (1) In the normal individuals there is a gradual age-related reduction in endothelial function, which can be exacerbated by the presence of cardiovascular risk factors and associates with the future risk of clinical cardiovascular disease. (2) Women who experience pre-eclamptic pregnancies are known to have impaired endothelial function during pregnancy and up to 3 years following an affected pregnancy. It is possible that these women begin life with normal endothelial function, which is acutely impaired during a pre-eclamptic pregnancy. This is followed by age-related decreases in endothelial function and together these cause the increased incidence of cardiovascular disease in these individuals. (3) Alternatively, women who develop pre-eclampsia may have primary endothelial dysfunction which both puts them at risk of preeclampsia, this may then be exacerbated by the pre-eclamptic pregnancy (solid line), or simply persist (dotted line), in either case leading to higher incidence of cardiovascular disease.

There is also a large body of epidemiological evidence supporting the proposal that a pre-existing dysfunction is present in those who develop a hypertensive pregnancy. Of particular interest is data from the longitudinal follow up of the Norwegian Nord-Trondelag cohort (the HUNT1, 2 and 3 studies). These were population-based, open cohort studies from 21 years prior to pregnancy to 41 years after the index pregnancy from 1984 onwards [32]. This cohort contained 22,308 normotensive women, 1092 of whom developed pre-eclampsia and 478 of whom developed gestational hypertension. Haug et al show that in women with HDP; adverse levels of adiposity; blood pressure; heart rate; serum lipids and serum glucose, are all present before the first pregnancy and remain higher in this cohort compared to normotensive women. This group conclude that the progression of cardiovascular risk factors from age 20-60 years occurred in parallel for women with and without a history of HDP, with greater increases in BP and adiposity in women with a history of HDP, i.e. they suggest the dotted line

in model 3 above is the more likely pathophysiological explanation, with HDP representing a continuation of an already 'bad' life-course trajectory in these women.

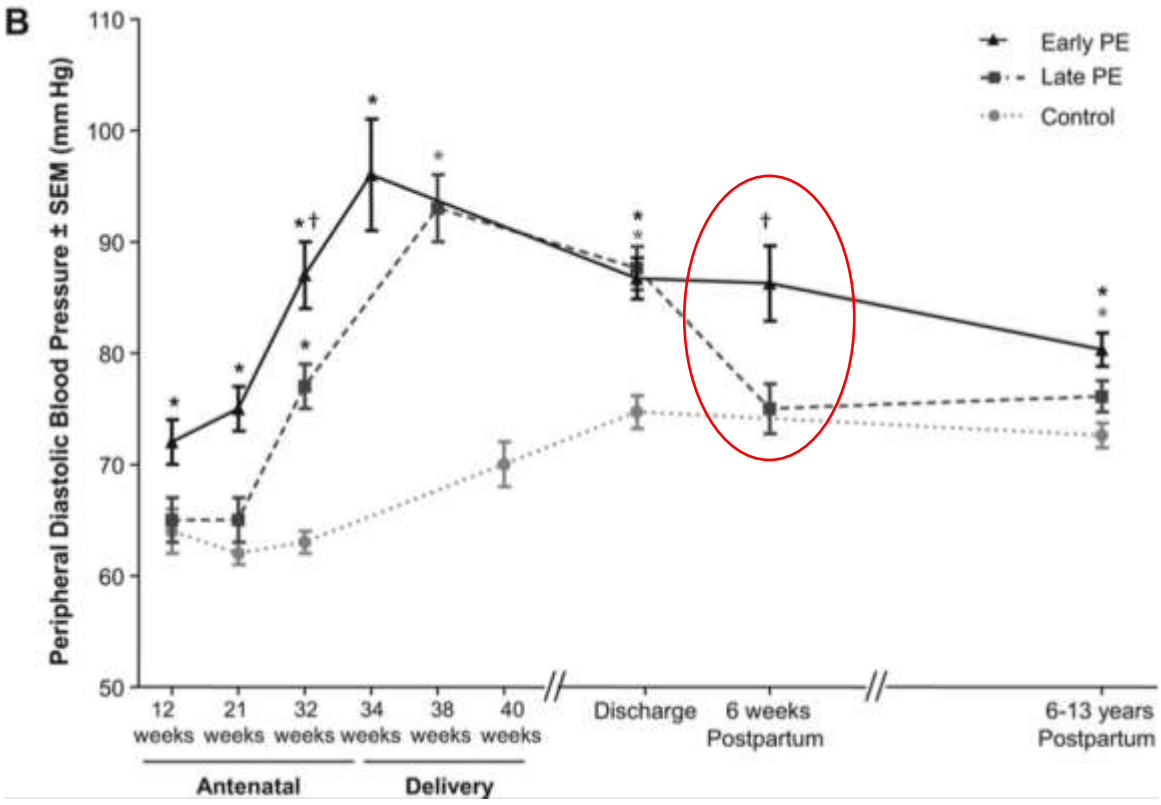
However, the fact that women with a reoccurence of pre-eclampsia in their 1st and 2nd pregnancies have a more adverse CV profile than women with only one occurrence of pre-eclampsia [26] also suggests each pregnancy provides an acute cardiovascular stress i.e. favours the solid line in model three rather than the dotted one. In essence each pregnancy provides an acute deterioration in already impaired vascular function, with each insult lowering the age threshold for clinical cardiovascular disease. Given that cardiovascular remodelling precede clinical symptoms, and that there is basic science and epidemiological correlation between endothelial and cardiovascular indices, model 3 most likely represents the pathophysiology of hypertensive risk.

The HUNT data also highlights a unique pattern of diastolic BP in the HDP cohort, something not commented on by the authors and which is not explained by pre-existing differences in blood tests and adiposity [27]. In the HDP cohort the diastolic BP does not return to normal postpartum as it does in the normotensive group. I hypothesise that this step change in diastolic BP [27] may relate to an interaction between preexisting microvascular dysfunction and the acute stress of the hypertensive pregnancy. This persistent elevation of diastolic BP/failure of normalisation to 'booking' (i.e. antenatal) levels of BP, also correlates with the historical findings of the FRAMINGHAM study, in which it is diastolic BP elevation, rather than systolic, which better correlates to long-term risk of cardiovascular disease in those aged<50 [33]. This is also reflected in the 2018 ESC hypertension guidelines [34], which state that 'High DBP is associated with increased CV risk and is more commonly elevated in younger (<50 years) vs. older patients.' In summary , persistent elevation of diastolic (and later systolic) BP seems to result in further longer-term cardiovascular risks such as ischaemic heart disease, heart failure and valvular heart disease [14].

III. Potential importance of postpartum period as a 'critical window'

As mentioned in section II, the data from the HUNT studies [27] highlight an interesting window post-natally where a lack of normalisation of diastolic BP leads to an accelerated trajectory towards hypertension over subsequent years. This was also true in the long term follow up of a pre-eclampsia cohort by my group [35]. This work (shown below in figure 4) showed the greatest rise in long-term BP was seen in those with persistently elevated diastolic BP at six weeks postpartum in women, and in those with the most severe form of pre-eclampsia (early-onset pre-eclampsia). In contrast, a normal blood pressure at six weeks, even after a hypertensive pregnancy, is predictive of a lower long-term blood pressure trajectory.

Figure 4: Timeline of diastolic BP trends from 12 weeks antenatally to 6-13 postpartum (reproduced with permission from Lazadam et al 2012): Women with early onset pre-eclampsia had significantly higher diastolic BP (DBP) (*) throughout pregnancy and at 6 weeks postpartum vs. those with late-onset pre-eclampsia. Women with late-onset pre-eclampsia had comparable DBP with controls at booking and slightly higher 6 week BPs but higher levels by 6-13 years later (grey asterisks) suggesting a slower trajectory in this sub-group. **(**Error bars represent mean±SEM; †significant difference between early and late-onset groups)**.**



Although the postpartum period has traditionally been considered a low risk period [5], as the above figure illustrates, the first 6-8 weeks, can be accompanied by rapid, often unpredictable changes in BP. Another study showed that up to 50% of women with pre- eclampsia had persistent significant hypertension on day 5 following delivery [6], with BP control problematic for six weeks postpartum. This may be critically important for determining long term blood pressure trajectories because significant cardiac and vascular remodelling is occurring during the puerperium. Normal pregnancy is associated with substantial cardiac and vascular remodelling over a period of nine months [36]. The added burden of hypertension, in combination with the acute inflammatory, anti-angiogenic and oxidative stress of a hypertensive pregnancy, results in additional significant adverse cardio-vascular changes [37, 38] such as left ventricular hypertrophy (LVH) and diastolic dysfunction. Postpartum these cardiac and vascular changes are known to reverse but, in a proportion of those who had hypertension during pregnancy, differences can still be observed up to one year after delivery [36, 39]. Furthermore, Melchiorre et al demonstrated that persistent LV dysfunction/presence of LV hypertrophy at one year postpartum, in women who had preterm preeclampsia, is strongly associated with risk of development of essential hypertension within the subsequent 2 years. Therefore, several years ago the research group in Oxford proposed the hypothesis that postpartum blood pressure optimisation may be critically important in determining long term trajectory for blood pressure control after a hypertensive pregnancy because of its impact on postpartum cardiovascular 'repair'.

IV. Role of BP self-management in improving BP control postpartum:

Treating hypertension in the general population has been shown to result in marked reductions in risk of long-term cardiovascular disease [40, 41]. Despite strong evidence for such treatment, it is widely recognised that many people remain undiagnosed (between a third and a half of patients), indicating the need for better screening [42], and 40% of those on hypertensive registries remain sub-optimally controlled [43]. It is important to note that the BP management postpartum in the historical epidemiological studies quoted above, such as the HUNT studies, was poorly defined and in many patients it is likely there would have been no significant blood pressure intervention. Cairns et al

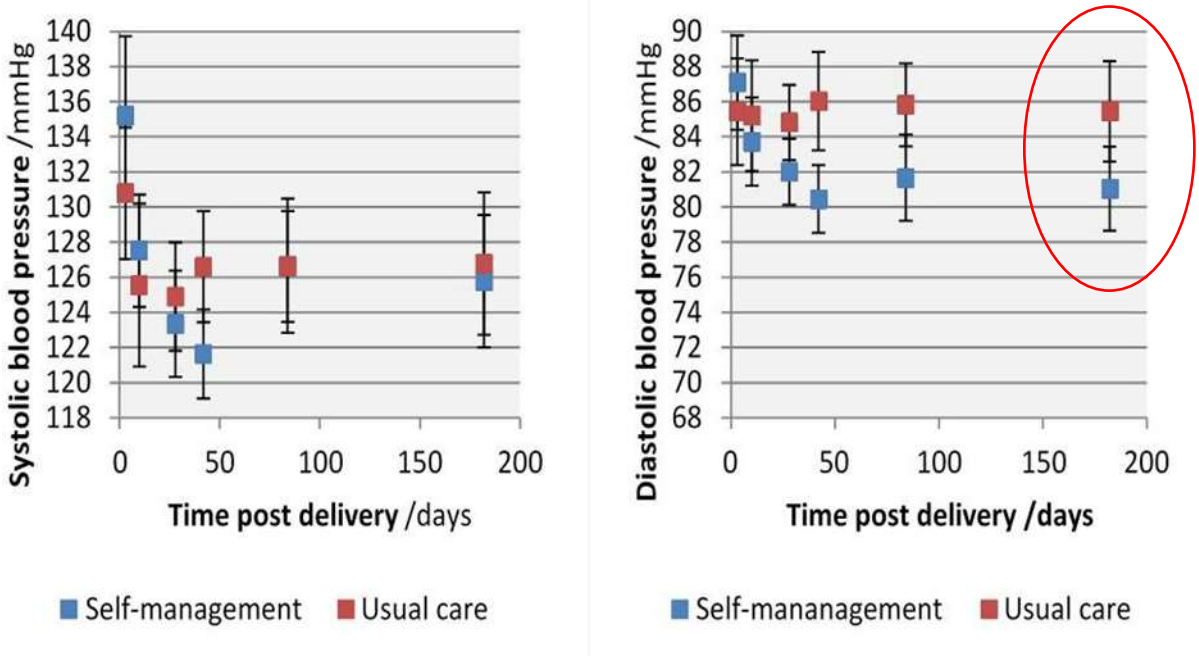
published a systematic review in 2017 [44] showing 'there was no gold standard' postpartum BP management. 39 studies were included (n=2901) with insufficient data to recommend any single pharmacological intervention. 18 studies reported that calcium channel blockers, vasodilators and beta-blockers all lowered BP postpartum but only 12 of these reported safety data, and limited data existed regarding choice of medication in the puerperium with a wide variation in BP targets. There were also no algorithms historically for which drug should be 1st line and for medication up-titration and it is only the latest iteration of the NICE guidance in 2019 [45] that attempts to valiantly do so based on very limited evidence.

New approaches, including new technologies, are now available to improve screening, detection and control of raised blood pressure. Trials of self-monitoring outside of pregnancy, repeatedly show it can improve BP control, and it is an increasingly common part of hypertension management. Home BP monitoring has in fact been included in the NICE guidelines for adult hypertension since 2011 because it is well tolerated by patients and is a better predictor of end organ damage than clinic measurement [46, 47]. It works best in the context of co-interventions such as pharmacist/nurse led support [47]. This is because self-monitoring relies on good communication between patients and physicians [48]. One solution to this communication problem is the remote monitoring of BP readings measured at home (telemonitoring). Until recently, key evidence missing from trials of telemonitoring was, whether it actually led to lower BP. In 2018, the TASMIN-H4 randomised trial [49] showed that GPs using self-monitored BP to titrate anti-hypertensives, with or without telemonitoring, achieved better BP control when using telemonitoring. As with previous trials, the mechanism of action appeared to be medication optimisation. A recent systematic review of blood pressure self-monitoring by Sheppard *et al* [50] that included 22 eligible trials and 6,522 participants revealed that self-monitoring was associated with an improvement in clinic BP vs. standard care at a 12-month time-point (−3.12 mmHg systolic BP, [95% confidence intervals −4.78, −1.46 mm Hg]. This remained true irrespective of the number of hypertension-related co-morbidities.

Telemonitoring can also be combined with self-titration of medication, a process known as self-management, which can take the form or in person or remote doctor support by telephone or, another option to enhance self-monitoring compliance is the use of a BP monitoring app. This is a rapidly expanding field, with > 180 Apps now existing relating to blood pressure monitoring[51] but a vital issue with both Apps and novel cuffless devices is the lack of an agreed standard for validating the technology. These devices are even foraying into derived measurement, for example the Cardiogram® on the Apple® watch has been evaluated for its efficacy at using deep learning algorithms to predict hypertension from inputs of heart rate and step count. However, the involvement of medical experts in the development process has only taken place in <5% of blood pressure Apps®[52]. At present, no mobile Apps® have obtained approval for use as BP measuring/diagnostic devices by the US Food and Drug Administration or European Commission, though clinic validation has now been sought by some manufacturers [53].

If the process of self-management could be combined with novel validated technology this could create a new gold-standard for BP measurement in pregnancy and the postpartum period. Two large trials that have recently published (BUMP1 and BUMP2 [54, 55]) assessed if BP self-monitoring via an app improved detection and/or control of hypertension during the pregnancy itself i.e. antenatally. Although these trials showed no improvement in BP control or earlier detection, they were well-liked interventions. To test the applicability of self-management methodology postpartum, the SNAP-HT pilot trial was performed by my group in 2017 [56]. SNAP-HT allowed women to record self-monitored BP, receive reminders to monitor BP, and provided real-time medication titration feedback. The results demonstrated the technique was both acceptable; women self-monitored daily with 85% adherence, and accurate (median accuracy 94%), with no adverse safety signal. Moreover, there was a significant improvement in BP control. In keeping with other self-monitoring studies [46], BP control was better whilst on treatment in the self-management arm, being most marked at 6 weeks (with a mean systolic BP difference of 5.2mmHg and mean diastolic BP difference of 6mmHg) but, a striking finding was that diastolic BP was a mean 4.5mmHg lower six months postpartum; even after all but 1/91 mothers had ceased medication [see figure 5 below].

Figure 5: Comparison of the systolic and diastolic BP in the self-management vs usual care groups at different time-points postpartum



If the 4.5mmHg diastolic BP difference at 6 months (circled in red in figure 5 above), were to be maintained long-term it would correlate to an approximate 40% reduction in life-time stroke and 20% reduction in life-time coronary heart disease risk [40]. If a short-term intervention postpartum can result in long term resetting of BP, the optimisation of postpartum BP may represent a highly cost-effective way to reduce risk in women with HDP. However, the reason(s) for this resetting of BP and, whether this is a longer-term effect remain unclear. It is these key questions that this thesis aims to address.

V. Cardiovascular differences after hypertensive disorders of pregnancy and the role of self-management in beneficial remodelling

Normal pregnancy is associated with substantial cardiac and vascular remodelling over a period of nine months [36]. The added burden of hypertension, in combination with the acute inflammatory, anti-angiogenic and oxidative stress of a hypertensive pregnancy, results in additional significant adverse cardiovascular changes [37, 38] such as left ventricular hypertrophy (LVH), increased LV mass, diastolic dysfunction and left atrial enlargement. In a proportion of those who had hypertension during pregnancy,

differences can still be observed up to one year after delivery [36, 39] . Preterm preeclampsia is associated with altered left ventricular geometry and stage B (asymptomatic) heart failure; whereas both preterm and term preeclampsia were associated with left ventricular systolic and diastolic dysfunction and right ventricular diastolic dysfunction at 1 year postpartum. Melchiorre et al also demonstrated that persistent LV dysfunction/hypertrophy at 1 year postpartum in women who had preterm preeclampsia is strongly associated with the risk of development of essential i.e. chronic hypertension within the subsequent 2 years [39].

It is important to note that phenotypic differences in women who have had a hypertensive pregnancy extend beyond the heart. My group have now studied women from 1-15 years after hypertensive and normotensive pregnancies and characterised their cardiovascular, vascular and cerebrovascular systems. Consistent with previous reports [57-59] and the paper by Melchiorre described above, the adverse cardiovascular changes seen following hypertensive pregnancies were the presence of LVH, an increased LV mass, impaired diastolic function and an increased left atrial volume index [60]. Boardman's study also demonstrated lower global longitudinal strain, which may be a valuable surrogate marker for identifying high risk populations and potentially a therapeutic target in those with a history of hypertensive pregnancy as it is now becoming part of routine echo analysis in sub-group populations e.g. in cardio-oncology [61].

Vascular changes following hypertensive pregnancy have also been well reported in several studies and a review by Lazdam et al in 2012 [29] highlighted a range of differences in vascular function in the months-years after the index pregnancy. Although many of these studies were small (see Table 1; Chapter 1) with the sample size in most being n= 20-30; flow mediated dilatation (FMD) was reduced in almost all between 3months-3 years postpartum (indicating impaired endothelial function), and the pulse wave velocity and augmentation index were increased (equating to increased aortic i.e. large vessel stiffness) in several of the studies in this review. A further meta-analysis of arterial stiffness [62] during and after preeclampsia showed increased pulse wave velocity up to 2 years after the index

pregnancy. The impact on small vessel (microvascular function) such as capillaries seems more equivocal with several studies reporting conflicting results [29].

Women with preeclampsia are at risk of eclampsia and death [63] but cerebral changes are also noted in preeclampsia without fulminant eclampsia itself. These include increased cerebral blood flow and impaired autoregulation [64], which could be a risk factor for vasogenic oedema, and may explain the postpartum phenotype described by Boardman et al. in his recent multi-modality phenotyping study published in 2020. In this study of 103 hypertensive and 70 normotensive pregnancies at 5-10 years postpartum, the adverse cardiovascular phenotype described above was found to cluster with adverse cerebrovascular changes in the hypertensive cohort. This included lower grey matter volumes and greater white matter lesion density when compared to the control population [65]. Vascular changes also clustered in the same women, including reduced capillary density and increased aortic stiffness [60] further supporting the findings described in the paragraph above.

The early emergence of changes in cardiac, vascular and brain structure and function is a significant finding in women who have had hypertensive pregnancies and more importantly, it is out of proportion to their cardiovascular risk profile at 5-10 years postpartum [60, 65, 66]. It is possible these phenotypic differences emerge during the pregnancy itself and persist long term, independent of postpartum BP variability, but the significant cardiovascular adaptations that emerge during HDP are known to reverse to some extent during the postpartum period [57, 58, 67, 68] so it seems unlikely the pregnancy period itself is the sole driving mechanism behind these phenotypic changes, and in turn, the increase in long-term cardiovascular risk. This theory is supported by a causal mediation analysis from the Honigberg et al paper, which investigated the proportional contribution of chronic hypertension, hyperlipidaemia, and diabetes mellitus to the risk of incident cardiovascular diagnoses associated with HDP, adjusting for other conventional risk factors (age, race, BMI at study enrollment, ever-smoking, in addition to hypertension, hyperlipidaemia, and diabetes mellitus). This analysis suggested that chronic hypertension accounted for 64% of the association between HDP and incident CAD (95% CI: 36% to 100%; $p < 0.001$)

and 49% of the association with incident heart failure (95% CI: 27% to 100%; p = 0.02) [14].

Therefore, a realistic hypothesis to explain the increased long term 'risk' following a hypertensive pregnancy is that it reflects a failure of the cardiac, vascular and cerebrovascular systems to 'normalise' after pregnancy [29, 69], and that adverse changes that arise during the pregnancy are compounded by hypertension-mediated adverse remodelling during the first few months following birth. It is this mechanistic element that I aimed to explore further in the POP-HT trial, with it being the first study to perform multi-organ deep phenotyping in > 200 women 6-12 months after giving birth.

Table 1: Studies assessing the long-term impact of preeclampsia on vascular function. AIx (augmentation index) and PWV (pulse wave velocity) are robust surrogate markers of aortic stiffness. Endothelial-mediated vasodilatation was measured in conduit arteries by FMD (flow-mediated dilatation) and in the resistance arteries using VOP (venous occlusion plethysmography) to measure FBF (forearm blood flow) or peripheral arterial tonometry (PAT) to measure RHI (reactive hyperaemic index). Mircovascular endothelial responses were quantified in the microcirculation using LDF (laser Doppler flowmetry) and iontophoresis. SGA refers to small for gestational age.

Study	Subjects (Preeclampsia/control)	Interval after delivery	Vascular measures	Results in women with previous preeclampsia
Aortic stiffness				
Robb et al. 2009 [13]	15/22	7 weeks	AIx, PWV	Elevated PWV and AIx.
Yinon et al. 2010 [14]	24/16	6–24 months	AIx	Increased AIx in women with early onset preeclampsia.
Evans et al. 2011 [15]	18/50	6–36 months	PWV	No significant differences in central arterial stiffness.
Páez et al. 2009 [16]	20/20	2 years	PWV, AIx	Elevated PWV and AIx.
Elvan-Taşpinar et al. 2005 [17]	44/46	4–56 months	PWV	Elevated PWV.
Lampinen et al. 2006 [18]	30/21	5-6 years	AIx	No significant differences in AIx.
Subclinical atherosclerosis				
Blaauw et al. 2006 [19]	22/22	≥3 months	Femoral and carotid IMT	Increased IMT with early onset preeclampsia.
Conduit artery endothelial function				
Kuscu et al. 2003 [20]	15/11	2 and 6 weeks	FMD	Reduced FMD both during pregnancy and postpartum (no control data postpartum).
Noori et al. 2010 [21]	45/21	12 weeks	FMD	No significant differences in FMD compared to controls.
Yinon et al. 2010 [14]	24/16	6–24 months	FMD	Reduced FMD in women with early onset preeclampsia.
Hamad et al. 2007 [22]	18/17	15 ± 3 months	FMD	Reduced FMD and endothelial independent dilatation in women with severe preeclampsia.
Germain et al. 2007 [23]	25/22	16 ± 3.5 months	FMD	Reduced FMD.
Páez et al. 2009 [16]	20/20	2 years	FMD	Reduced FMD.
Chambers et al. 2001 [24]	113/48	3 years median	FMD	Reduced FMD particularly in women with recurrent preeclampsia and recovery of endothelial function with ascorbic acid.
Resistance artery endothelial function				
Lommerse et al. 2007 [25]	32/10	0.64–1.6 years	VOP	No significant difference in FBF.
Agatisa et al. 2004 [26]	16/14	9.9 ± 0.5 months	VOP	Reduced endothelium-mediated FBF.
Evans et al. 2011 [15]	18/50	6–36 months	VOP	Reduced FBF in response to mental stress.
Lampinen et al. 2006 [18]	30/21	5-6 yrs	VOP	Significantly reduced FBF to acetylcholine (ACh) and sodium nitroprusside (SNP).
Kvehaugen et al. 2011 [27]	26/17	5–8 years	PAT	RHI comparable between preeclamptic women and controls. Women with SGA baby had significantly lower RHI.
Cutaneous microvascular function				
Khan et al. 2005 [28]	15/54	6 weeks	LDF and iontophoresis	No significant differences between women in endothelial dependent or independent microvascular dilatation.
Blaauw et al. 2005 [29]	25/23	7.0 ± 2.8 months	LDF and iontophoresis	Greater microvascular vasodilator responses in preeclampsia.
Ramsay et al. 2003 [30]	10/10	16–25 years	LDF and iontophoresis	Reduced response to endothelial-dependent and -independent dilatation.

Table 1: Review of studies assessing vascular function after preeclampsia by Lazadam et al 2012.

VI. Other postnatal interventions to protect the cardiovascular system in women with hypertensive disease in pregnancy: Lifestyle and behaviour-based approaches

Several trials are evaluating lifestyle, behaviour and diet interventions in the puerperium to determine if they alter maternal cardiovascular risk trajectory. The Heart Health 4 Moms study 9-month [70] was a randomised controlled trial of 151 US women with preeclampsia within the 5 years prior. The intervention group received a patient-centred program, created with input from preeclampsia patients and the Preeclampsia Foundation. The program included online educational modules, a community forum, heart healthy resources (e.g. meal plans), and communication with a lifestyle coach including 6 scheduled phone calls. The control group received access to a website with links to CVD risk reduction websites accessible to the general public. After 9 months, intervention participants reported increased self-efficacy for healthy eating (p=0.03), greater knowledge of CVD risk factors (p=0.01), and less physical inactivity (p=0.0006) than individuals in the control arm. The groups did not differ in personal control over CVD risk, self-efficacy for physical activity, or reported physical activity levels. There were no improvements in BP control or weight between the groups sadly but this was a small study with a short-term period of follow up.

'Be Healthe for your Heart' was a small, pilot RCT of web-based lifestyle intervention following pre-eclampsia [71]. 31 Australian women with a recent history (≤4 years post diagnosis) of preeclampsia were randomised to two study arms: (1) 16 women were allocated to 'Be Healthe for your Heart', a web-based behavioural intervention and; (2) 15 to the control arm, access to the National Heart Foundation website. Assessments were conducted at baseline, and after three months. Intervention acceptability and impact on absolute CVD 30-year risk score, CVD risk markers and health behaviours were assessed at each timepoint. Although compliance was good (77.4%), and almost 85% of the intervention arm agreed/strongly agreed they were satisfied with the program, there were no significant between group differences in absolute CVD risk, CVD risk markers or health behaviours from baseline to three months. 'RedCarRisk' is another study evaluating lifestyle intervention postnatally. In this instance, a 6 months supervised exercise programme is being used to assess whether this can improve arterial stiffness

following a hypertensive pregnancy. This study is yet to publish however as is BP2 from Australia. BP2 [72] is a three-arm multicentre randomised trial in Australia (registration: ACTRN12618002004246) with a target sample size of 480 and, in which participants are randomised to one of three groups: 1) optimised usual care: information package and family doctor follow-up 6 months postpartum; 2) brief intervention: information package as per group 1 as well as a clinical assessment and brief lifestyle and diet counselling at a specialised clinic with an obstetric physician and dietitian at 6 months postpartum; 3) Extended intervention: as per group 2 but also with enrolment into a 6 month telephone-based lifestyle counselling program from 6 to 12 months postpartum. All women will have an outcome assessment at 12 months with the aim of detecting differences in anthropometry and BP control by 1 year postpartum.

Another systematic review from 2019 [73] reports details of several other observational studies, investigating the role of lifestyle and behaviour modification, all with non-statistically significant trends towards an improvement in 'health' e.g. a decrease in BMI and increase in physical activity. A more recent review published in JAMA Cardiology in 2021 [74]highlights a potential role for transitional clinics to perform a CVD risk assessment e.g. cholesterol, BP and BMI check and counselling at 6 months postpartum, to continue education after a HDP, to ensure blood pressure stability in women with HDP, and to facilitate the transition to longitudinal primary care. This obviously depends on the model of primary and secondary/tertiary care within the healthcare system of a particular country. In Canada, one such MDT clinic comprising dieticians, pharmacists, obstetricians, and nurse practitioners, to educate postpartum women with preeclampsia about their CVD risk and address their modifiable risk factors significantly increased the patient's physical activity and demonstrated improvements in body mass index and weight by ~5 months postpartum. These clinics did report problems with attendance rates, likely due to the perceived low level of risk mentioned previously, and the studies themselves are limited by the lack of control groups and again by small sample sizes.

VII. Other postnatal interventions to protect the cardiovascular system in women with hypertensive disease in pregnancy (drug interventions)

Beyond the AHA recommendation of incorporating HDPs as a risk-enhancing factor to guide statin prescribing, no other specific drug interventions exist to direct screening strategies or therapies for long-term cardiovascular risk reduction postpartum. Recent trials however have suggested there may be specific benefits related to choice of medication in the postpartum period. The Postnatal enalapril to Improve Cardiovascular fUnction following preterm Preeclampsia (PICk-UP) trial published in October 2020 [75], was a randomised double-blind placebo-controlled feasibility trial in the highest risk preeclampsia group (early onset preeclampsia). 40 women completed six months' treatment with enalapril to improve postnatal cardiovascular function (enalapril was titrated as follows: 5mg once daily for 1 week, then 10mg for 2 weeks then 20mg maintenance dose). Echocardiography and haemodynamic measurements were performed at baseline (< 3 days), 6 weeks and 6 months post-delivery on 60 women. At randomisation, 88% of women had diastolic dysfunction and 68% had concentric remodelling/hypertrophy. There was no difference in the primary outcome (TVR) between groups at 6 months postpartum interestingly and similarly, there was no difference in systolic function (measured by LVEF / GLS / S'). However, women who were treated with enalapril had significantly better diastolic function at 6 months than those treated with placebo, as measured by E/E' (adjusted difference -1.07, 95% CI -2.08 - -0.06, p=0.04). Allocation to enalapril was also associated with improved LV remodelling at 6 months, compared with placebo (LVMi adjusted difference -9.23g/m^2, 95% CI -7.73 - -0.71, p=0.03). The supplementary tables published with this paper also reveal that there was a significant improvement in diastolic BP in the intervention arm (79.6 (10.9) mmHg in the ACEi group vs 86.9 (10.6) in the placebo group). Interestingly, worse diastolic dysfunction and increase TVR also correlated to a lower birth weight centile i.e. more severe disease phenotype.

A 2nd RCT specifically assessed the role of targeted calcium therapy in the puerperium as part of a sub-group analysis of the WHO Calcium and preeclampsia study, which in itself is a subset of the PRE-EMPT (Pre-eclampsia, Eclampsia, Monitoring, prevention, and Treatment). This trial was a placebo-controlled trial investigating the pharmacological intervention of the addition of 500 mg/day of calcium to non-

pregnant women who have a low dietary calcium intake in South Africa, Zimbabwe and Argentina. Eight hundred and thirty-six women were randomised however a complete dataset was only available for 201 women. Follow-up was at recruitment and then every 12 weeks until the next pregnancy. Recruitment fell short of the power calculation but baseline characteristics were the same across both groups. Although there was a non-statistically significant trend toward a decrease in systolic blood pressure at follow-up (reduction of 1–2.5 mmHg), there was a statistically significant reduction in diastolic blood pressure of the sub-group of women who had a pregnancy previously affected by severe preeclampsia (defined here as eclampsia, HELLP syndrome (as defined by NICE NG133), systolic blood pressure >160 mmHg, diastolic blood pressure >110 mmHg, onset earlier than 28 weeks gestation or ICU admission). In this group, there was a mean difference in diastolic blood pressure between the treatment group and placebo of −3.4 mmHg (95% CI −0.4–6.4, p = 0.025).

The role of other medications beyond anti-hypertensive therapy following HDPs is poorly studied. The Postpartum Low-Dose Aspirin After Preeclampsia for Optimization of Cardiovascular Risk trial [https://clinicaltrials.gov/ct2/show/NCT04243278] is evaluating whether aspirin after severe preeclampsia can influence longer-term endothelial and vascular function but this trial has not yet published its findings. AHA/ACC guidelines also encourage statin use in women with prior HDP [76] and intermediate calculated 10-year ASCVD risk but no trials to date have specifically evaluated the role of statins in cardiovascular and cerebrovascular risk reduction in women with prior HDP.

VIII. Thesis aims and hypotheses

HDP affect 1 in 10 pregnancies [1]. Both pre-eclampsia and gestational hypertension have significant impacts on maternal health postpartum as well as longer-term. A third of women after hypertensive pregnancy represent with essential/chronic hypertension within 10 years [8] and HDP are associated with a significant increase in the risk of subsequent cardiovascular disease throughout their life-time [14, 77]. While I remain unable to effectively prevent hypertensive pregnancy, attempts to reduce its long-term impact are vital. Whilst the pilot work, described above in SNAP-HT, showed self-management of blood pressure postnatally may provide a means of reducing blood pressure out to 6

months postpartum but it was unclear if such a benefit was maintained longer-term or diluted out by 'unhealthy lifestyles' soon after. Furthermore, studies including a mechanistic evaluation of the altered cardiovascular, vascular and cerebrovascular phenotype in the 6-12 months postpartum may provide unique insights into the pathophysiological links between hypertensive pregnancy and long-term cardiovascular risk. The findings may identify novel screening and treatment strategies as well as help 'understand how these factors should be incorporated into risk prediction alongside well established risk factors' for this large cohort of women [77].

Part 1: The aim of this work was to determine if postpartum blood pressure self-management can result in a longer-term improvement in blood pressure control following a hypertensive pregnancy (Chapters 2-3)

Specifically, I hypothesised that:

a) Self-management of BP postpartum, achieved through tele-monitored BP and physician guided medication adjustment, can result in longer-term improvement in BP control

b) Traditional hypertensive risk factors such as a raised BMI, poor diet and/or smoking amongst others may dilute out some of the benefit seen in the pilot RCT (SNAP-HT) at 6 months

Part 2. The aim of this larger body of work (Chapters 4-6) was to determine if tele-monitored, physician guided self-management of blood pressure can reproduce such an improvement in blood pressure control in the 1st 6-9 months following a hypertensive pregnancy, whilst remaining safe, acceptable and feasible.

This work included performing a Prospective Randomised Open, Blinded End-point (PROBE) trial of postpartum BP self-management following hypertensive pregnancy. This built upon the previous SNAP-HT pilot RCT [56], which utilised self-management to guide medication down-titration or readmission for high BP, by incorporating physician guided self-management. Utilising novel Bluetooth enabled ® monitors and an updated App®, the telemonitoring system enabled up titration (as well as down-titration) for BP values outside of the target range, that were deemed 'safe' by

predefined algorithms with the aim of enabling stricter BP control to be achieved. This trial was definitively powered to detect a diastolic BP difference between the intervention and the usual 'NHS'-led' care arms.

Specifically, I hypothesised that:

1) BP self-management postnatally with physician/clinician oversight would reduce diastolic BP by 6-9 months postpartum (chapter 5)

2) This process would result in fewer post-natal readmissions than in the usual care arm (chapter 5)

Part 3. The aim of this body of work was to determine if improved postpartum BP control would result in beneficial remodelling of the cardiovascular systems [Chapters 6] by 6-12 months postpartum.

I proposed the hypothesis that the sustained blood pressure reduction, observed in SNAP-HT out to 6 months, occurred as a result of improved BP control during the postpartum period, which in turn resulted in beneficial cardiovascular vascular remodelling of the acute adverse changes that occurred during the hypertensive pregnancies. I planned to explore potential mechanisms for the increased long-term cardiovascular risk in this cohort of women by utilising T1 and T2 tissue mapping to assess for myocardial oedema and in a sub-set of women the use of late gadolinium imaging to assess for fibrosis. Specifically, I hypothesised that:

1. Left ventricular mass index would be higher in women in the usual care arm of the study where their BP is higher at 6-9 months postpartum.

2. Diastolic function would be more impaired in women in the usual care arm of the study where their BP is higher at 6-9 months postpartum.

3. Aortic stiffness would be higher in women in the usual care arm of the study where their BP is higher at 6-9 months postpartum (and similarly aortic distensibility would be reduced).

4. A higher BP at 6-9 months postpartum may correlate to elevate T1 and T2 values on cardiac MRI tissue mapping and may correlate with the presence of early myocardial fibrosis.

IX. General comments

Chapter 2 deals with the SNAP-HT Extension Study, and Chapter 3 with the results from this study. Chapter 4 will then explain the POP-HT methodology and Chapters 5 and 6 the POP-HT results. Given that my thesis involved two separate studies, SNAP-HT and POP-HT, each performed at separate time points, and with separate study populations, I have split the methodology into separate chapters, which flow chronologically in the way that this body of work progressed. To avoid duplication any study procedure/share methodology used in both studies will only be described once and cross-referenced where needed.

Next, I present a brief introduction to the SNAP-HT Extension study, building upon the background described in this chapter. I then present an overview of the study population and study outline, followed by details of the investigations and methods of data collection undertaken. The methodology was performed in exactly the same manner for all study participants to allow valid comparisons to be made between the groups.

CHAPTER 2 – SNAP-HT EXTENSION – INTRODUCTION AND METHODS

I. Introduction

Prior research shows that persistently high blood pressure six weeks after a hypertensive pregnancy is associated with a greater increase in blood pressure over the next five to ten years [35]. This is independent of blood pressure levels during early pregnancy, or at time of delivery, and is evident both in those with more severe HDP, such as early onset preeclampsia, and later onset, milder disease. A plausible explanation might be that blood pressure at six weeks postpartum is merely a marker of blood pressure trajectory over the life course for that individual [29]. However, without intervention, blood pressure remains unstable for up to 50% of women for several months after a hypertensive pregnancy [6, 78]. An alternative explanation is that uncontrolled blood pressure in the puerperium directly affects the cardiac and vascular remodelling, known to occur in the weeks after a hypertensive pregnancy in both mother and child [60, 65, 79-81]. In turn, this may lead to a long-term persistence of elevated blood pressure, accelerating a life-long trajectory of increased vascular risk. To test this hypothesis required a randomised controlled trial of blood pressure optimisation after a hypertensive pregnancy. In the Self-management of postnatal hypertension (SNAP-HT) trial [56] my group confirmed that postpartum self-management was feasible, safe and acceptable. In addition, six months later, those randomised to postpartum self-management had a persistent 4.5mmHg reduction in diastolic blood pressure. In the first year of my thesis, I performed a long-term follow up of this cohort (the SNAP-HT Extension study), to formally test the hypothesis that interventions, which improve blood pressure in the puerperium can result in longer-term improvement of blood pressure control in the mother.

II. Study population

The SNAP-HT Extension study [REC reference19/SW/0017], was a long term follow up of the SNAP-HT pilot RCT (REC Reference 14/SC/1316). This study involved this pre-defined cohort of women who had pre-eclampsia or gestational hypertension and who required BP lowering medication in the postpartum period. Of the 101 women who enrolled in the original trial, 70 consented to future

research. The 70 eligible women were 36-48 months postpartum at the time of enrolment into the SNAP-HT Extension study. After enrolment, the data collected was anonymised and coded with study specific IDs (e.g. SNAP-HT EXT 01-001) to ensure confidentiality and blinded analysis. The study visit was conducted as a home visit, if preferred, or as a single visit to CCRF at John Radcliffe Hospital. Figure 6 below is a schematic of the study design

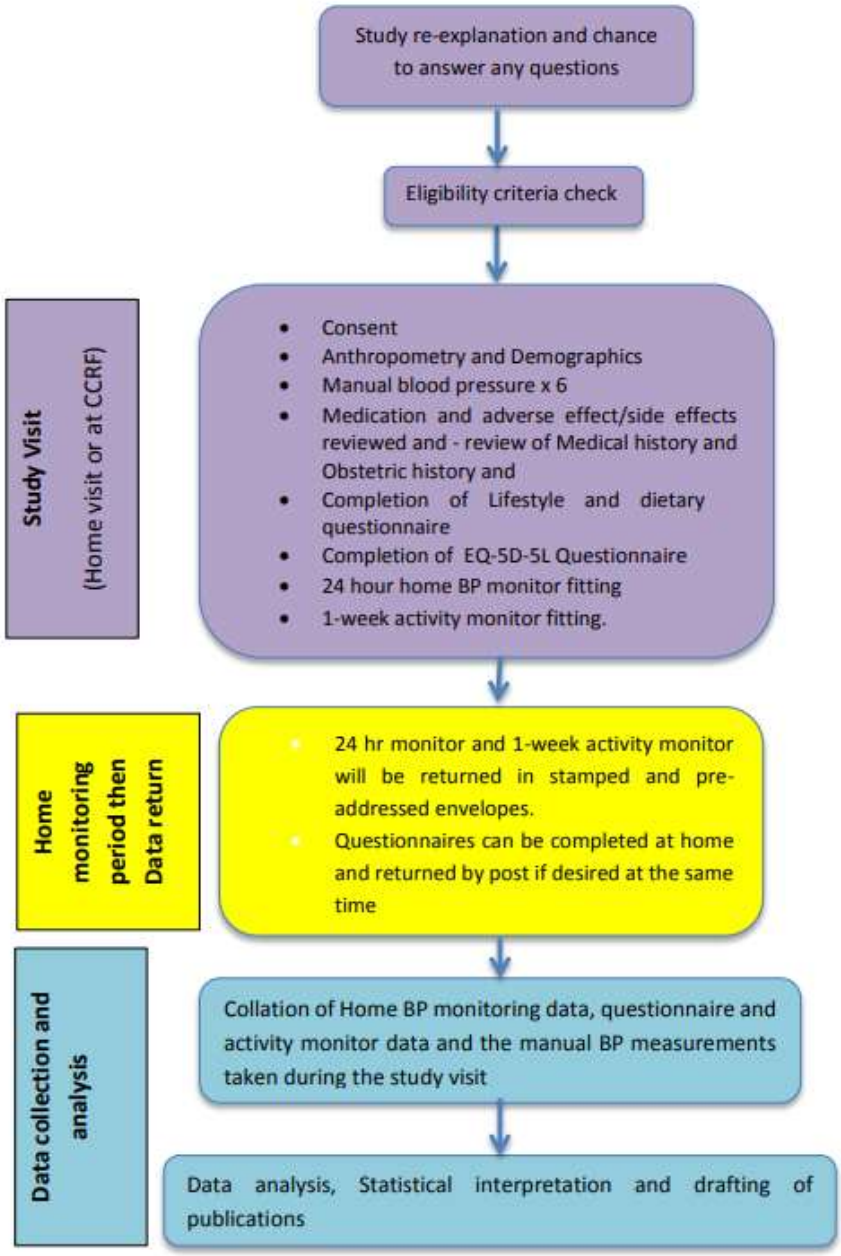


Figure 6: Schematic of SNAP-HT EXT Study Design

III. Trial inclusion and exclusion criteria

Inclusion criteria for the trial were as follows:

- Participant was willing and able to give informed consent for participation in the study
- The participant was in the original SNAP-HT RCT study
- The participant in the original SNAP-HT RCT gave consent for future contact
- Permission given to access the data from the original SNAP-HT trial

Exclusion Criteria were more limited as this was a pre-defined cohort. The participant was not enrolled into the study if ANY of the following applied:

- Further pregnancy at time of reassessment
- A significant new co-morbidity that made enrolment unsafe or impractical

IV. Recruitment and enrolment:

In the original SNAP-HT trial, women were randomised to usual care (control arm) or blood pressure (BP) self-management (the intervention). After discharge from hospital, women in the usual care cohort visited their community midwife for BP monitoring and their general practitioner for titration of antihypertensive medication. Women allocated to the self-management arm of the trial self-monitored their blood pressure once daily, at approximately the same time each day, using a validated automatic BP monitor (WATCHBP®HOME monitors by Microlife®). Blood pressure readings were entered by participants into their mobile phone, and automatically transmitted to the study server. In response, the telemonitoring service provided automated replies that informed women how to down-titrate their medications, according to a pre-specified individualised medication reduction schedule. If readings were 'high', according to an algorithm based on NICE guidance at that time (CG107) [78] participants were asked to contact their NHS care team immediately. Self-management was continued while taking antihypertensive treatment and self-monitoring continued for five days after treatment was ceased. Once treatment was ceased, if the participant's BP remained within normal limits for five consecutive days, they were instructed to change to weekly self-monitoring until the trial was completed to ensure medication did not need to be re-started if readings moved out of the target range again. [56]

Participants in the original SNAP-HT trial were recruited from five National Health Service (NHS) hospital sites in England and at the time of the study were asked whether they were willing to give consent to be contacted about future research projects. All participants recruited to the Extension Study were asked to give permission to access the data from the original trial. In the SNAP-HT Extension study members of the original SNAP-HT research team contacted eligible participants, and once verbal consent was obtained, the SNAP-HT Extension team performed telephone screening for eligibility according to the inclusion and exclusion criteria above. Women participated in either a home visit, or a single study visit to the Oxford Cardiovascular Clinical Research Facility (CCRF) in the John Radcliffe Hospital, based on participant preference. This study was prospectively registered and approved by a National Research Ethics Service Committee (19/SW/0017).

V. Informed Consent

Copies of the PIS and ICF were presented to the participants detailing no less than: the exact nature of the study; what it involved for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It was clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal. The same information was presented verbally, using the PIS as a guide, at the outset of the study visit and prior to consent being taken. Written Informed Consent was obtained by means of participant dated signature and a dated signature of the person who presented and obtained the Informed Consent. The person who obtained consent was suitably qualified and experienced, and was authorised to do so by the Chief/Principal Investigator. A copy of the signed informed consent was given to the participant and the original signed form was retained at the study site.

VI. Procedural Methodology

1. <u>The CASTOR® electronic data capture system</u>

This electronic case report form (eCRF) was used to record all data collected in both studies including demographics, anthropometry, current medications, side effects, serious adverse events, blood pressure data, blood results and more. All data collected were fully anonymised. The specific use of

the database and its other functionalities are explained for each study in more detail subsequently. Data were entered into a dedicated, secure study lap-top PCs during the study visit procedures to allow real-time data entry.

2. Review of medical and obstetric history and any medication side effects

The study investigator reviewed the current medications the participant was taking, if any, and any side effects to blood pressure medications they may have had since the original study completed. Any side effects to current/previous medications and/or any relevant adverse events that may had occurred since SNAP-HT were also documented. They were also questioned about any subsequent medical problems that had developed since completion of SNAP-HT and, in particular, any problems related to blood pressure. This information was obtained from the participant and did not require access to their medical notes. All data were entered into CASTOR edc® directly using a dedicated, secure study lap-top PC as described in section one.

3. Peripheral blood pressure measurement

The blood pressure was measured six times, in the left arm, unless a specific reason precluded the use of the left. The first measurement was taken after at least five minutes rest as per the original study. The next 5 readings were taken at one-minute intervals. Measurements were done using the same blood pressure monitors used in the original study (Microlife Watch BP®). These were well-validated monitors in pregnant [82]and in non-pregnant populations [83], and were appropriately calibrated prior to use. The left arm was chosen to match that used as in the original study. The measurement techniques advised by the British Heart Foundation and British and Irish Hypertensive Society were strictly followed i.e. participants were sat or laying with the arm supported, and elevated to the height of the heart, legs uncrossed and they were asked not to talk during the readings (https://bihsoc.org/resources/bp-measurement/measure-blood-pressure/).

4. 24-hour Blood pressure measurement

Participants were fitted with calibrated and serviced SPACELABS® 90217 or 90217A 24-hour ambulatory blood pressure monitors using a cuff that had been measured to appropriately fit their

mid left arm circumference. The monitor consists of a blood pressure cuff, which was fitted on the left arm (right if a specific medical reason e.g. lymphoedema precluded use of the left). The participants were also provided with a standardised blood pressure monitoring diary sheet to detail time participants went to sleep/awoke and any periods of cardiovascular activity such as running for the bus/cycling to work. Once fitted a single manual reading (excluded from analysis) was taken using the 'manual blue' button to confirm correct functioning of the monitor. The monitors were programmed using proprietary SPACELAB software (SENTINEL®) to take an automated BP measurement at 30-minute intervals between 8am and 10pm and 60-minute intervals from 10pm-8am. No readings were shown by the monitors during the period of assessment, as programmed in advance, to minimise any 'white-coat' response.

Twenty-four-hour blood pressure data were analysed as per NICE NG 136 criteria [45]. Any manual measurements made at the time of monitor fitting were excluded, as were any measurements obtained at a time of documented pre-specified form of exercise on the patient's diary. Twenty-four-hour blood pressure data were only included if an average value of at least 12 measurements taken during the person's usual waking hours, and at least 6 night-time reading, were obtained. If the recording did not fulfil these criteria [84], then the 24-hour blood pressure recording was repeated at the next available opportunity within the pre-specified study-time windows.

In SNAP-HT Extension the 24hr BP monitor was fitted at the end of the one-off study visit, which was performed at home for 61/63 of the participants or, in the case of 2/63 participants at the Cardiovascular Clinical research facility (CCRF) of the John Radcliffe hospital.

5. Questionnaires

a) Quality of life questionnaire

The 5-level EQ-5D version (EQ-5D-5L) was introduced by the EuroQOL Group in 2009 [85, 86] to improve the instrument's sensitivity and to reduce ceiling effects, as compared to the EQ-5D-3L. The EQ-5D-5L essentially consists of two pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression (the 1st three of which are most affected by postpartum BP

issues). Each dimension has five levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient was asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a one-digit number that expresses the level selected for that dimension. A standardised mapping equation is then used to transform the EQ-5D-5L responses into a EQ-5D-3L utility score that describes the patient's health state. The EQ VAS also records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' (100) and 'The worst health you can imagine' (0). The VAS can be used as a quantitative measure of health outcome that reflect the patient's own judgement.

It is widely used in the UK and Europe, including by the National Institute for Clinical Excellence (NICE) in their decision-making processes. It was thus chosen due to its validation and widespread use. In SNAP-HT Extension this questionnaire was completed at a single timepoint; when the women were enrolled.

b) Diet and lifestyle

A detailed questionnaire was completed to identify possible lifestyle and dietary factors, that could confound any blood pressure differences detected in the studies. Information was collected on factors that affect blood pressure including: smoking frequency, alcohol and salt intake, exercise and family history. This was done via e-mail to minimise paper use, especially important during the COVID-19 pandemic, and participants were able to complete this at a later date in their own time as the questionnaire takes over 30 minutes to complete. This included a validated British Heart Foundation diet and lifestyle questionnaire [87].

6. Fitting of an activity monitor (AX-3® Axivity wrist-worn accelerometer)

To obtain a validated objective measure of physical activity, participants in both studies were fitted with Axivity AX3® wrist-worn accelerometer for seven days to ensure high compliance and measurement reliability. The accelerometers were pre-programmed based on the participants' height, weight and reported hand dominance and were then fitted to their non-dominant wrist.

Participants were asked to perform whatever activities they would normally do, whilst wearing the accelerometer, to try and accurately reflect their normal levels of daily activity.

7. Anthropometry

Anthropometric measurements including height, weight, body mass index (BMI) and waist to hip ratio were performed. Demographic data were also be updated at this point. After removal of shoes and wearing light clothing only, subjects had their height and weight measured standing to the nearest centimetre and 0.1Kg respectively. Body mass index (BMI) was calculated using the following formula: BMI (kg/m^2) = Weight (kg)/height $(m)^2$.

Waist and hip measurements were measured in centimetres and the waist: hip ratio calculated.

VII. Outcomes

The pre-specified primary outcome of the SNAP-HT Extension study was 24-hour overall average diastolic blood pressure as assessed by 24-hour ABPM. Secondary outcomes included: 24-hour average systolic blood pressure, mean diurnal diastolic blood pressure, mean diurnal systolic blood pressure, mean nocturnal diastolic blood pressure and mean nocturnal systolic blood pressure. As per the original SNAP-HT trial, mean clinic systolic blood pressure and diastolic blood pressure obtained during the study visit (mean of second and third readings, and mean of second to sixth readings), were also explored as secondary outcomes, as well as mean EQ-VAS scores between groups. Dietary and lifestyle factors known to influence hypertensive risk were also assessed, including salt intake, alcohol consumption, BMI, smoking history, arm circumference, waist to hip ratio measurements and objective measurements of activity level from the seven-day wrist-worn accelerometer.

VIII. Statistical analysis

Analysis was conducted according to a statistical analysis plan prepared prior to analysis. Data obtained in the SNAP-HT Extension study was linked back to the original SNAP-HT data, with participant consent. Participants in the original trial had been randomised by computer-generated and secure web-based randomisation software to ensure allocation concealment. In this study, the

investigators were blinded to this allocation until data collection and analysis was complete. Analyses were performed with IBM SPSS Statistics version 26.

Continuous variables were reported as means ± standard deviations, or medians with interquartile ranges [IQR] if skewed. Categorical variables were reported as counts with percentages. Differences between groups were reported with 95% confidence intervals (95% CI) and significance tests with p values. Linear regression modelling fitted with treatment group as the independent variable was used to evaluate differences in blood pressure between the self-management and usual care groups.

The pre-specified primary outcome of the SNAP-HT Extension study was 24-hour average diastolic blood pressure as assessed by 24-hour ABPM. Secondary outcomes included: 24-hour average systolic blood pressure, mean diurnal diastolic blood pressure, mean diurnal systolic blood pressure, mean nocturnal diastolic blood pressure and mean nocturnal systolic blood pressure. As per the original SNAP-HT trial, mean clinic systolic blood pressure and diastolic blood pressure obtained during the study visit (mean of second and third readings, and mean of second to sixth readings), were also explored as secondary outcomes, as well as mean EQ-VAS scores between groups. Dietary and lifestyle factors known to influence hypertensive risk were also assessed, including salt intake, alcohol consumption, BMI, smoking history, arm circumference, waist to hip ratio measurements and objective measurements of activity level from the seven-day wrist-worn accelerometer. A small number of participants (n=2) were identified as having been started on antihypertensive medication, and, in view of the effect of medication on average blood pressure levels, were excluded from analysis post-hoc. Linear regression modelling, fitted with treatment group as the independent variable, was used to evaluate differences in blood pressure between the self-management and usual care groups

Primary and secondary blood pressure outcomes were adjusted for the blood pressure readings from the original SNAP-HT baseline visit (taken between the first and sixth day postpartum), in which a notable difference in blood pressure between the self-management, and usual care groups, was seen in the original SNAP-HT paper [56]. Adjustment was performed using three models:

1) The first model adjusted for the mean of the second and third blood pressure readings from the original SNAP-HT baseline visit, as this the adjustment was used in the original SNAP-HT analysis.

2) The first sensitivity analysis performed, adjusted for the mean of the second to sixth blood pressure readings at the SNAP-HT baseline visit, as this was felt to better represent a mean ambulatory blood pressure. Ambulatory BP was not used in the original study so this was felt to be the closest surrogate.

3) A second sensitivity analysis was also performed to adjust for antenatal blood pressure readings. This was performed based on the antenatal blood pressure recorded at the 'booking visit'. [27] The purpose of this was to assess what impact pre-pregnancy blood pressure had, if any, on the postpartum results.

Due to a small amount of missing baseline (n=3), and antenatal (n=3) blood pressure readings, a sensitivity analysis was also performed replacing missing covariate data with mean imputation.

Exploratory analyses were conducted to assess the effect of potential confounding factors (age, parity, BMI, activity, smoking, alcohol intake, salt intake, arm circumference and waist to hip ratio) on 24-hour diastolic blood pressure. These variables were fitted as independent variables in univariable linear regression models and if found to significantly ($p< 0.05$) influence 24-hour diastolic blood pressure were included in a multiple regression analysis with treatment group and baseline blood pressure.

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Exclusion criteria (the participant may not enter the trial if any of the following apply)

- Significant renal or hepatic impairment that would have affected safe medication titration and adjustment as part of the trial, as deemed by the chief investigator.
- Participant with life expectancy of less than 6 months.
- Any other significant disease or disorder which, in the opinion of the investigator, may have put the participant at risk through participation in the trial, influence the result of the trial, or impair the participant's ability to participate in the trial.
- Participants who had participated in another research trial involving an investigational medicinal product in the past 12 weeks.
- Women with pre-existing hypertension were excluded, as this was a separate pathology that would affect the efficacy of the study intervention and affect the primary and secondary outcomes of the study.

Randomisation

Randomisation was performed as soon as possible following the baseline visit. Randomisation was carried out using a secure web-based randomisation software (embedded within Castor®). Participants were randomised on a 1:1 basis and two minimisation factors were used to ensure that the groups were as well matched as possible:

Primary factor: Gestational age at the time of presentation with pre-eclampsia/gestational hypertension (agreed on as a surrogate marker of disease severity by the TSC).

Secondary factor: Prescription of ACE inhibitor (Enalapril) at the time of randomisation.

CHAPTER 3 - SNAP-HT EXTENSION: RESULTS AND DISCUSSION

I. Results

Of the 101 women enrolled to the original SNAP-HT trial, 70 provided consent for re-contact regarding future studies. All 70 were approached between 1st April 2019 and 1st December 2019 and 63 agreed to participate in this Extension study. As explained in the previous chapter (SNAP-HT Extension methodology), two women in the usual care group were excluded from the data analysis post-hoc as they reported antihypertensive medication on their health questionnaire, which had not been

disclosed during their actual study visit, which was then confirmed with their primary care practitioners. Of the 61 women then included in analysis, 31 received usual care and 30 were randomised to self-management. Follow up occurred at a mean of 3.6 years ±0.4 years postpartum. This is further illustrated in the CONSORT flow chart below.

Study population characteristics

Table 1 below (Chapter 3) demonstrated that pregnancy characteristics did not differ significantly between participants in the SNAP-HT Extension study according to whether they originally received self-management or usual care. Table 1 also demonstrates that mean age, BMI, parity, activity levels, mean arm circumference and EQ-VAS scores were similar between self-management (intervention) and usual care (control) groups at time of their participation in the SNAP-HT Extension study.

The mean age was 34.6 (SD5.3) overall with the self-management group being marginally older at 35.2 (SD 4.3) vs. 34.1 (SD 5.3) in the usual care arm. Approximately 60% had 2 or more children (56.7% in the self-management arm vs 64.5% in the usual care arm) with a similar number of women having had a further pregnancy since enrolment in the original SNAP-HT trial (37% in the self-management arm vs 41.9% in the usual care arm). Twenty-two women had one subsequent pregnancy in the intervening years between the original trial and follow up (usual care n=12; self-management n=10), and two women had two pregnancies (one in each group) during this interval. Rates of a further hypertensive pregnancy were similar between groups (n= 3 (10%) in self-management and n=4 (12.9%) in the usual care group). In terms of factors known to influence long-term blood pressure control, BMI, waist: hip and mean left arm circumferences i.e. indicators of adiposity, at a mean 3.6 years postpartum (SD 0.4) were very similar between groups. They were non-significantly higher in the self-management arm (BMI 28.5 vs 27.7; mean arm circumference 31.8 vs 31.4 and mean waist: hip 0.88 vs 0.6) vs. the usual care arm respectively. There was no difference in objectively measured levels of activity at the time of the study with both groups sleeping between 8-9 hours a night (8.5hrs in self-management vs 8.8hrs in the usual care arm), being sedentary between 9-10 hours or their awake hour (9.8hrs in self-management vs 9.2 hrs in the usual care arm) and levels of light-moderate activity were also similar (5.4hrs in self-management vs 5.2 hrs in the usual care arm). There were four current smokers, all in

the usual care group. Alcohol intake did not differ significantly between the groups with >90% in each arm sticking to the recommended weekly intake of <14 units from the Department of Health. There were 3 (10%) women in the self-management who exceeded this.

Table 1. Characteristics of each study group in SNAP-HT Extension at time of re-recruitment (mean 43.4 months postpartum)

Parameter, unit	Overall (n=61)	Self-management (n =30)	Usual care (n =31)
Mean age at re-recruitment, y ± SD	34.6±5.3	35.2±5.3	34.1±5.3
Parity at re-recruitment, n (%)			
1	24 (39.3)	13 (43.3)	11 (35.5)
≥ 2	37 (60.7)	17 (56.7)	20 (64.5)
Women with further pregnancies since SNAP-HT trial (n %)	24 (39.3)	11 (36.7)	13 (41.9)
Women with further hypertensive pregnancies since SNAP-HT trial (n %)	7 (11.5)	3 (10.0)	4 (12.9)
Contraception at re-recruitment, n (%)			
Combined oral contraceptive pill	1 (1.6)	1 (3.3)	0 (0)
Progesterone only contraceptive pill	15 (24.6)	7 (23.3)	8 (25.8)
Implanon implant	4 (6.6)	2 (6.7)	2 (6.5)
Mirena® IUD	5 (8.2)	3 (10)	2 (6.5)
Median BMI at re-recruitment, kg/m^2 (IQR)	28.2 (24.6, 32.5)	28.5 (25.6, 33.3)	27.7 (23.9, 31.4)
Activity[*], hours/day (IQR)			
Sleep	8.7 (7.9, 9.4)[†]	8.5 (7.9, 9.3)[‡]	8.8 (8.2, 9.7)[§]
Sedentary	9.5 (8.9, 10.7)[†]	9.8 (9.1, 10.7)[‡]	9.2 (8.3, 11.0)[§]
Light activity	1.2 (0.7, 1.6)[†]	1.2 (0.9, 1.6)[‡]	1.1 (0.6, 1.6)[§]
Walking	2.5 (1.7, 3.1)[†]	2.4 (2.1, 3.1)[‡]	2.5 (1.7, 3.3)[§]
Moderate activity	1.7 (1.0, 2.3)[†]	1.8 (1.0, 2.3)[‡]	1.6 (1.0, 2.2)[§]
Moderate-vigorous activity	1.2 (0.7, 1.7)[†]	1.1 (0.9, 1.7)[‡]	1.4 (0.5, 1.7)[§]
Current smokers, n (%)	4 (6.6)	0 (0.0)	4 (12.9)
Alcohol consumption, units/week n (%)			
0	32 (52.5)	15 (50.0)	17 (54.8)

1-7	22 (36.1)	10 (33.3)	12 (38.7)
8-14	4 (6.6)	2 (6.7)	2 (6.5)
15 +	3 (4.9)	3 (10.0)	0 (0.0)
Salt intake[&], n (%)			
Low	32 (52.5)	18 (60.0)	14 (45.2)
Moderate	25 (41.0)	10 (33.3)	15 (48.4)
High	4 (6.6)	2 (6.7)	2 (6.5)
Mean arm circumference, cm ± SD	31.6±4.9	31.8±4.7	31.4±5.1
Mean waist to hip ratio ± SD	0.87±0.08	0.88±0.10	0.86±0.05
EQ-VAS score ± SD	80.3±15.8	81.1±12.1	79.6±18.9

BMI indicates body mass index; EQ-VAS, EuroQol-visual analogue scale from the E5-5D-5L questionnaire; IQR, interquartile range and SD, standard deviation.

*As measured with Axivity AX3® accelerometers

†n=57, missing data for n=4

‡n=27, missing data for n=3

§n=30, missing data for n=1

[&]Salt intake at follow-up, was categorised as low, medium and high in accordance with their answers to the British Heart Foundation dietary questionnaire. Low intake was classed as 0-1 positive responses to the salt intake questions, 2-3 as moderate intake and 4 or more answers to the salt questions as high intake.

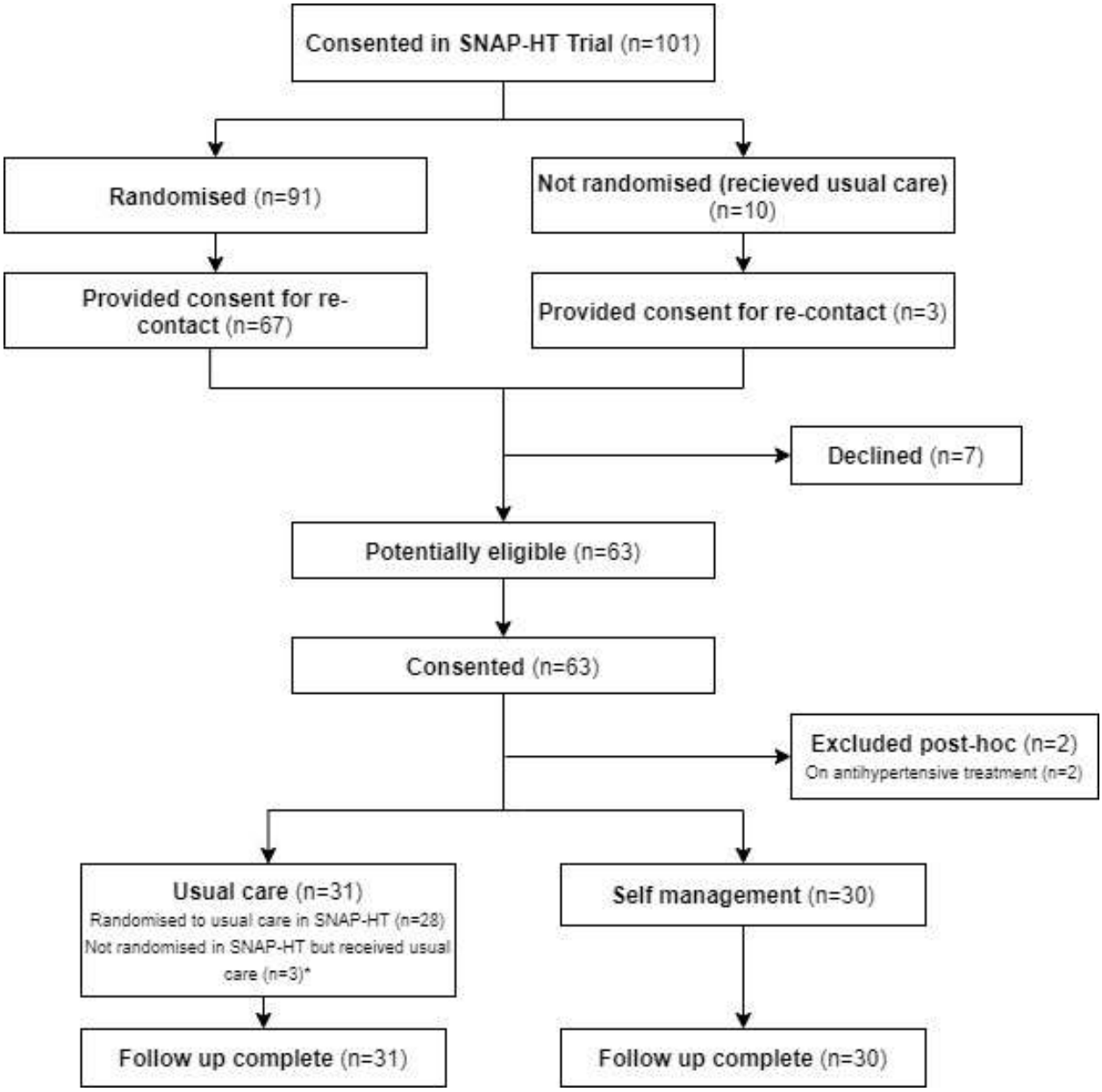


Figure 7: CONSORT (Consolidated Standards of Reporting Trials) Flow chart. *The usual care group included three women originally consented in SNAP-HT antenatally but who withdrew prior to randomization and did not receive the intervention. They were included in the usual care group, as this was felt to be consistent with their postpartum follow up.

Primary outcome: 24-hour overall average diastolic blood pressure

At a mean time period of 3.6 years postpartum, women who had self-managed their blood pressure postpartum in the SNAP-HT RCT had significantly lower 24-hour diastolic blood pressure; 73.7±5.0mmHg compared with 80.7±7.4mmHg in the usual care group (adjusted mean difference -7.4mmHg; 95% CI -10.7 to -4.2; P<0.001) (table 2 of Chapter 3; figure 8a).

Results were similar when non-randomised participants (i.e. the 3 who withdraw from the original SNAP-HT RCT control arm), were excluded from the analysis with the adjusted mean difference then being -7.4mmHg; 95% CI -10.5 to -4.4; P<0.001. These participants had baseline data but were not

randomised in the original trial due to their medication being stopped prior to hospital discharge. The results were similar when missing covariate data were replaced with mean imputation (adjusted mean difference -7.3mmHg; 95% CI -10.4 to -4.1; P<0.001).

Table 2. Summary results for the SNAP-HT Extension Study

Parameter, unit	Self-management (n =30)	Usual care (n =31)	ΔI-C, mmHg (95% CI)* adjusted for baseline BP (mean 2nd and 3rd)†	ΔI-C, mmHg (95% CI)* adjusted for baseline BP (mean 2nd and 3rd)† and salt intake at 4 year follow up
PRIMARY OUTCOME				
Mean 24 hr average DBP‡, mmHg ± SD	73.7±5.0	80.7±7.4	-7.4 (-10.7, -4.2)§ P < 0.001	-6.8 (-9.9, -3.7)§ P < 0.001
SECONDARY OUTCOMES				
Mean 24 hr average SBP‡, mmHg ± SD	121.8±9.4	126.1±10.9	-4.6 (-10.0, 0.8) P = 0.09	-4.1 (-9.4, 1.3) P = 0.14
Mean diurnal DBP‡, mmHg ± SD	78.4±4.9	83.3±7.6	-5.3 (-8.6, -2.0)§ P = 0.002	-4.7 (-7.8, -1.5)§ P = 0.004
Mean diurnal SBP‡, mmHg ± SD	126.4±10.1	128.9±10.6	-3.0 (-8.4, 2.4) P = 0.27	-2.3 (-7.5, 3.0) P = 0.40
Mean nocturnal DBP‡, mmHg ± SD	63.9±5.9	71.3±9.3	-7.8 (-11.9, -3.7)§ P < 0.001	-7.4 (-11.5, -3.2)§ P = 0.001
Mean nocturnal SBP‡, mmHg ± SD	108.9±11.0	115.8±14.4	-7.4 (-14.2, -0.7)§ P = 0.032	-7.0 (-13.8, -0.2)§ P = 0.045
Mean Clinic DBP (readings 2nd and 3rd), mmHg ± SD	83.3±9.1	86.6±8.2	-3.4 (-8.1, 1.2) P = 0.14	-3.0 (-7.6, 1.7) P = 0.20
Mean Clinic SBP (readings 2nd and 3rd), mmHg ± SD	130.9±11.8	130.7±12.1	-0.3 (-6.5, 6.0) P = 0.93	0.3 (-6.0, 6.6) P = 0.93
Mean Clinic DBP (readings 2nd to 6th), mmHg ± SD	83.3±8.0	85.8±7.0	-2.8 (-6.8, 1.2) P = 0.17	-2.5 (-6.5, 1.5) P = 0.22
Mean Clinic SBP (readings 2nd to 6th), mmHg ± SD	131.4±10.1	131.0±11.2	-0.2 (-5.7, 5.3) P = 0.95	0.2 (-5.4, 5.8) P = 0.95

ΔI-C indicates difference between intervention and control groups; DBP, diastolic blood pressure; SBP, systolic blood pressure and SD, standard deviation. * n=58, three missing baseline blood pressure measurements from control group.

†mean difference adjusted for baseline blood pressure values in SNAP-HT, day 1-6 after birth.

‡measured by SPACELAB® 90217 ambulatory blood pressure monitor

§95% CI around adjusted difference does not cross zero

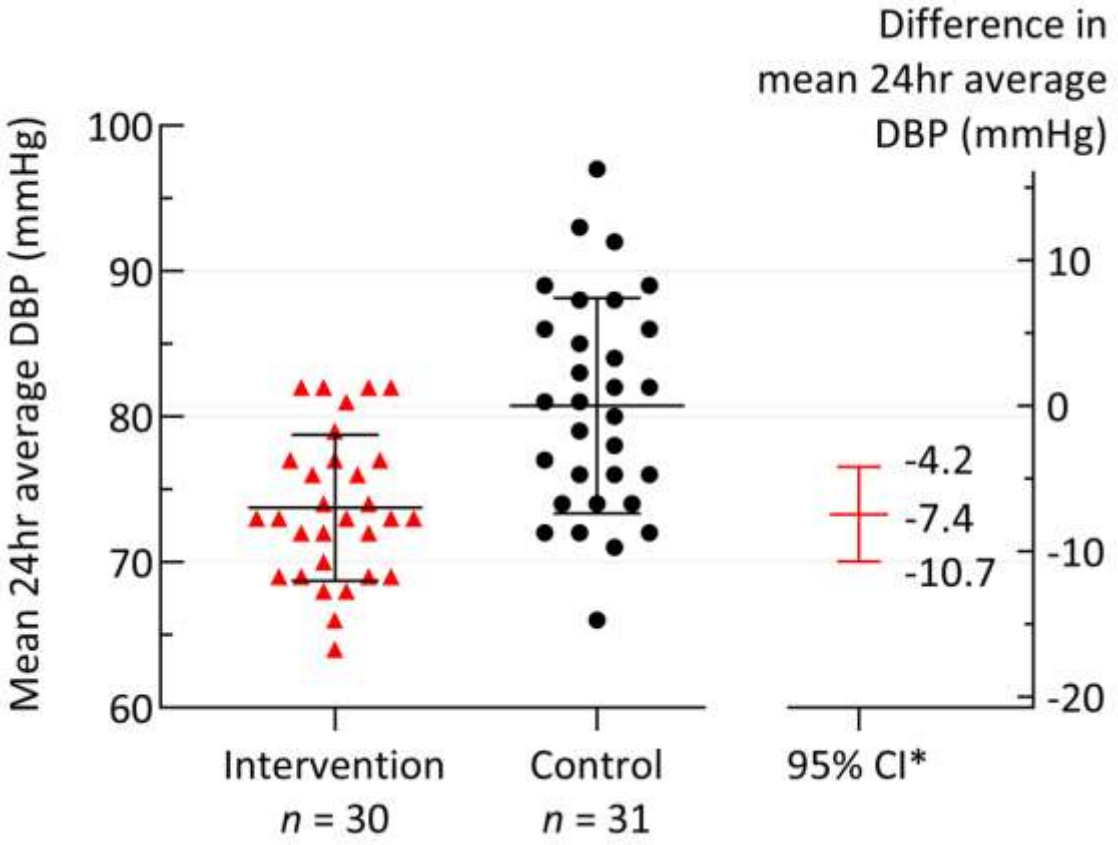


Figure 8: a) Primary outcome adjusted for baseline blood pressure in SNAP-HT (mean of 2nd and 3rd readings). DBP indicates diastolic blood pressure, CI indicated confidence interval.

Additionally, in sensitivity analyses, the difference in 24-hour diastolic blood pressure between the cohorts was maintained when adjusting for the baseline diastolic blood pressure using the mean of second to sixth readings, as a surrogate for an ambulatory BP, to try and minimise any white-coat effect. In this instance, the adjusted mean difference was -7.3mmHg (95% CI -10.5 to -4.0; P<0.001). In a further sensitivity analysis, in which the results were adjusted for the antenatal booking diastolic blood pressure, taken from their 12 week 'booking' midwife visit approximately 4.5 years prior to this repeat BP assessment, the adjusted mean difference still remained almost 7mmHg (-6.9mmHg; 95% CI -10.3 to -3.6; P<0.001).

Secondary outcomes

On analysis of the secondary outcomes (see table 2 above) based on 24HR ABPM, diurnal diastolic blood pressure was 5.3 mmHg lower in the self-management group (95% CI -8.6 to -2.0; P=0.002), and

both nocturnal diastolic and systolic blood pressure were significantly lower in the self-management group (nocturnal diastolic blood pressure adjusted mean difference -7.8mmHg; 95% CI -11.9 to -3.7; P<0.001; nocturnal systolic blood pressure adjusted mean difference -7.4; 95% CI -14.2 to -0.7; P=0.032). Twenty-four-hour and diurnal systolic blood pressure did not differ significantly however. As for the clinic readings, as were used in the original study, the diastolic blood pressure and systolic blood pressure readings, both the mean of the second and third, and the mean of second to sixth, did not significantly differ between groups although there was a trend towards a lower BP in the self-management arm (Table 2; Chapter 3). There was a -2.8mmHg diastolic improvement when using the mean of the 2nd to 6th and -3.4mmHg when using the mean of the 2nd and 3rd (as was published in the original study).

In my analysis the women in both the self-management and usual care arms, were well-matched in terms of their BMI, waist: hip ratios and mid-left arm circumference (as seen in Table 1; Chapter 3), suggesting any differences in blood pressure were not due to differences in their lifetime trajectory but either a result of the intervention, or differences in their hypertensive risk factors since the original study. To determine if it was the latter i.e. hypertensive risk factors differing between the two arms, influencing the BP data at the time of follow up (mean 3.6 years postpartum), additional sensitivity/post-hoc analyses were performed to explore the impact of each of the risk factors known to influence blood pressure trajectory postpartum, and in the general adult population [33]. These included: age, parity, BMI, activity levels, smoking rates, salt and alcohol intake, waist to hip ratio and arm circumference. Of these risk factors, only salt intake showed a significant association with 24-hour diastolic blood pressure (see supplementary table S2 in the published paper from this trial [88]). Salt intake was judged by a validated BHF diet questionnaire [87]. The salt intake did not differ hugely between the two groups with approx. 90% in both arms having a low-moderate intake but the control arm did have a slightly higher number of women with a moderate intake (48.4 vs 33.3%). The difference in 24-hour diastolic blood pressure in those randomised to self-management remained almost 7mHg even after adjustment for difference in salt intake (adjusted mean difference -6.8mmHg; 95% CI -9.9 to -3.7; P<0.001, as illustrated in figure 8b below.

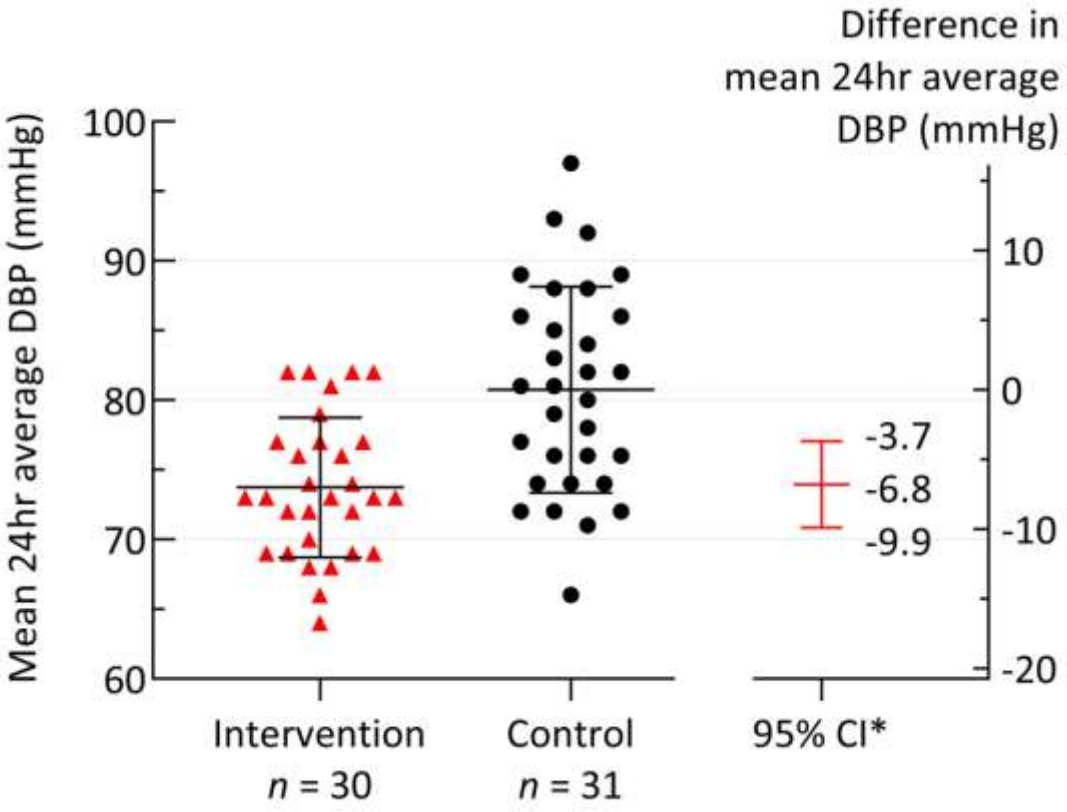


Figure 8 b) Primary outcome adjusted for baseline blood pressure (mean of 2nd and 3rd) and salt intake at 4 years postpartum. DBP indicates diastolic blood pressure, CI indicated confidence interval.

II. Discussion

This study demonstrated that almost four years after a hypertensive pregnancy, women who received a short period of postpartum blood pressure self-management had persistently lower diastolic blood pressure, when measured by the gold standard method of 24hr ABPM. These findings were consistent with the findings of a mean -4.5mmHg lower diastolic BP at six months in the original SNAP-HT study and suggest that the original intervention 'triggered' a resetting of blood pressure levels' and alteration of their life-time trajectory (as illustrated in figure 9 below).

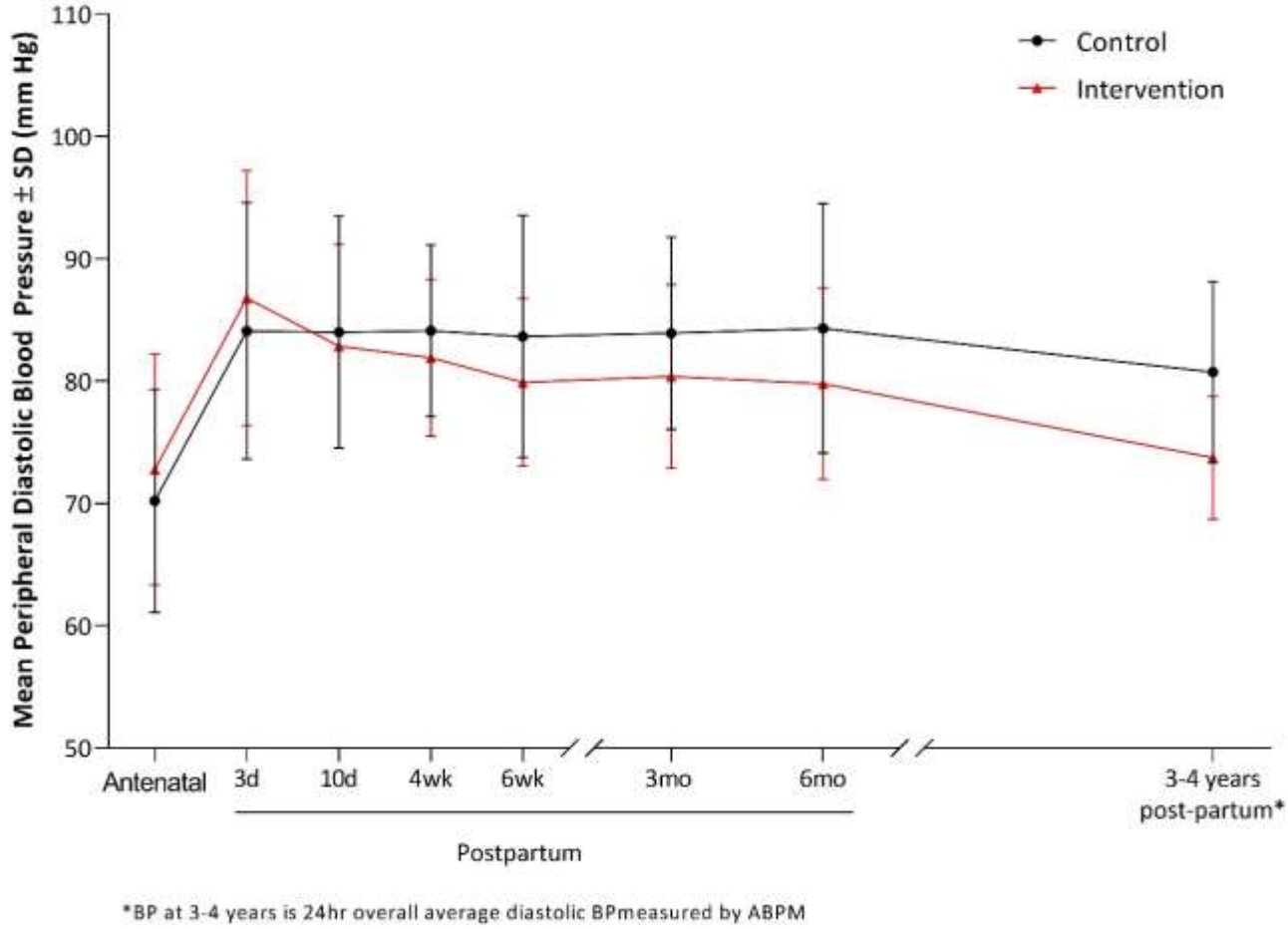


Figure 9: Longitudinal Diastolic blood pressure data for SNAP-HT and SNAP-HT Extension from antenatal booking blood pressure to 3-4 years postpartum, demonstrating the long-term benefit of self-management on blood pressure control following a hypertensive pregnancy

The original SNAP-HT trial [56] was designed to assess feasibility and safety of a self-management digital intervention in the postnatal period but exploring the impact of the intervention on blood pressure was an important secondary outcome [56]. The finding in SNAP-HT of a persistently lower diastolic blood pressure at six months, when almost all women had stopped treatment, prompted the development of the Extension study. The primary aim of the SNAP-HT Extension study was to assess whether this reduction in diastolic blood pressure persisted several years after the original intervention had finished, because if so, it offers a chance to alter lifetime cardiovascular risk through a short-term intervention in the puerperium using widely available, well liked [89, 90] and readily translatable management strategies [91].

Differences in BP control were not explained by variation in contraception use between groups (with the combined pill known to influence BP in young women), parity, BMI, age or by a difference in the number of further hypertensive pregnancies in either arm in the interim. It is worth noting that the baseline characteristics of participants included in the SNAP-HT Extension study analysis were similar to the original SNAP-HT participants, as well as being similar to those participants who were not re-recruited/excluded [88]. This demonstrated that I did not re-examine a selective sub-set of the original trial, but rather, that the results seen in the smaller sample size of SNAP-HT EXTENSION study represented the population in the original study.

In the intervening period, traditional hypertensive risk factors may have diluted any ongoing blood pressure benefit, [92] with additional regression to the mean possible. To allow evaluation of this potential effect, data on salt and alcohol intake, as well as objective measures of exercise, BMI and smoking, were collected. Ultimately, in the sensitivity analyses, only self-reported salt intake was found to have any significant impact on blood pressure differences between groups, but a mean 6.8mmHg diastolic difference between groups remaining following adjustment. Admittedly, the sample sizes for these sensitivity analyses were small and I cannot fully exclude an effect of these traditional hypertensive risk factors on such a small sample. Nonetheless, the impact of salt is apparent even with this sample size, whichsuggests women should be counselled about the importance of lifestyle and diet change following a HDP as even at 3-4 years postpartum salt intake can start to have an impact on BP. The original self-management intervention in the puerperium still provides longer-term protection to this cohort however, meaning that if both diet and lifestyle advice and self-management are combined, it offers a real window to alter life-time BP and cardiovascular risk trajectory.

Mechanism

The mechanism through which self-management results in a longer-term BP improvement is not fully understood from these results and is one of the things explored in Chapters 5 and 6 for the POP-HT trial results and in chapter 7, the overall conclusion. What can be discussed based on SNAP-HT and SNAP-HT Extension nonetheless, was the impact of dosing and BP control throughout the original

SNAP-HT trial. The number of antihypertensives prescribed, as assessed by the median (IQR) World Health Organisation defined daily dose (WHO DDD) [93], was similar in the self-management and usual care cohort at four and six weeks, [56] (WHO DDD at four weeks: 0.4 (0 to 1) in usual care, 0.3 (0 to 0.7) in self-management; six weeks: 0.4 (0 to 0.8), 0.2 (0 to 0.5). There was no formal objective assessment of compliance e.g. urinary drug testing, but self-reported compliance in the self-management arm was excellent. Therefore, given that the WHO DDD was actually lower in the self-management vs. usual care arm (0.4 vs 0.3 at 4 weeks; and 0.4 vs 0.2 at 6 weeks), it was highly unlikely that effects of self-management on BP in the intervention group were mediated through greater prescription of anti-hypertensives but, consistent with previous reports on the impact of self-management on blood pressure control [94], were more likely to relate to greater medication adherence. This conclusions was supported in a qualitative follow on study of SNAP-HT [91], in which self-management was perceived as more flexible, better able to detect BP problems, and enable more targeted medication adjustment, consistent with other work evaluating blood pressure self-management in pregnancy [89] and outside of it [50]. Participants also reported higher levels of confidence in down-titrating medication than described previously in self-management studies of chronic hypertension involving medication up-titration.

Although there was only a small difference in the number of readmissions in each arm (five in the self-management and three in the usual care arm), these numbers, albeit small, likely indirectly reflect better BP control and better monitoring throughout the puerperium, resulting in more postnatal readmissions in the intervention arm of SNAP-HT. This was further supported by the lower BP readings that were recorded at weeks 1, 4, 6 and so on, in the original study in the self-management arm vs. usual care arms. Post-hoc analysis revealed that the class of antihypertensive used did not differ between trial arms [88]. It seems reasonable to conclude therefore, that through greater adherence, those in the self-management arm may have had greater exposure to the antihypertensive medication, which may have aided cardiovascular remodelling postpartum, leading to lower BP at 6 months and at 3.6 years. Based on prior work from Lazdam et al [35], as discussed in the opening chapter of this thesis, BP at 6 weeks postpartum appears to predict BP in later life. The findings of the

SNAP-HT Extension study support the hypothesis that intervention in the early postpartum period can alter this lifetime diastolic BP trajectory.

In the intervening years between the original trial and follow up, 40% of women had a further pregnancy. Although rates of hypertensive pregnancy were similar between groups (10% in self-management vs 12.9% in the usual care), further work, in a larger sample, is required to understand whether a persistent seven to eight mmHg reduction in blood pressure could result in a meaningful reduction in risk of hypertensive pregnancy in subsequent pregnancies. This is something my larger POP-HT RCT [95], may be able to start to address in subsequent follow up, as well as larger, multi-centre RCTs planned for the near future such as SNAP-HT 2, which has just received NIHR funding.

The SNAP-HT Extension study utilised ambulatory blood pressure measures rather than clinic readings to improve precision of the blood pressure estimate in a small sample size and maximise power to identify differences between groups [96-98]. Reassuringly, differences in diastolic blood pressure were evident on both diurnal and nocturnal ambulatory measures, and the difference in ambulatory measures identified was in fact greater than the 4.5mmHg difference in clinic diastolic blood pressure recorded at six months, fitting with the hypothesis of trajectory alteration discussed above. However, although the differences in clinic BP measures in the EXTENSION study were not statistically significant, they also trended towards improved clinic diastolic BP control (-3.4mmHg with SD -8.1 to 1.2). The fact this did not reach statistical significance may reflect a lack of power due to the inherent variability in clinic blood pressures within a smaller sample (61 in this study vs. the 91 completing the original trial). This explanation was supported by the larger standard deviations (12.1mmHg in the usual care arm and 11.8mmHg in the self-management arm for clinic BP vs 7.4mmHg and 5mmHg respectively for BP measured by ABPM). Additionally, as a significant difference in nocturnal, but not diurnal, ambulatory systolic blood pressure was seen between groups, it was possible a greater alerting/ 'white coat' response further reduced variation in clinic readings, and daytime systolic blood pressures. This is something widely reported in the literature, particularly in pregnancy, with up to 40% of women following a hypertensive pregnancy experiencing white coat hypertension [99]. Given that fifty-nine of

sixty-one visits were conducted at the participants' homes with only two at the John Radcliffe Hospital, any possible effect of the clinic setting on blood pressure measures was likely to be too small to have influenced the results.

Why a permanent change in blood pressure can be induced by a short-term postpartum intervention remains under investigation in ongoing studies, and is discussed further in the next chapters, but it may relate to cardiovascular adaptations associated with the hypertensive pregnancy [36, 39]. Remembering that normal pregnancy is itself associated with substantial cardiac and vascular remodelling [36], the addition of acute inflammatory, anti-angiogenic and oxidative stress of a hypertensive pregnancy, result in further significant adverse changes [37, 38]. Persistence of left ventricular hypertrophy at one year postpartum in women with pre-term preeclampsia was strongly associated with risk of developing essential hypertension within the subsequent two years [39, 57]. Our group have previously described left ventricular hypertrophy, diastolic dysfunction, capillary rarefaction and reduced aortic compliance [60] at five to ten years following a hypertensive pregnancy, compared to a normotensive pregnancy. I hypothesised that the longer-term improvements in blood pressure I have observed following short term 'tighter' BP control in the puerperium may reflect a regression of these elements of adverse vascular, and cardiovascular remodelling at that time. A diastolic BP specific effect was consistent with the longitudinal cohort data described in the HUNT studies [27]. In these studies, described in more detail in Chapter 1.II, it can be observed that diastolic BP does not return to pre-pregnancy levels postpartum following an HDP. This was in contrast to the pattern seen with normotensive pregnancies. This persistent elevation of diastolic BP/failure of normalisation to 'booking' (i.e. antenatal) levels of BP can help explain the increased longterm cardiovascular risk as it correlates with the historical findings of the FRAMINGHAM study, in which it was diastolic BP elevation, rather than systolic, which correlates better to long-term cardiovascular risk in young adults <50 years old [33]. This is reflected in the 2018 ESC hypertension guidelines [34], which state that 'High DBP is associated with increased CV risk and is more commonly elevated in younger (<50 years) vs. older patients.'

The hypothesis that improved hemodynamic control during the puerperium could have long-term BP and CV risk reduction benefits has also been supported by findings from another randomised trial (PICk-UP). Postpartum treatment with enalapril, in addition to usual blood pressure care, also resulted in lower blood pressure at six months postpartum, even after the enalapril had been withdrawn [100]. The role that angiotensin converting enzymes (ACEi), such as enalapril, have in beneficial remodelling is widely reported outside of pregnancy, and hence their widespread recommendation in international guidelines [101] and their routine clinical prescription for heart failure, after myocardial infarction, in the treatment of general adult hypertension, and in diabetic nephropathy, amongst other indications. In the PICk-UP trial, women who received enalapril had improved diastolic function (E/E') and left ventricular remodelling assessed by trans-thoracic echo (relative wall thickness; 0.38 in enalapril arm (0.07) vs 0.45 in the control arm (0.10); 95% CI -013 to -02.02 with P<0.01) compared with placebo. This remodelling was mirrored by a significant improvement in their diastolic BP (6-month diastolic BP in the enalapril arm was 79.6mmHg (SD 10.9) vs 86.9mmHg (SD 10.6mmHg) compared with the placebo arm [100]. The significance of these findings is considered more in Chapter 6 during the discussion of the POP-HT cardiovascular remodelling results.

Limitations

It is important to recognise that the conclusions from the SNAP-HT Extension study have several limitations. Firstly, the small sample size of the original trial population. Secondly, the participants were largely Caucasian and tended to be from higher socioeconomic classes, which limits my ability to generalize my findings to the broader population. In addition, hypertensive risk factors were only assessed at a single time point of 3.6 years postpartum, and this may not have reflected the lifestyle characteristics of the participants throughout this entire postpartum time period. Furthermore, whilst activity levels, BMI, arm circumference and waist to hip ratio were measured objectively, other diet and lifestyle factors relied on participant self-reporting, which may have influenced the accuracy of these results [102]. Adjustment for baseline blood pressures needs to be viewed cautiously, as this relied on averaged clinic readings at baseline in contrast to the 24-hour ambulatory blood pressure readings in the current study. However, given the practical limitations of performing 24hr ABPM when

women have just given birth, and are on a postnatal ward, clinic BP at baseline was a realistic assessment, and one I reproduced in the POP-HT study methodology discussed in Chapter 4.

III. Conclusion

The long-term follow-up of the pilot randomised trial SNAP-HT, in the SNAP-HT EXTENSION study, demonstrated a mean 7.4mmHg improvement in diastolic BP through postpartum BP self-management at a mean 3.6 years postpartum. This persisted even when adjusting for hypertensive risk factors with an almost 7mmHg DBP improvement maintained. This finding suggests the natural history of disease progression after a hypertensive pregnancy may not be fixed but, rather, a potentially modifiable phenomenon [27], with changes at six months persisting to almost four years, and presumably brought about by the impact of the intervention. A mean seven to eight mmHg reduction in 24-hour ambulatory diastolic blood pressure, if maintained, would be expected to reduce cardiovascular risk by ~30% and, thereby, have a meaningful impact on reducing the increased incidence of cardiovascular and cerebrovascular disease seen following HDPs [40]. Indeed, two women who originally received usual care following their hypertensive pregnancy had already developed chronic hypertension in the interim 3.6 years, requiring ongoing treatment, and were excluded from the analysis for this reason. Hypertension is the leading risk factor for loss of disability-adjusted life years (DALYs) in high and low-middle income countries and short-term, targeted postpartum interventions could offer a clinically translatable approach to improve BP outcomes for women within this population. This study has shown in a small RCT that it was possible to lower BP for at least four years postpartum by ensuring tighter BP control during the puerperium while women require ongoing antihypertensive treatment after birth. Critically, this study also highlights that there may be a window postpartum where a relatively affordable, readily translatable process of home blood pressure self-management can impact long-term blood pressure trajectory after a hypertensive pregnancy, and reduce the later burden of cardiovascular and cerebrovascular disease. Self-management of BP has been shown to be cost effective in other clinical scenarios [103] and due to its patient acceptability, and ease of use in remote healthcare, it has been proposed in recent national

guidance [104] for provision of postpartum care during the COVID-19 pandemic. The POP-HT trial, which will be considered next was designed with the aim of testing the reproducibility of the impact of a form of self-management of BP postpartum, as well as investigating whether early improvements in BP control during the puerperium could alter the adverse cardiovascular remodelling process [105].

CHAPTER 4 – The POP-HT – INTRODUCTION AND METHODS

I. Introduction

In the general population, high blood pressure is strongly related to long-term risk of cardiovascular disease and is the leading risk factor for loss of disability-adjusted life years (DALYs) in high and low-middle income countries. Every 10 mmHg in systolic and 5mmHg in diastolic reduction of blood pressure associates with a ~40% reduction in lifetime stroke risk and ~20% reduction in coronary heart disease risk [40]. SNAP-HT demonstrated a 4.5mmHg lower diastolic BP in the self-management arm at 6 months postpartum, and in the SNAP-HT Extensions study, longer-term follow-up of these women demonstrated that DBP remained significantly lower in the intervention group [24hr overall average DBP was 6.8mmHg lower and clinic DBP was 3.4mmHg lower), ~four years postpartum, even when adjusted for 'lifestyle risk factors' [88]. In those aged <50 diastolic blood pressure is a better correlate and predictor of long-term cardiovascular risk and is the predominant pathophysiology in young adults [106].

If these BP improvements could be translated to all women who have a hypertensive pregnancy, a significant reduction in disease burden could be achieved in the population. However, several questions remained to determine the potential clinical translational benefits of self-management in the treatment of postpartum blood pressure. Firstly, could a similar reduction in blood pressure be achieved in a trial adequately powered to detect diastolic (and systolic) BP differences at 6 months. Secondly, could updated technology (Bluetooth-enabled, validated, wireless home blood pressure monitors), which facilitate automated upload of readings to the app, reduce the demand on participants and user error during a busy period in the patients' lives. The aim was to provide 'more accurate' telemonitoring given the ~5% error rate reported in a follow-on mixed methods paper on SNAP-HT [91]. Thirdly, by involving physicians who could review and advise on BP self-management based upon the telemonitored readings [107-109] it allowed for semi-automated uptitration, as well as the down-titration algorithms developed in SNAP-HT, as explained in more detail in a dedicated Intervention overview section below. Lastly, did improved postpartum blood pressure control result in reduced end organ damage in the cardiovascular system? As outlined in Chapter one, hypertensive

pregnancies are associated with early changes in cardiac, vascular and brain structure and function, which are disproportionate to their cardiovascular risk profile [39, 65, 66], which may explain why this population have an increased risk of later cardiovascular, and cerebrovascular disease. It is possible these changes may emerge during pregnancy and persist long-term, independent of postpartum blood pressure variability but, an alternative hypothesis it that the long-term risk reflects a failure of the cardiovascular system to 'normalise' after pregnancy [29, 69]. If so, improved postpartum blood pressure control may offer a new approach to modify these long-term end organ changes, in addition to any beneficial effects on blood pressure. It was these questions that the POP-HT trial was designed to answer. Due to time limitations resulting from COVID-19, and the volume of data acquired in the trial, the focus of this thesis was on blood pressure control, and cardiovascular and vascular remodelling. The remaining data on brain and retinal vasculature, and cardio-pulmonary exercise testing will be analysed outside of this thesis.

II. Summary of the intervention

The intervention comprised the provision of a wireless Bluetooth® enabled OMRON Evolv® blood pressure monitor, validated for widespread clinical use, including in pregnancy [110] , alongside the installation of a proprietary smartphone app called POP-HT®. The app® was used for assisting in the self-management of postpartum blood pressure readings, with physician oversight of medication adjustment done via a secure web-based interface system. The system was developed by the Oxford Institute of Biomedical engineering (IBME) who have successfully developed Apps for several other blood pressure studies including SNAP-HT [56], TASMIN [111] and the BUMP trials[54, 55].

For those randomised to the intervention, the participants were helped to download the proprietary POP-HT smart-phone app®, and taught to use the OMRON Evolv cuff® and the POP-HT app® whilst on the postnatal ward of the Oxford Women's Centre. The participant had the remainder of their stay in hospital to practice using the BP cuff and app® and were able to contact the study team to resolve any problems. They were also provided with an 'intervention-arm information sheet' electronically, which was also contained in the HELP section of the APP. This contained information about the self-

management process as well as a frequently asked questions (FAQ) section and a contact telephone number (8-7 pm Monday-Friday). E-mail address were also provided for any technical problems or clinical concerns from participants.

Participants in the intervention arm were asked to start home blood pressure readings on the day/night of discharge and they would be asked to submit their readings daily (or twice daily) depending on the values submitted. The medications prescribed to each participant at discharge were decided by their NHS clinical care team. The medication schedules were based on the inpatient anti-hypertensive medications and these were then uploaded to a secure NHS hosted web-based platform, which synchronised automatically with the app so this could be cross-checked against their discharge letters prior to going home.

Following discharge from hospital, participants were asked to upload their home blood pressure readings in a standardised manner (explained in much more detail in Appendix B). These readings were in turn uploaded to the secure NHS hosted web-based platform called EDGE®. The readings were then automatically cross-checked against pre-defined algorithms and an appropriate notification was generated in response. This approach was trialled successfully in the SNAP-HT pilot trial [56] and medication down-titration in the intervention arm was performed using the same methodology as SNAP-HT for consistency between the two trials. Medication uptitration schedules were novel in POP-HT and were designed around the updated NICE guidance NG133, and following detailed consultation with an expert-panel comprising obstetric physicians, obstetricians and cardiologists to determine guiding principles. The schedule was tailored according to participant factors such as ethnicity, renal function, allergies and prior response to a given medication ante and/or postnatally. For those in the control arm, clinicians were anticipated to also follow the new NICE guideline NG133 for up and down titration [107].

Down-titration was triggered when a participant's BP was consistently <130 mmHg systolic and <80 mmHg diastolic; and the process and timing triggers for medication down and up titration is explained in much more detail in Appendix B. The algorithms went through rigorous testing for different simulated patient behaviours and went through detailed real-word testing by members of the PPI

group and study team before being used in the trial itself. Figure 10 below briefly illustrates how this process worked.

The key advances in the POP-HT intervention compared to SNAP-HT were as follows:

- SNAP-HT relied on SMS messages in >75% of participants and required significant user input for BP measurement, data input and an SMS response to advised changes in medication. As well as testing the blood-pressure lowering reproducibility of SNAP-HT, POP-HT provided data on whether 'more-user-friendly' approaches could reproduce similar results i.e. Blue-tooth BP monitors automate the upload readings reducing the amount of 'time' and 'effort' women have to contribute during a 'busy' time in their lives.
- The advancement of the app and automated blue-tooth synchronisation with the monitor was designed to reduce user input errors, sometimes evident in SNAP-HT. This Blue-tooth methodology has been widely used in other studies and notably has been well validated by the OX-VASC group [108, 109].
- Women had the option of adjusting medication for elevated BP readings (medication up-titration) when in safe predefined ranges (as outlined in Appendix B), rather than just being down-titrated for low readings as in SNAP-HT. This process was safety-netted by remote supervision from clinicians in the research team in this instance. The aim of offering up-titration was to reduce unnecessary admissions, something seen in SNAP-HT, as well as to further improve BP control.
- Participants could also opt to see their own GP/midwife for abnormal readings as well as, or instead of, self-management, which provided additional information about the likely uptake of self-management in a real-world setting, given the ultimate aim was to embed this app and model of BP self-management into secondary and/or primary care under the supervision of obstetricians and/or general practitioners.

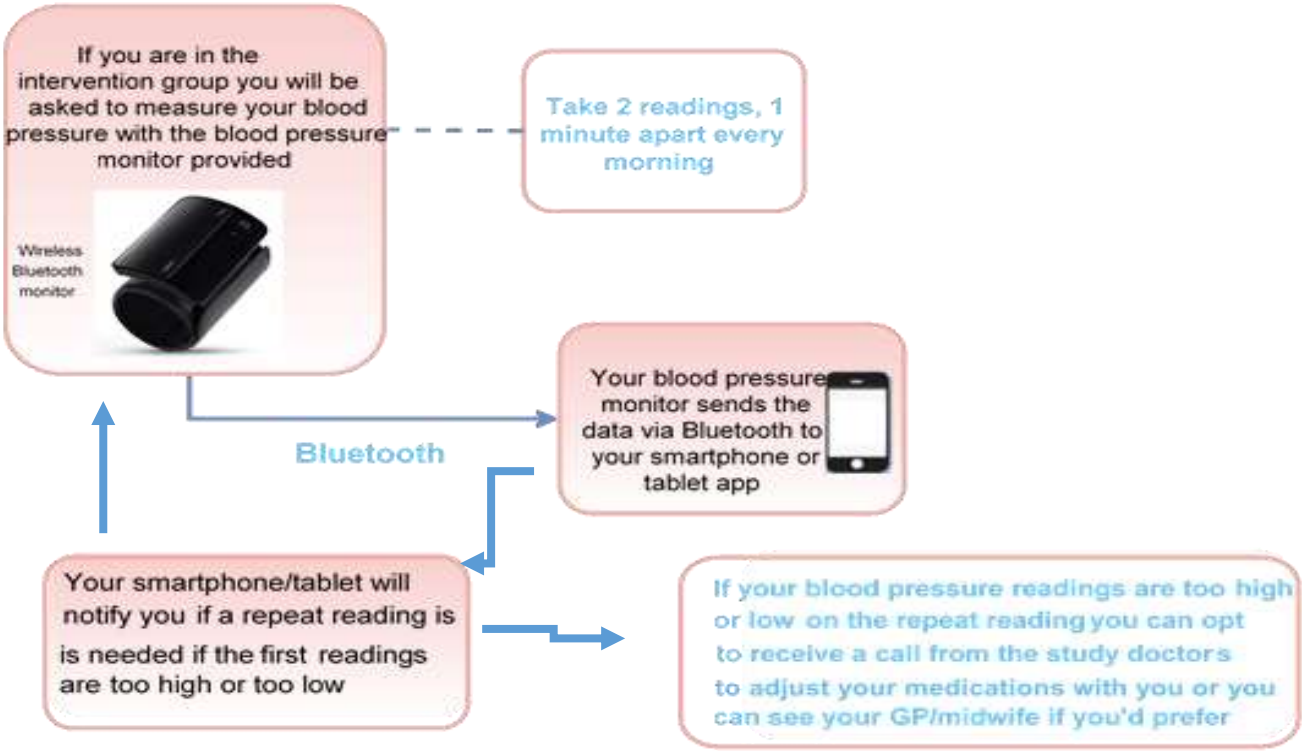


Figure 10: Illustration of the process of self-management of BP for women randomised to the intervention (participants could opt for a 'call' to discuss adjustment and then the app would confirm; or the app would adjust automatically after a physician had reviewed the readings triggering a notification to the participant and an updated medication list on their app)

The control arm

The control arm received 'standard' levels of NHS care from their GP, midwives and/or health visitors following discharge from hospital, which at the time of the trial, was expected to comprise a day 7-10 blood pressure review with a community midwife and a 6-8 week review with their GP at the very minimum (based on NICE NG133 guidance[13]).

However, during the COVID-19 pandemic, section 3.1.5 of the 'RCOG Guidance for maternal medicine in the evolving coronavirus (COVID-19) pandemic', recommended 'self-monitoring 2-3 times in the first week after discharge' for women who have had a hypertensive pregnancy [9]. Therefore, those women allocated to the control arm, who were unable to obtain a monitor from the NHS, were also provided with a validated home-monitoring BP device by the trial team to ensure they could adhere to the RCOG guidance. These monitors were provided to enable the control arm participants to

monitor their own blood pressure and in turn liaise with their own GP/midwife to adjust their management based on their readings. The study team did not offer remote management to the control arm or provide them with the app, or interpretation of the readings. If out of range they were instructed to contact their GP or the Maternity assessment unit as per usual NHS-led care given to the women on discharge i.e. management decisions were led by their own GPs/clinicians.

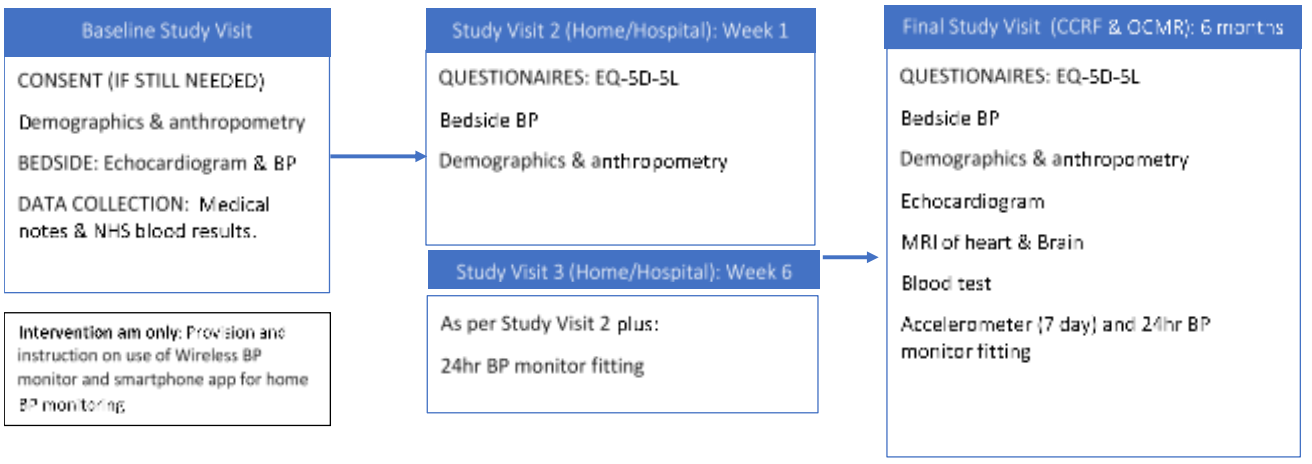
III. Methodology in the POP-HT RCT

Here I have presented an overview of the study design and visits, followed by the details of the investigations and methods of data collection undertaken, and how they were analysed and their intra- and inter-observer coefficients of variation. Finally, I describe the statistical methods employed. The full protocol was published in BMJ Open [95], but the key points and a trial flow chart/schematic **(Appendix C)** have been included in my thesis for ease of reference.

Study Design

POP-HT was a single centre, open label, two-arm Parallel, Randomised Open Blinded End-point (PROBE) study in women who had a hypertensive disorder of pregnancy, and who required anti-hypertensive treatment at the time of discharge. The study recruited 220 participants, who were randomly allocated in a 1:1 fashion to either the intervention or control arm. After enrolment, the data collected were anonymised and coded with study specific IDs (e.g. POP-HT 01-001) to ensure confidentiality and blinded analysis downstream. This trial was conducted in accordance with relevant regulations and Good Clinical Practice guidelines[112]. The trial protocol and all accompanying documentation and amendments were approved by the Sponsor, an external REC, the HRA (Ethics Ref: 19/LO/1901; IRAS Project ID: 273353) the OUH (the local NHS trust) trial management authority (TMA) and following consultation with and approval by the MHRA. The participant had to personally sign and date the latest approved version of the Informed Consent form(s) before any trial specific procedures were performed. Full details on the consent process are in the fully published study protocol [95]. All participants were recruited from the Oxford Women's Centre at the John Radcliffe Hospital.

The expected duration of participant involvement was up to 12 months from enrolment to study completion and participants were asked to attend four study visits after their pre-screening and enrolment: baseline, at 1 week, at 6 week and at 6-12 months. At times when face to face appointments were restricted due to regulations related to the COVID-19 pandemic, the week 1 and week 6 visits could be done remotely to avoid putting participants at undue risk. The primary outcome was studied over a narrower time frame of 6-9 months as originally planned at the studies outset, prior to the COVID-19 pandemic, but a further amendment was approved to allow all BP based primary and secondary outcomes to be done remotely if needed. The other secondary outcomes could be done over a wider timeframe of 6-12 months to allow participants to safely attend their study visit at the hospital. An optional sub-study involving administration of Gadolinium contrast was offered as an additional component to the MRI during the final study visit in those women who were not breast feeding to look for the presence of myocardial fibrosis as a possible mechanism for long-term CV risk. During the baseline visit, the study investigators performed all procedures for participants in both arms i.e. the intervention and the control arm. The provision of the study intervention was for the intervention arm only as explained above. A trial flow chart is presented in figure 11 below and a schedule of procedures can be found in appendix B.



All aspects of each visit contained in the boxes above are 'essential' to the study but a number of other 'desirable' procedures will be offered where possible:

1. Lifestyle & diet questionnaire at baseline & 6 months (can be completed at a later date in participants own time)
2. Vicorder® assessment of aortic BP and aortic distensibility/compliance at baseline & 6 months
3. Retinal Imaging at 6 month visit
4. CPET with a focused exercise echo at 40% of maximal predicted workload (mild exertion on a static bike) at 6 month visit
5. Formal review of medical and obstetric history at the final 6 month visit

Figure 11: Flow Chart/Schematic of Proposed Study visits in the POP-HT trial

As the flow chart above illustrates, there were 'essential' components for each study visit, but given the research involved women with newborn babies, and to limit face-face contact during COVID-19, some components were classed as 'desirable' to allow shortening of the study visits if required.

During the COVID-19 pandemic, the POP-HT trial was amended as mentioned with a brief interruption to the trial running during April and May 2020. On restarting recruitment in June 2020, the study visits were adjusted as described in the published study protocol to reduce the length of time of direct patient contact. All procedures were performed in appropriate PPE.

Recruitment

All trial participants were recruited locally from the Women's Centre at the John Radcliffe Hospital, Oxford. Screening was carried out by the patient's clinical care team. Consent was performed by the research team, once verbal consent was given to the clinical team for them to be approached.

Main trial participants

All participants were females of childbearing aged 18 years or over. Entry into the trial required a clinician confirmed diagnosis of either gestational hypertension or pre-eclampsia, as defined by NICE NG 133 [13] , without prior evidence of chronic hypertension, and that required antihypertensive medication following delivery.

Inclusion criteria

- Participant was willing and able to give informed consent for participation in the trial.
- Female, aged 18 years or above.
- Clinician confirmed diagnosis of either gestational hypertension or pre-eclampsia, as defined by NICE NG 133 and remained in hospital after delivery.
- Requiring antihypertensive medication at the point of discharge from secondary care.
- Participant has clinically acceptable laboratory results and clinical course postpartum with no other adverse complicating factor requiring prolonged admission postpartum that would make participation unfeasible as judged by the CI. Examples would include stroke sequalae, ongoing DIC or another significant life-threatening comorbidity

- In the investigator's opinion, was able and willing to comply with all trial requirements including ownership of a smartphone or tablet and willing to use the smart-phone app if randomised to that arm.
- Sufficient competence in English language to follow the app instructions and partake in the study, as judged by the CI.

Exclusion criteria (the participant may not enter the trial if any of the following apply)

- Significant renal or hepatic impairment that would have affected safe medication titration and adjustment as part of the trial, as deemed by the chief investigator.
- Participant with life expectancy of less than 6 months.
- Any other significant disease or disorder which, in the opinion of the investigator, may have put the participant at risk through participation in the trial, influence the result of the trial, or impair the participant's ability to participate in the trial.
- Participants who had participated in another research trial involving an investigational medicinal product in the past 12 weeks.
- Women with pre-existing hypertension (defined as a booking BP >140/90mmHg and or prior treatment for essential hypertension at the time of booking) were excluded, as this was felt to represent a separate pathology, that may influence the efficacy of the study intervention, and in turn the primary and secondary outcomes of the study.

Randomisation

Randomisation was performed as soon as possible following the baseline visit. Randomisation was carried out using a secure web-based randomisation software (embedded within Castor®). Participants were randomised on a 1:1 basis and two minimisation factors were used to ensure that the groups were as well matched as possible:

Primary factor: Gestational age at the time of presentation with pre-eclampsia/gestational hypertension (agreed on as a surrogate marker of disease severity by the TSC).

Secondary factor: Prescription of ACE inhibitor (Enalapril) at the time of randomisation.

IV. Study Procedures

a) Data Capture

The eCRF that was used in POP-HT was called CASTOR® edc and is described in CHAPTER 2 in more detail. In POP-HT it allowed direct real-time data entry during study visits wherever possible and enabled the study to be paperless, consent forms aside

b) Anthropometry

During the baseline assessment (on the postnatal ward of the Oxford Women's centre), this included recording the antenatal booking height, weight and BMI (obtained from electronic and paper notes) and the mid-left arm circumference was measured using a tape-measure. During the in-person/face to face, week 6 and the 4th/final study visits, anthropometric measurements including height, weight, body mass index (BMI) and waist to hip ratio were performed. Demographic data were also updated at each of these points. After removal of shoes and wearing light clothing only, subjects had their height and weight measured standing to the nearest centimetre and 0.1Kg respectively using the same calibrated scales and height chart. Body mass index (BMI) was calculated using the following formula:

$$BMI\ (kg/m^2) = Weight\ (kg)/\ [height\ (m)^2$$

Waist and hip measurements were measured in centimetres and the waist: hip ratio calculated.

Body surface area (BSA) was calculated using the Mosteller formula:

$$BSA\ (m^2) = \sqrt{([Height\ (cm) \times Weight\ (kg)]/\ 3600)}$$

For those visits done remotely participants were asked to weight themselves and measure their left arm during the video call to ensure reliability of the readings, although different scales were used during these remote visits, which the team could not ensure were calibrated/accurate. For home visits the same calibrated scales and height recorder were used as for those measured in CCRF.

c) Collation of obstetric and medical history

At the baseline visit, and once consented, a study team member reviewed the medical notes (paper and electronic) to document the following information: Gestation at diagnosis, gestation at delivery,

the numbers of days of antenatal blood pressure treatment, the mode of delivery, the number and doses of anti-hypertensive drugs used post-natally, whether ACE inhibitors (enalapril) were prescribed at the time of enrolment, the baby (babies) weight (s) and, the presence of IUGR (defined as a drop in abdominal circumference between growth scans of >40%). The team also recorded the relevant day 1 post-natal blood results, the urine PCR at its peak and the sFLT/PIGF ratio was recorded if it had been taken. All medications prescribed at the time of enrolment and, any other medical and obstetric history of note was also recorded directly into CASTOR edc®.

During all follow up visits the medication(s) and doses were updated, adverse reactions/side effects to medications were documented, details of any post-natal readmissions were recorded and cross-checked to their medical records, and any other relevant medical/obstetric history was also updated. During the final study visit (either in CCRF or as a home visit), if participants agreed, I performed semi-fasting blood tests (>2 hours without food or any fluid except water). This was performed in 186/203 final study visit (91 .6%) with some women declining this optional part of the study visit due to needlophobia, and in remote home visits this was not possible. Bloods tests included a full blood count, renal function, liver function tests, Total, LDL and HDL cholesterol and, random glucose and insulin levels.

d) Questionnaires

In POP-HT an E5-5D-5L questionnaire was sent out at baseline, weeks 1, week 6 and the final visit at 6-9 months to allow longitudinal tracking of subjectively reported quality of life throughout the study's duration. This questionnaire was explained and referenced in CHAPTER TWO as it was also used in the SNAP-HT Extension study. A diet and lifestyle questionnaire was also e-mailed to participants for completion to identify possible lifestyle and dietary factors, which could confound any blood pressure differences detected in the study. Information was collected on factors that affect blood pressure including: smoking frequency, alcohol and salt intake, exercise and family history. These questionnaires were explained further in CHAPTER 2 (SNAP-HT Extension methodology).

e) Vascular phenotyping

24-hour Blood pressure analysis

The 24hr hour monitoring periods were performed to allow identification of masked and white-coat hypertension at the different time-points and because it is the widely accepted gold-standard tool [96] for measuring peripheral blood pressure. White-coat hypertension is blood pressure that is unusually raised when measured during consultations with clinicians but is normal when measured in 'non-threatening' situations [113]. It is reported to occur in about 15–30% of the population, although this may be even higher in HDP [97]. As defined by the National Institute for Clinical Excellence (NICE) adult hypertension guidance (NICE NG136) [114], a 'white-coat' effect is a discrepancy of more than 20 systolic /10 diastolic mmHg between clinic and, average daytime readings on 24hr ABPM, or average home blood pressure measurements (HBPM) blood pressure measurements at the time of diagnosis. Masked hypertension is when clinic blood pressure measurements are normal (less than 140/90 mmHg) but blood pressure measurements are higher when taken outside the clinic using average daytime ABPM or average HBPM blood pressure measurements.

24-hr blood pressure monitors were fitted at two time-points: visit three (week six) and at the final visit (V4) performed at six-nine months postpartum.

On March 17th 2020, the COVID-19 pandemic meant that all research across Oxford University and OUH NHS Foundation Trust had to be halted, which affected POP-HT as a consequence and requires us to make several amendments, which I've summarized below. Minor amendment 2.0 (approved 06/05/2020) allowed us to continue the follow up of 18 women already recruited, who then had their V3 24hr BP monitors fitted during home visits wearing appropriate PPE. Further amendments were then submitted, to enable the POP-HT RCT to restart during the COVID-19 pandemic as covered by 'exception 3' of the OUH NHS Foundation Trust research guidance for COVID-19. These amendments enabled remote follow up visits for people unwilling/not allowed to attend the hospital during times of national lockdown. The OUH trial management authority (TMA) then granted permission for the trial to restart in June 2020. Most remaining week 6 (visit 3) 24hr BP monitors were fitted remotely over ZOOM® by the study midwife Yvonne Kenworthy, research assistant Annabelle McCourt, or

myself. Women were self-instructed on how to fit to the cuff to their mid-left arm. A single manual reading (excluded from analysis) was taken to confirm correct placement over ZOOM®. Monitors were then returned by post as explained previously. Perhaps not unsurprisingly a larger number of the 24hr monitor readings performed were invalid when fitted remotely over ZOOM (183/213 monitors fitted remotely fulfilled NICE NG136 criteria but 30/213 had to be excluded due to failure to meet the pre-specified criteria stated above). During the final visit (V4), performed at 6-9 months postpartum, the 24hr BP monitors were fitted in person at the end of the study visit in CCRF. This was the case for the vast majority of participants who attended the hospital in person for their visit (187 were fitted in CCRF of the 202 participants still enrolled at V4). 13/202 women had the monitor fitted as part of a home V4 visit, and a further 2/202 women opted for a remote home visit due to concerns about COVID-19. The remoted 24hr APBM was performed as described above. In 6/202 sets of readings, the 24hr ABPM readings failed to fulfil the NICE criteria for a valid set of 24-hrBP readings and were repeated as soon as possible within the 9-month time-window. 200/202 24hr BP monitors done at V4 were valid by trial completion as, two of the six repeated still had an inadequate number of valid readings to be included.

Peripheral blood pressure measurement

During the baseline visit, participants had their blood pressure checked after 5 minutes' rest using the automated mode of a validated sphygmomanometer. Three blood pressure readings were taken at intervals of one minute. The first reading was 'discarded' and not used toward the mean blood pressure calculated for the visit. Measurements were taken on the left arm (unless a specific medical reason precluded its use,) using automated DINAMapV100® blood pressure monitors. The arm circumference was measured beforehand and recorded as part of the anthropometry to ensure the appropriate cuff size was used for the arm circumference. The measurement technique advised by the British Heart Foundation (BHF) was strictly followed in all cases i.e. participants were positioned at 45 degrees in their hospital bed, legs were uncrossed, they were advised not to talk at the time of measurement and, the arm was supported and elevated to the height of the heart using an appropriate support e.g. pillows or their height adjustable side-table.

At weeks one, six and the final study visit (visits two, three and four respectively), the peripheral blood pressure was measured using validated, calibrated OMRON Evolv® blood pressure monitors [110] . These wireless monitors were easy to use with intelli-360 degrees accuracy, and all women were taught how to take readings prior to discharge, as well as being provided with an instruction manual. For those follow up visits done in person (face-face), the study investigators took three BP readings one minute apart, using the same BHF recommended technique described above, but sitting. For those visits performed remotely, the video call allowed investigators to ensure the correct technique was followed i.e. the readings were taken at the end of the video consult when the women had been sat rested for at least 5 minutes, with legs uncrossed, arm supported on a table/desk and not speaking. The monitor was fitted to the left arm whilst on the video call under observation; and the three readings were read from the OMRON Evolv®'s display screen to ensure accuracy. Data were recorded directly into CASTOR edc® during all study visits.

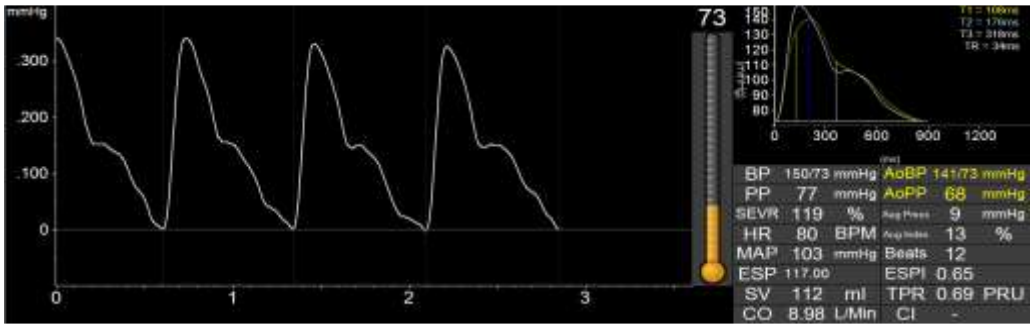
Pulse wave analysis and velocity measurement

Pulse wave velocity was measured between brachial and femoral arteries. The validated Vicorder® system (SMT Medical, formally Skidmore Medical, Taunton, UK) was used to obtain pressure waveforms of the brachial and femoral pulse. The Brachial artery pressure waveform was used to derive central blood pressure as illustrated in the figure below.

For brachial-femoral pulse wave velocity brachial and femoral cuffs were fitted (a known measured distance apart) and connected to an oscillometry device (Vicorder®). The cuffs are then partially inflated and used to detect pulse arrival and thus derive pulse wave velocity from the difference between the cuffs. This technique was used during the baseline visit on the postnatal ward with women reclined to supine using their electronic hospital beds to allow standardisation of the procedure. In addition, aortic blood pressure was used during the final visit during their Cardiac MRI scan whilst participants lay supine in the MRI scanner. The measurements were taken at the end of the scan, immediately following sequence to measure aortic distensibility, using a brachial cuff connected to an oscillometry device. For brachial-femoral pulse wave velocity a femoral cuff was also

fitted (a known distance apart) and connected to an oscillometry device (Vicorder®). The cuffs were then partially inflated and used to detect pulse arrival and thus derive pulse wave velocity from the difference between the cuffs.

Figure 12. Pulse wave analysis using Vicorder. Brachial artery pressure waveforms were used to derive central blood pressure.



For a small number of women who opted for home visits (13 were home and 2 were remote), for their final V4 visit, the Vicorder assessment of pulse wave velocity and central blood pressure was performed for the 13 done at home, when equipment was available. It was done in a standardised manner with participants laid flat on a collapsible table at the end of the study visit and the same technique outline above was employed to obtain the measures.

f) Cardiac phenotyping

Cardiovascular magnetic resonance

Cardiac structure and function were assessed using cardiovascular magnetic resonance (3T Siemens PRISMA® scanner) with 12 channel body and spine array, Siemens, Munich, Germany). Images were retrospectively ECG gated with a precordial three lead ECG.

Ventricular structure (volumes, mass, wall thickness)

Steady state free precession (SSFP) images during breath hold at end expiration were acquired with the following sequence parameters: repetition time 45.72 ms, echo time 1.07 ms, flip angle 60^0, calculated phases 25 (temporal resolution 40 ms at a heart rate of 60 beats per minute), in plane resolution 2.8 x 2.0 mm, slice thickness 8.0 mm. Using 2, 3 and 4 chamber views to plan images in line

with the atrio-ventricular valves a stack of short-axis images were acquired at 1cm intervals to include the entire left and right ventricles.

Image analysis was performed using CVI42 versions 5.1.1 (Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada). Left and right ventricular endocardial and epicardial borders were manually contoured at end-diastole and endocardial borders only in end-systole. Papillary muscles and trabeculations were excluded from the LV myocardial mass in line with previous pilot work by my group [60] and OCMR protocols based on JCMR guidance [115]. Myocardial mass was calculated from the sum of the myocardial area in the stack of images multiplied by 1.05g/cm^3 (specific gravity of myocardium per cm^3). End-diastolic and end-systolic volumes were also calculated from the sum of ventricular areas in the stack of images. Stroke volume is the difference between end-diastolic and end-systolic volume. Ejection fraction is calculated stroke volume divided by end-diastolic volume. Wall thickness was measured at mid-ventricular level in 6 segments (anterior, lateral, inferior, inferolateral, inferoseptal and anteroseptal) as represented in standard international guidelines [116]. Mean wall thickness values were calculated from these 6 measures.

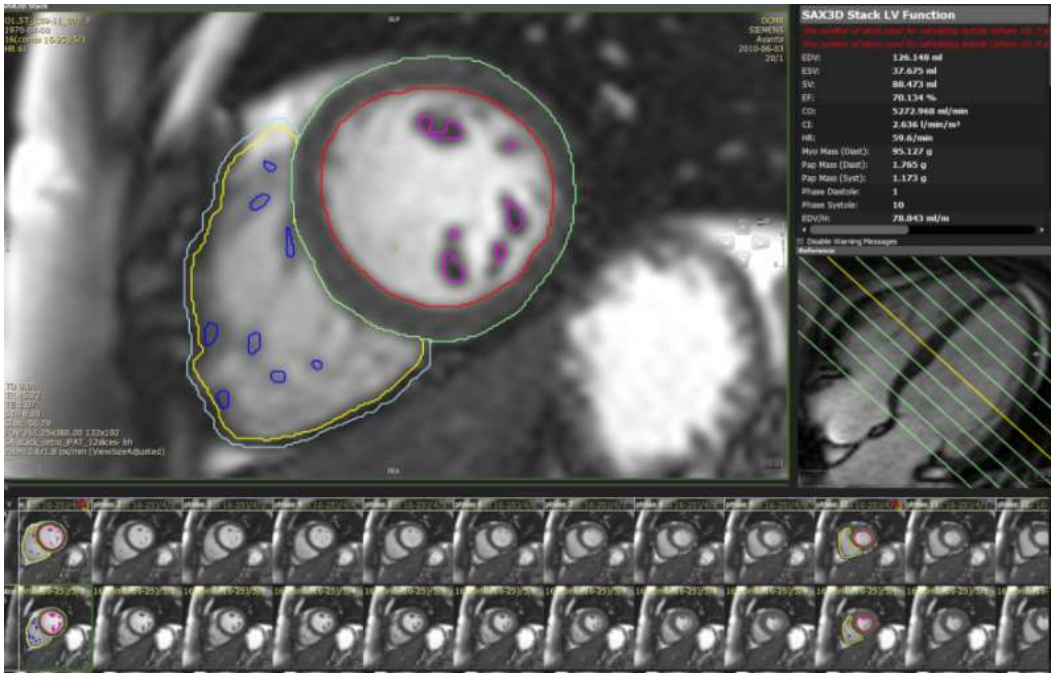


Figure 14. Example of cardiac analysis using CMR. Stack of short axis CMR images viewed in CMR42 with contouring of myocardium to calculate ventricular volumes and myocardial mass

Myocardial T1 and T2 mapping

Myocardial T1 values were measured from short modified look locker images during breath hold at end expiration with the following sequence parameters: repetition time 198.77 ms, echo time 1.07 ms, flip angle 35^0, in plane resolution 1.8 x 1.8 mm, slice thickness 8.0 mm. A modified stack of short-axis images corresponding to the slices acquired for ventricular volumetric analysis was acquired at the mid-level of the left ventricle. A single slice SSFP T2 map was performed by copying the same image position as the T1 map performed in the mid-ventricular position.

All T1 and T2 maps analyses were performed blinded to the clinical information. T1 maps were analysed using in-house software Mc-Roi (programmed by S. Piechnik in IDL, v8.8, Exelis Visual Information Solutions, Inc., Boulder, USA). T2 maps were analysed on commercially available post-processing software (CMR42, Circle Cardiovascular Imaging, Calgary, Alberta, Canada, v5.12.1). Endo- and epicardial contours were manually placed within the left ventricular myocardium on short-axis T1 and T2 maps, with care to avoid partial volume with surrounding tissue, such as fat or blood pool. Raw images were examined for breathing or cardiac motion, or SSFP artefacts. For T1, quality control maps for 'goodness of fit' (R2) were assessed for image quality as previously published (Ferreira et al. 2012). Segments affected by artefacts were excluded from analyses. Normal values for comparison were obtained on the same 3T PRISMA scanner in 15 age matched females using the same T2 SSFP and T1 192i WIP sequences used in the POP-HT trial.

Intra- and Inter-observer coefficients of variation for cardiac structure

Measurement	Intra-observer CoV (%)	Inter-observer CoV (%)
Volumes and mass		
LV end diastolic volume	1.5	4.1
LV end systolic volume	2.0	3.0
LV stroke volume	0.5	1.1
LV ejection fraction	0.9	1.2
LV myocardial mass	2.5	4.5
RV end diastolic volume	1.9	5.9
RV end systolic volume	1.7	4.9
RV stroke volume	2.3	4.7
RV ejection fraction	1.2	4.1
Wall thickness		

Anterior	5.5	6.5
Lateral	6.8	7.5
Inferolateral	3.2	4.0
Inferior	6.0	7.3
Inferoseptal	5.8	7.4
Anteroseptal	5.9	6.8
Mean wall thickness	6.53	7.4

CoV: coefficient of variance; LV: left ventricle; RV: right ventricle

Left atrial volumes

SSFP images at breath hold during end expiration were acquired in 2 and 4 chamber views, with the following sequence parameters: repetition time 39 ms, echo time 1.1 ms, flip angle 60^0, calculated phases 25 (temporal resolution 40 ms at a heart rate of 60 beats per minute), in plane resolution 1.9 x 1.9 mm, slice thickness 7.0 mm. Mean left atrial volumes were calculated using standard and recognised methods [116]. In brief, maximal left atrial volumes were contoured in 2 and 4 chamber views. Left atrial appendage and pulmonary veins were excluded. Left atrial volume index was calculated by dividing mean left atrial volume by body surface area (the Mosteller equation). Maximal transverse (A-P) dimensions was measured in the LVOT (3 chamber) view. As this data was calculated in echo also for diastolic function the MRI equivalent data has not be presented in this thesis too as analysis is ongoing for the LA data

Gadolinium contrast:

Gadolinium was offered as an additional optional component to the MRI in those women who were not breast feeding. This was part of exploratory work that may feed into a larger future trial to assess for the presence of any myocardial fibrosis and determine if there were any patterns of gadolinium enhancement. Before any gadolinium was administered, the last creatinine value taken prior to discharge postpartum (up to 9 months prior) was reviewed and if normal, a repeat was not needed. If not available, or if elevated, or of clinical judgement deemed it necessary, a repeat finger prick creatinine was done. If the reading demonstrates an eGFR<60mls/min, the gadolinium was not given and a procedure for incidental abnormal clinical findings was followed. If women consented to late gadolinium imaging, their blood tests described above were obtained during cannula insertion in

OCMR and an additional vial of blood was collected to measure serum haematocrit, which enabled extra-cellular volume to be calculated in these cases.

Transthoracic echo

Echocardiography were performed using a Philips CX50® portable echo machine for all baseline visits at V1. All follow up 2D echo scans at the final/4th study visit were done using a Philips Epiq 7® or IE33®. All echo machines were equipped with a 2D (and 3D) phased array transducer and scans was performed in the left lateral decubitus position. Echo was used to principally assess diastolic function including PW Doppler assessment of the mitral valve inflow and pulmonary vein inflow, TDI of lateral and septal walls of LV and assessment of LA volume using the algorithms recommended by BSE and ASE guidelines [117, 118]. All echo analysis was performed blinded to allocation as discussed in statistical analysis section.

Echo was also used to calculate global longitudinal strain: Assessment of strain by speckle tracking was undertaken offline using semi-automated 2D Cardiac Performance Analysis Software (TomTec®, Munich, Germany). Apical 4, 2 and 3 chamber 2D images were processed and the endocardial border delineated in end diastole. The endocardial border was tracked through a single cardiac cycle and the tracking then inspected and manually corrected if poorly correlated with myocardial margin. Peak global values of longitudinal strain in systole and strain rate in systole and diastole were measured.

Intra- and Inter-observer coefficients of variation for echo assessment of cardiac strain are shown below

Measurement	Intra-observer CoV (%)	Inter-observer CoV (%)
Longitudinal		
Systolic velocity	8.4	11.0
Displacement	5.0	8.4
Strain	6.2	9.1
Systolic strain rate	6.2	8.8
Diastolic velocity	8.1	8.4
Diastolic strain rate	7.3	10.5

CoV: coefficient of variance

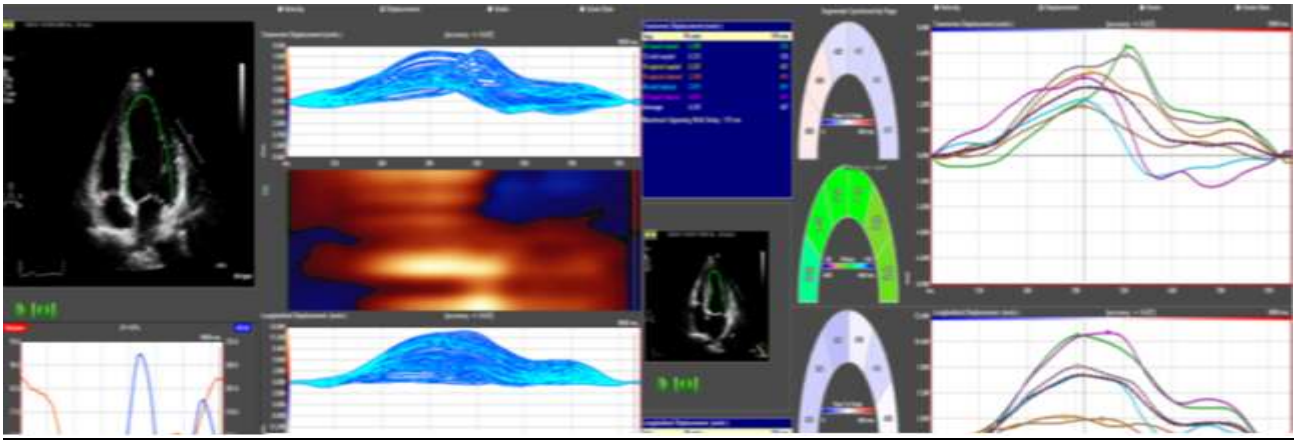


Figure 15: An example of echo strain analysis using Tomtec®

g) Cerebrovascular phenotyping: Brain magnetic resonance

Overall brain volumes and specifically grey matter volumes are closely associated with cardiovascular risk. Brain weight at death has been shown to be inversely associated with blood pressure in midlife [119]. Grey matter volumes are reduced in those with a higher prevalence of cardiovascular risk factors [120] and furthermore accelerated grey matter atrophy has been shown in hypertensive individuals despite treatment [121]. In addition, work on the Framingham cohort by Maillard et al [122] showed that subtle vascular brain injury develops insidiously during life, with discernible effects even in young adults. These findings emphasise the need for early and optimum control of blood pressure, which is particularly important in pre-eclampsia and gestational hypertension where the brain is exposed to accelerated hypertension. The study also involved Brain MRI at this time-point so that I can better understand the time course of cerebrovascular changes described in this patient cohort in prior work by my group [123]. As mentioned in the introduction and hypotheses section of this chapter above, due to time limitations the Brain MRI data has not been analysed in time for the presentation of this thesis, with data analysis ongoing.

h) Fitting of an activity monitor (AX-3® Axivity wrist-worn accelerometer)

At the end of the final study visit (V4) participants were fitted with a wrist-worn accelerometer for 7 days as described further in section 2 SNAP-HT Extension methodology.

i) Blood test

An optional venous blood sample (approximately 25 mL) was taken at rest at the 4th and final study visit, with verbal consent, and included samples for (1) whole blood, plasma and serum lipid and inflammatory marker analysis and (2) analysis of biochemistry and metabolism.

V. Outcomes

For clarity; the time point of the primary and BP based outcomes were 6–9 months postpartum, whereas an extra 3 months (6–12 months) was approved by the trial steering committee (TSC), REC and HRA for completion of the other secondary outcome data collection (as part of an amendment to mitigate against the impact of the COVID-19 pandemic on follow-up rates for these additional measures). This explains the different time points shown in table 1 below.

The primary outcome for this study was 24hr overall average diastolic BP as measured by 24hr ABPM. The secondary outcomes were divided into BP based secondary outcomes and those based on imaging to assess the impact of BP control on cardiovascular remodelling as described in the hypotheses section of Chapter 1. The brain and retinal based secondary outcomes, the CPET, kidney mapping and exercise echo based tertiary outcomes are not considered within the scope of this thesis as previously mentioned but are listed here as per the published protocol paper.

Outcomes for the POP-HT trial as described in the published protocol paper [95]

	Objectives	Outcome Measures	Timepoint(s)
Primary	To compare postpartum diastolic BP in the intervention arm to the control arm.	24-hour average diastolic BP measured by assessed by SPACELAB 90217 24hr Ambulatory blood pressure monitoring (ABPM)	6-9 months postpartum
Secondary	To compare the effect of the intervention on cardiovascular, cerebrovascular	**BP based** a) 24 hr. average systolic blood pressure assessed by SPACELAB 90217 24hr ABPM b) Mean diurnal diastolic blood pressure assessed by SPACELAB 90217 ABPM	Week 6 and 6-9 months for the 24 hr ABPM data

	and vascular phenotypes	c) Mean diurnal systolic blood pressure assessed by SPACELAB 90217 ABPM d) Mean nocturnal diastolic blood pressure assessed by SPACELAB 90217 24hr ABPM e) Mean nocturnal systolic blood pressure assessed by SPACELAB 90217 24hr ABPM f) Mean clinic diastolic blood pressure measured during study visit (mean of 2+3) g) Mean clinic systolic blood pressure measured during study visit (mean of 2+3) **Cardiac MRI** h) Left ventricular (LV) mass indexed to end-diastolic volume and body surface area (BSA) i) LV EDV indexed to BSA j) LV wall thickness k) LA volume indexed to BSA l) Right ventricular (RV) mass indexed to end-diastolic volume and body surface area (MRI) m) RV EDV indexed to BSA n) RA volume indexed to BSA o) LV ejection fraction (EF) & RV EF p) LV and RV stroke volumes indexed to BSA q) Myocardial fibrosis r) ECV (extra-cellular volume) **Echo** s) LV Diastolic function: E/E' average, E/A ratio, E deceleration time t) Global longitudinal strain (GLS) u) LV systolic function (EF by Biplane Simpson's) v) LA volume by Biplanar assessment **Vascular**: w) Pulse wave velocity x) Augmentation index y) Aortic BP z) Aortic distensibility (MRI)	Baseline, week 1, week 6 and 6-9 months for the clinic blood pressures For Cardiac MRI at 6-12 months postpartum At baseline and at 6-12 months postpartum for Echo outcome measures PWV, Aortic BP & AI at baseline and at 6-12 months

			Aortic distensibility at 6-12 months (MRI)
		Cerebrovascular aa) Total white matter hyperintensity volume bb) Cerebral blood flow cc) Mean vessel thickness of the middle and posterior cerebral arteries and internal carotid artery	6 -12 months postpartum for all Brain MRI measures.
		Retinal dd) the corrected central retinal arteriolar equivalent ee) the corrected central retinal venular equivalent ff) corrected central retinal arteriolar equivalent/corrected central retinal venular equivalent ratio.	6-12 months postpartum for all retinal measures
Tertiary/Exploratory	To explore the impact of exercise of cardiovascular physiology	**Exercise Echo** Exercise ejection fraction (echo) at 50% of peak workload during a bicycle cardio-pulmonary exercise test (CPET) Exercise LA volume at 50% peak workload	6-12 months postpartum
		CPET VO2 at VT1	6-12 months postpartum
	To explore presence/absence of kidney injury and fibro-	T1 mapping of the kidneys	6-12 months postpartum

	inflammatory status		
	Quality of life assessment	EQ-5D-5L health questionnaire results	Baseline, week 1, week 6 and 6-12 months postpartum
	Number of readmissions in intervention vs control arm	Readmission number in each arm	0-12 months postpartum
	Side-effect impact	Number and frequency of side-effects reported (intervention via the app and control during follow up calls/SMS)	0-12 months postpartum

VI. Statistical analysis

As described earlier in Chapter 4, the participants in the trial were randomised by computer-generated and secure web-based randomisation software (built into CASTOR edc®) to ensure allocation concealment. In this study, the investigators were aware of allocation as part of the process of self-management, but were blinded to this allocation when performing data analysis i.e. this was a prospectively randomised, open blinded end-point study. Analyses were performed with IBM SPSS Statistics version 28.0.0 and STATA® SE version 16 was used by the study statistician to cross-check my findings.

Power calculations

Power calculations to determine adequate sample sizes for this trial are summarised below. There were used to determine the trial sample size for the primary, and key secondary outcomes.

Primary outcome measure sample size calculation:

The primary outcome was 24-hour average diastolic blood pressure in mmHg at 6–9 months postpartum as assessed by SPACELAB 90217 ABPM.

The calculation of the sample size for this primary outcome was based on the mean diastolic BP difference detected between the two arms of the trial in the pilot SNAP-HT study at 6 months. The mean BP difference detected between the intervention and control arm at the 6-month time point in SNAP-HT was -4.5mmHg [56] . I have used a more cautious SD of 10 mm Hg for the power calculations for POP-HT (in SNAP-HT the SD was 8.2 mm Hg in the intervention arm and 9.8 mm Hg in the standard care arm) despite using a 24hr ABPM rather than clinic readings where the SDs are larger. A 10 mm Hg SD was also in keeping with pooled SDs for ambulatory diastolic blood pressure readings from other studies [47].

To detect a treatment effect on diastolic blood pressure of −4.5 mmHg, powered to >80% at p=0.05 required a total sample size of 158 and with 1:1 randomisation this would require 79 in each arm (total sample size of 158). During COVID-19 a Royal College of Obstetricians and Gynaecology guideline [104] was issued that recommended a home BP monitor be given to all women who had had a hypertensive pregnancy for the first week following hospital discharge. As a result of the potential dilution that self-monitoring in the control group could have, I recalculated my sample size. One systematic review [50] concluded self-monitoring in the control arm could lead to a potential 0.42 mmHg dilution of the impact of self-management on diastolic BP, when measured using 24 hours ABPM. Therefore, assuming the same SDs of 10 mm Hg in each arm as in my original power calculation, I subtracted 0.42 mm Hg from the 4.5 mm Hg between group difference I had originally powered on. To remain powered at >80% and I would require 95 in each group (190 total) and hence I planned to over-recruit to 220 participants (rather than the original 200) to allow for this potential effect.

Key secondary outcome power calculations:

The imaging based secondary outcomes in the POP-HT trial were based on the hypothesis that improved blood pressure control in the postpartum period would result in improved cardiovascular and vascular phenotypes by 6–12 months postpartum

Cardiac remodelling

Studies using echocardiography have compared BP and LV mass in pre-eclampsia patients and control patients, at one year postpartum [36, 39]. They found that a difference in BP at one year of 10 mm Hg in diastolic BP corresponded to significant differences in LV mass. SNAP-HT appeared to achieve a 50% reduction of the anticipated BP difference seen between pre-eclamptic and normotensive women at one year by 6 months postpartum (i.e. approximately 5 mm Hg). Assuming that the structural/phenotypic benefit results from the BP benefit, as hypothesised, the study was powered to detect 50% of the phenotypic difference. In previous work significant differences in LV mass/EDV (g/mL) were demonstrated in a similar age and female population, who also had a similar mean diastolic BP differences between the two groups to that seen in SNAP-HT [60]. The LV mass/EDV (g/mL) in the group with high normal blood pressure was 1.54 g/ml vs 1.22 g/ml in those with optimal blood pressure with a standard deviation (SD) of 0.33 and 0.27, respectively, at $p<0.001$. Based on these assumptions, to observe a treatment effect of 0.16 (50% of the difference between 1.54 g/mL and 1.22 g/ml) on LV mass/EDV, required 67 in the intervention arm and 67 in the control arm (132 total). This was calculated using the larger of the SDs referenced above (0.33) at a power of >80% to detect a difference between the groups at $p=0.05$. This number also allowed for the greater anticipatory drop-out rate often seen in MRI based studies.

Aortic compliance

Several studies assessing the impact of blood pressure on aortic compliance have shown that even modest reductions in systolic/diastolic blood pressure increase aortic distensibility/compliance [124]. One such study had a mean difference in systolic blood pressure of 4.6 mm Hg between the two arms [124], akin to the same mean difference in SNAP-HT at 6 months [56], and other studies have suggested diastolic BP may be even more important in influencing aortic compliance [125]. In the

study with a mean 4.6 mm Hg difference in BP there was a treatment difference of 0.12 (95% CI −0.35 to 0.60, p=0.60) in aortic compliance between the two arms. Based on these assumptions, to observe a treatment effect from the POP-HT intervention, with 100 in the intervention and 100 in the control arm the study was powered at >90% to detect a difference at p=0.05 in POP-HT. In this thesis, data is presented on aortic compliance/stiffness (by Vicorder PWV and AI).

Statistical analysis plan

The statistical aspects of the study are summarised below with details fully described in the statistical analysis plan (SAP) (see appendix D).

Description of statistical methods

The analysis was carried out on the basis of intention-to-treat (ITT). This was, after randomisation, participants were analysed according to their allocated intervention group irrespective of what treatment they actually received. Patient demographic characteristics and other baseline information were summarised by treatment group. Numbers (with percentages) for binary and categorical variables and mean (SD), or median (IQR or full range) for continuous variables are presented in this thesis (see Chapter 5-6). A linear mixed model was applied to compare the groups with respect to the primary outcome described in the power calculations section above. The model included baseline clinic/clinical diastolic BP, taken as the mean of the second and third clinic diastolic BPs. As per the trial steering committee's advice, the baseline postnatal BP was felt to be sufficiently robust despite the natural variation there would be in this from D1-6 post-natally, given the trial was in a single centre, the fact the measures were done in a standardised manner, and given the well powered sample size in each arm of the trial. Further covariates were not added on advice on the trial statistician.

Randomised group, the studies minimisation factors (gestational age at the time of presentation with pre-eclampsia/gestational hypertension (continuous), and the prescription (or not) of an angiotensin converting enzyme (ACE) inhibitor at randomisation, were fixed effects in this model. Participant was included as a random effect. For all participants included in the primary outcome analysis, the mean

24 hours average diastolic BP was reported by randomised group. Adjusted mean differences between randomised groups with 95% CI and p value were estimated from the model for the following comparison: self-management (intervention) versus usual care (control) at a single time point (V4: the final study visit).

Sensitivity analysis

I performed sensitivity analysis on the primary outcome for the following factors:

(i) Antenatal booking blood pressure recorded from the participants' week 12 booking visit to their midwives was included as a covariate in the model. The reason I are performing a 2nd adjusted model was to assess the impact that antenatal values have on the intervention tested in this trial. Some groups argue that pre-eclampsia is merely a progression/acceleration of higher antenatal blood pressure values, BMI and adiposity levels, and I wished to explore this in the POP-HT RCT [95] with this 2nd model of adjustment. Data in the pilot SNAP-HT trial did not differ significantly when adjusted for antenatal booking blood pressure, notably.

(ii) Participants with missing primary outcome data at six-nine months would also have their six-nine-month data imputed using multiple imputation where needed (MI). If any baseline factors were associated with missingness then these variable(s) were to be included in the mixed effect model, since the assumptions of the mixed model are missing at random which means that variables related to missingness should be included as covariates in the model.

Secondary outcomes

Secondary BP based outcomes were analysed using the same method. Other secondary outcomes were analysed using analysis of covariance to establish a covariant model to examine the effect of BP control in the postpartum period on cardiac structure and function, vascular function and cerebrovascular structure and function. Where model assumptions were not met and evidence of departure from normality was observed, transformations of the data were employed and non-parametric tests carried out. Descriptive statistics (mean, SD, SE, range, etc) were calculated for each

outcome for each group. Differences in the secondary outcomes were compared between intervention and control groups.

Mean changes in BPs were compared across the population and correlated with cardiovascular endpoints including cardiac structure and function reported from cardiac MRI and echocardiogram. Demographic and physiological characteristics of the participants were added to regression models as covariates to explore the determinants of change in BP comparing intervention and control groups.

Analysis populations

The participants that were included in the analysis were all of those randomised. All data were included in the analysis as far as possible to allow full ITT analysis, though there was inevitably the problem of missing data due to withdrawal, lost to follow-up and non-completion of questionnaire data.

Decision points

There was no formal interim analysis. The results once analysed were reviewed by the research team, the TSC and Data and Safety Monitoring Committee (DMSC) and the PI/CI and other collaborators.

The level of statistical significance

Level of significance were tested as a 5% two-sided significant level.

Procedure for accounting for missing, unused and spurious data

Missing data were reported with reasons given where available and the missing data pattern was examined. I explored the mechanism of missing data, though the mixed effects model implicitly accounts for data missing at random. The need for a sensitivity analysis considering missing data using multiple imputation was considered and was outlined further in the SAP (see Appendix E). Spurious data were assessed using standard editing criteria and checked and corrected if needed prior to data lock and whilst investigators remained blinded.

Procedures for reporting any deviation(s) from the original SAP

The final statistical plan was agreed in September 2021 prior to the final data lock in March 2022 and prior to any analyses taking place. There were no deviations from the original SAP in the analysis presented in this thesis.

Tertiary analysis

These included:

- EQ-VAS scores and the measure of utility score from the EQ-5D-5L questionnaires at baseline, week 1 and week 6 and 6 months. These scores were presented as a mean and standard deviation in each group for each study visit.
- Readmission number in each arm (re-admissions included were those related to blood pressure/complications of the hypertensive pregnancy over the duration of the entire study participation; although note will also be made of non-blood pressure related readmissions for safety analysis). These were presented as an absolute number and percentage for each group of the study. No P value was reported.
- Side-effects reported. The side-effects were captured via the app for those in the intervention (self-management), and for the control arm, they were noted during follow up video calls/face-face visits/SMS (self-reported). For both arms, the medical notes (electronic patient records) were also consulted during the final follow up visit to document any further side-effects/adverse events. As the side effects were recorded in different ways in the two arms of the trial, there could be some bias with more reporting of side effects in the intervention arm expected. I therefore reported the two sources of data separately i.e. the app reported side effects were reported separately to those reported from the other sources. These were presented as an absolute number and percentage for each group of the study. No P value was reported.

CHAPTER 5 – POP-HT – BLOOD PRESSURE RESULTS AND DISCUSSION

I. Introduction

As previously described in Chapter 1 section one, HDP affect ~10% of pregnancies and have significant impacts on maternal and foetal health, in the immediate postpartum period, as well as longer-term. One third of women after hypertensive pregnancy represent with chronic (i.e. essential) hypertension within 10 years [8]. Consistent with these findings, HDP are associated with a two-fold increase in the risk of subsequent cardiovascular disease [9] [10] and, recent ESC [11] and AHA guidance [12] advise that women should be informed of this increased risk.

As mentioned in Chapter one section 5, trials of self-monitoring outside of pregnancy, repeatedly demonstrate it can improve BP control, and it is now an increasingly common part of hypertension management. Self-monitoring is well tolerated by patients and is a better predictor of end organ damage than clinic measurement [13, 46, 47] mainly in the context of co-interventions such as pharmacist/nurse led support i.e. self-management [47] . In 2018, the TASMIN-H4 randomised trial [49] showed that GPs using self-monitored BP to titrate anti-hypertensives, with or without tele-monitoring, achieved better BP control when using tele-monitoring. The SNAP-HT RCT compared self-management to usual GP and midwife led care in the UK, following hypertensive pregnancy, and as expected, in keeping with other self-management studies, BP control was better whilst on treatment. This difference was most marked at 6 weeks (with a mean systolic BP difference of 5.2mmHg and mean diastolic BP difference of 6mmHg) but, a striking finding was the fact the diastolic BP was a mean 4.5mmHg lower at six months postpartum; even after all but a few mothers had long-ceased medication [56]. The benefit of telemonitoring in pregnancy and its acceptability and 'preference' by women vs. standard levels of care is now well established in several other studies [90, 126]. The SNAP-HT Extension study went on to demonstrate that diastolic blood pressure was >seven mmHg lower in those originally randomised to self-management vs. those randomised to usual care by almost four years postpartum [88] . This difference remained significant after adjustment for blood pressure either at the time of delivery (-7.4mmHg; 95%CI -10.7 to -4.2, $p<0.001$), or for antenatal booking blood pressure (-6.9mmHg; 95% CI -10.3 to -3.6; $p < 0.001$). This exciting work suggested there was a window to optimise long-term

cardiovascular risk in the puerperium, because if a ~5mmHg diastolic BP difference was maintained long-term it would correlate to an approximately 40% life-time reduction in stroke and 20% life-time reduction in coronary heart disease risk [40]. Having described the methods used in POP-HT in Chapter 4, in this chapter, I consider the results of the POP-HT trial, first considering the impact on BP control at six-nine months postpartum, followed by a discussion on the implications of these results. This is followed by Chapter 6, which then summarises the results of the cardiovascular imaging work done as part of the trial, and discusses the impact that any BP difference achieved via the intervention had on cardiovascular and vascular remodelling.

II. Results

220 patients enrolled into POP-HT trial between February 2020 and March 2021, 202 completed all four follow up visits to complete the study (92%). Recruitment was halted for a period of two months due to cessation of all research across the UK during the COVID-19 global pandemic, but the trial's recruitment was achieved in the target time period as illustrated below in figure 16:

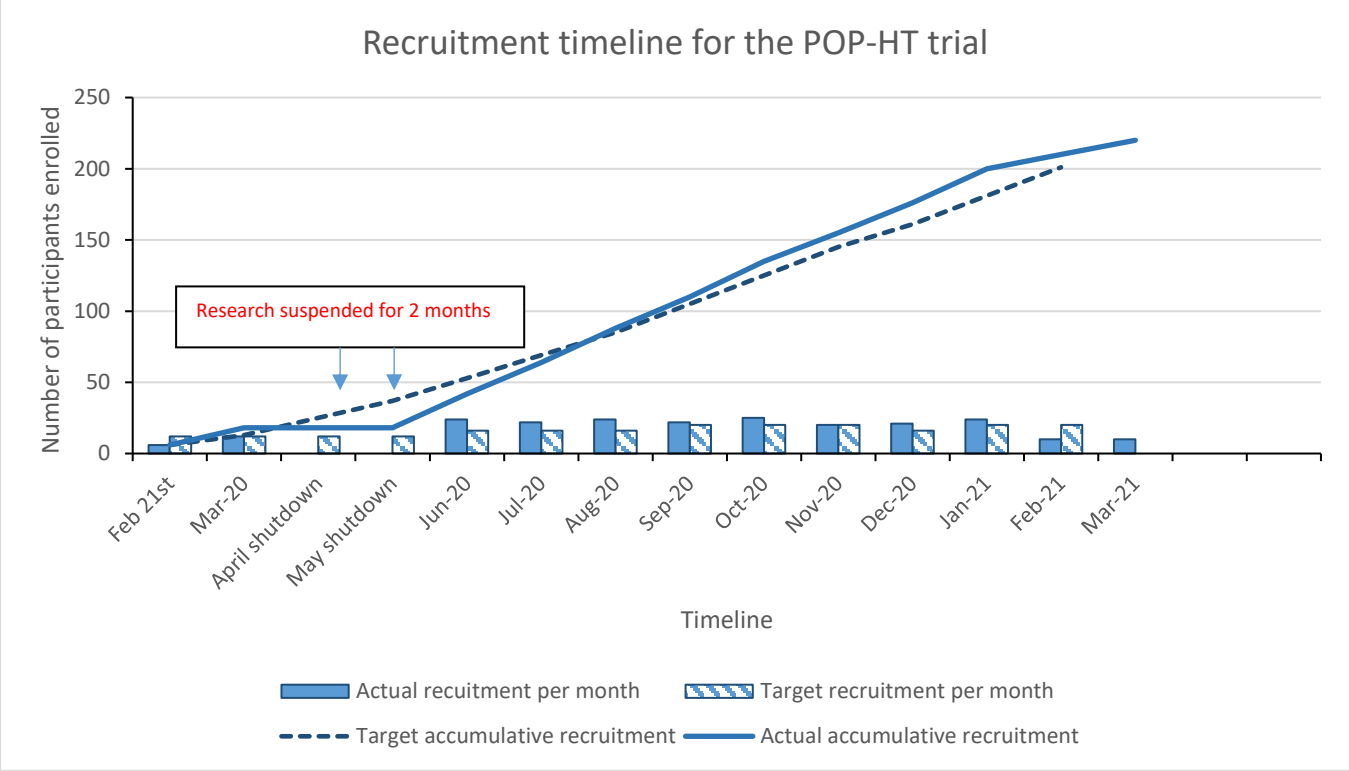
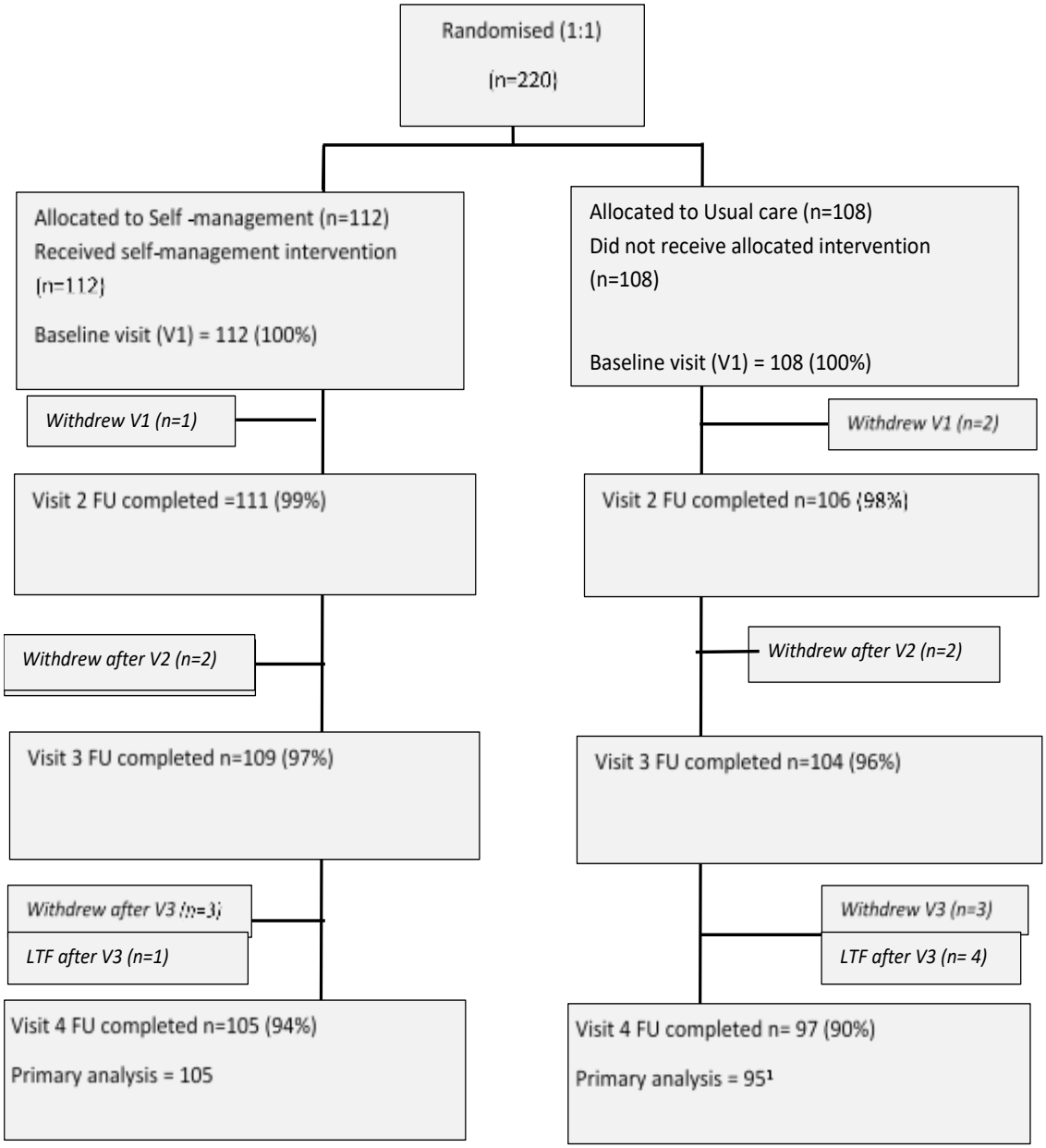


Figure 16: Recruitment timeline for the POP-HT trial

As the CONSORT flow chart on the page below shows there were six withdrawals from the intervention arm and seven from the control arm. There was one loss to follow up from the intervention arm and four from the control arm. Of the 112 allocated to the self-management arm, and the 108 randomised to the usual care arm there was one withdrawal from the intervention, and two from the usual care arm, after the baseline visit (V1) due to a change of mind. After the week one visit (V2), there were a further two withdrawals from each arm, and after the week 6 visit (V3) there were a further three withdrawals from each arm, with the majority of women reporting that the demands of the trial on their time was the reason. There was one loss to follow up before the final study visit (V4) from the self-management group, and four losses from the usual care group. For all cases of loss to follow up

at this final stage, the reason was either emigration as a result of COVID-19, the decision to relocate elsewhere in the UK, or the inability to travel back to the UK due to international travel restrictions. In both arms 90%, or more, of women enrolled completed all study visits.

CONSORT FLOW CHART FOR POP-HT



Key of abbreviations:

LTF = Lost to follow up (defined as being unable to contact and/or arrange the V4 visit in the 9 month time window from enrolment)

FU = follow up

Date completeness in the trial

As the figure below shows, data completion rates for the entire trial were excellent with even the questionnaire data achieving >80% completion rates. The data pertaining to the primary outcome were completed in 200/202 participants who completed the trial. In six participants the 24hr ABPM data did not fulfil the NICE NG133 criteria for a valid 24hr BP dataset and the monitoring periods were repeated at the earliest available opportunity within the nine-month window. Unfortunately, two of these six repeated 24hr ABPMs still failed to satisfy the criteria for a valid number of day and night-time consecutive readings and so were excluded. This provided a >90% valid data set for the analysis (92% of those due for V4 and 99% of those still enrolled at the time of the V4), of the primary outcome of the trial. 24hr BP data were obtained in a lower proportion of those undergoing 24hr ABPM assessment at the week 6 visit (86%), because most of the 24h ABPMs were fitted remotely, as described in Chapter 4, resulting in a larger number of invalid 24hr BP data-sets (13 participants) due to the cuff moving/slipping after fitting and failing to recording valid consecutive BP readings. A number of women also declined the test at the week 6 timepoint due to the fact there were many competing interests at this point early in their post-natal life (14 participants). The remaining three sent back the ABPM with no readings, which may have represented an equipment failure after the initial successful fitting of the device.

For Clinical blood pressure readings there were complete data for all study visits from baseline to V4. Vicorder® measures of aortic BP, aortic stiffness (augmentation index (AI%) and pulse wave velocity (PWV m/s) were obtained in all but one participant at baseline, and paired Vicorder® data were obtained in 6-12 months postpartum in 96% of those still enrolled at V4. Valid resting echo data were obtained in 98% (216/220) at the baseline visit with three participants declining the test and one data set being corrupt and unable to be analysed. Paired V4 resting echo data were obtained in 92% (187/202) of participants at V4. The 15 resting echocardiograms not done at V4 were due to the following reasons:

- 13 were home visits
- 2 were remote home visits done via ZOOM®

Quality of life data (EQ-5D-5L) were obtained for >80% of the participants randomised at each visit the questionnaire was sampled (baseline, V2, V3 and V4), with the exception being a slight drop off at the week 6 follow up (V3) for which there was only 77% completion rate.

Postnatal diet and lifestyle questionnaire data were obtained in 193/220 (88%) of those participants who were randomised into the trial, and this data is presented in table 5 of this Chapter. The objective measure of activity (a wrist worn accelerometers), were obtained in 91% of participants who underwent the final study visit. The 9% that didn't was either because the visit was done remotely or they declined to wear the 7-day wrist watch.

The anthropometric and demographic data presented in this chapter were obtained for all participants at all study visits, with the exception of five left arm circumferences measurements, which weren't obtained during their remote V3 follow up visits. Bloods including cholesterol, lipids and pancreatic function (as well as bone marrow, renal and liver function) were obtained in 186/202 participants partaking in the final study visit. The remaining sixteen blood tests were not taken due to needlophobia (five), remote home visits (two), and nine declined the blood test.

The number of participants undergoing cardiac and brain MRI, CPET, retinal imaging and exercise echo were >85% of those that remained enrolled at the time of V4 despite the tests being lengthy, demanding and claustrophobic, in the case of MRI. Cardiac MRI data were obtained in 175/202, but one scan was non-diagnostic due to artefact from breast implants so only 174 (84% of those enrolled at time of V4) were included in the CMR analysis. Further explanation of the CPET, retinal, exercise echo, and MRI Brain and aorta are not discussed further as the data is not included in this thesis due to ongoing analysis. Figure 17 details the data completeness rates for each study measure however:

Data completeness	**Number of participants partaking**	**% of total randomised (n=220)**
Baseline/V1		
Anthropometry	220	**100%**
Clinic BP	220	**100%**
Bloods	220	**100%**
Vicorder	219	**99%**
Echo	216	**98%**
EQ-5D-5L	177	**80%**

Week 1/V2	***217 remain enrolled***	
Anthropometry	217	**99%**
Clinic BP	217	**99%**
EQ-5D-5L	180	**82%**
Week 6/V3	***213 remain enrolled***	
Clinic BP	*213*	**97%**
Left arm circumference	208	**95%**
E5-5D-5L	170	**77%**
24HR BP	183	**83%**
6-12 month/V4	***202 remain enrolled***	
Anthropometry	202	**92%**
Demographics	202	**92%**
Clinic BP (6-9 months)	202	**92%**
24HR BP (6-9months)	200	**91%**
VICORDER	194	**88%**
POP-HT DIET & LIFESTLE SURVEY	193	**88%**
ACTIVITY monitor	191	**87%**
RESTING ECHO	187	**85%**
BLOOD TEST	186	**85%**
RETINAL IMAGING	180	**82%**
EXERCISE ECHO	173	**79%**
CARDIAC MRI	174	**79%**
CPET	171	**78%**
BRAIN MRI	170	**77%**
EQ-5D-5L SURVEY	156	**71%**

Figure 17: Data completeness results for each visit of the POP-HT trial

a) Study population characteristics

Baseline characteristics

Table 1 (of this Chapter) demonstrates that the two groups were well matched in almost all baseline features. In terms of obstetric characteristics, mean age was 33.4 vs 32.6 yrs., BMI 28.1 vs 28.6, and approximately 62% were nulliparous vs 69% in the intervention vs. usual care arms respectively. Ethnicity in both arms was predominantly White-Caucasian (82.1% vs 81.5%), but the remaining 20% comprised a similar number of Black (5.4% vs 3.7%), Asian (8.9% vs 7.4%) and Hispanic (3.6% vs 4.6%)

ethnicities in the intervention vs. usual care arms respectively. There was a similar socio-economic composition between the two arms of the trial, with approximately 80% from each arm in the first or second index of multiple deprivation (IMD) quintiles (70.6% in the intervention arm vs. 79.8% in the usual care arm). If anything, the intervention arm had more participants in the lower (3^{rd}-5^{th}) IMD quintiles (29.4% vs 20.2%).

The pregnancy characteristics were also well matched between the two groups. Just over 60% of women in each arm had the more severe disease phenotype (pre-eclampsia vs. gestational hypertension) with similar numbers of IVF (6.3% vs 10.1%) and multip pregnancies also (5.4 vs 7.4%) in the intervention vs usual care arms respectively. Disease onset and urine PCR, two other marker of disease severity, were also similar between the groups. 21.4% had early onset disease in the intervention arm vs 21.3% in the usual care arm, and the median urine PCR for the entire cohort was 30.9 mg/mmol in the intervention arm vs. 30.5mg/mmol in the usual care arm. Both arms had similar a duration, and total dose of anti-hypertensive treatment antenatally (median 4 antenatal days in intervention group vs. 5 days in the usual care group with mean WHO defined daily dose being similar in both groups also). By chance, the intervention arm had a higher proportion of women affected by a previous hypertensive pregnancy (approximately 27% vs 9% in the usual care arm). Delivery characteristics were also similar between both arms of the trial with just over 30% in each arm having a spontaneous vaginal delivery, and close to 40% having an emergency caesarean section (EMCS);42% in the self-management arm vs 37% in the usual care arm. Fetal outcomes, another marker of disease severity/complication were also well matched with 22.3% of babies in the s intervention arm fulfilling the NICE NG133 criteria for growth restriction (IUGR) vs. 25.9% in the usual care arm and overall mean birthweight was very similar between groups (3.07kg vs 3.12kg respectively). Both the antenatal booking BP from the 12-week antenatal midwife visit, and the postnatal baseline BP (mean of the 2^{nd} and 3^{rd} clinic readings) recorded during the baseline visit on the postnatal ward (day 0-5 postpartum) were similar, albeit there were marginally higher readings in the intervention arm (118.7/73.5mmHg vs 116.5/72.4mmhg in the control arm for antenatal BP; and 128.5/83mmHg vs 127.6/81.5mmHg respectively for the mean baseline postnatal BP).

Table 1 (Chapter 5). Baseline characteristics of the POP-HT trial participants			
Parameter, *Unit*	**Overall (n= 220)**	**Intervention (n =112)**	**Control (n =108)**
Mean age, y (SD)	33.1 (5.0)	33.4 (5.1)	32.6 (5.0)
Mean BMI, kg/m^2 (SD)	28.4 (6.4)	28.1 (5.1)	28.6 (7.6)
Mean left mid-arm circumference[*1], cm (SD)	30.0 (3.7)	30.1 (3.4)	29.8 (4.0)
Parity at enrollment, n (%)			
0	144 (65.5)	69 (61.6)	75 (69.4)
>1	76 (34.5)	43 (38.4)	33 (30.6)
Ethnicity, n (%)			
White-Caucasian	180 (81.8)	92 (82.1)	88 (81.5)
Black	10 (4.5)	6 (5.4)	4 (3.7)
Asian	18 (8.2)	10 (8.9)	8 (7.4)
Hispanic	9 (4.1)	4 (3.6)	5 (4.6)
Other[&]	3 (1.7)	0 (0.0)	3 (2.8)
IMD quintile, n (%)			
First	105 (49.3)	47 (43.1)	58 (55.8)
Second	55 (25.8)	30 (27.5)	25 (24.0)
Third	28 (13.1)	17 (15.6)	11 (10.6)
Fourth	17 (8.0)	10 (9.2)	7 (6.7)
Fifth	8 (3.8)	5 (4.6)	3 (2.9)
Diagnosis, n (%)			
Pre-eclampsia	133 (60.5)	68 (60.7)	65 (60.2)

Gestational hypertension	87 (39.5)	44 (39.3)	43 (39.8)
HELLP	6 (2.7)	5 (4.5)	1 (0.9)
IVF pregnancy, n (%)	18 (8.2)	7 (6.3)	11 (10.1)
Multiple pregnancy, n (%)	14 (6.4)	6 (5.4)	8 (7.4)
Previous hypertensive pregnancy, n (%)	40 (18.2)	30 (26.8)	10 (9.3)
Median gestational age at diagnosis			
≤33+6 wks	47 (21.4)	24 (21.4)	23 (21.3)
≥34 wks	173 (78.6)	88 (78.6)	85 (78.7)
Median gestation at delivery, wks (IQR)	39.1 (37.0, 40.4)	39.2 (37.0, 40.3)	39.1 (37.0, 40.7)
Median PCR[*2], mg/mmol (IQR)	30.6 (15.5, 72.7)	30.9 (16.5, 74.7)	30.5 (14.9, 70.5)
Median duration of antenatal treatment, d (IQR)	4.0 (1.0, 17.0)	4.0 (2, 15.3)	5.0 (1.0, 18.5)
Mean dose AHT at baseline visit (SD; WHO DDD)	1.3 (1.1)	1.2 (0.97)	1.4 (1.3)
Mode of Delivery, n (%)			
Spontaneous vaginal delivery	76 (34.5)	43 (38.4)	33 (30.6)
Instrumental	45 (20.5)	17 (15.2)	28 (25.9)
Emergency C/S	87 (39.5)	47 (42.0)	40 (37.0)
Elective C/S	12 (5.5)	5 (4.4)	7 (6.5)
IUGR[*3], n (%)	53 (24.1)	25 (22.3)	28 (25.9)

Special care baby unit admission, n (%)	62 (28.2)	29 (25.9)	33 (30.6)
Mean birthweight, kg (SD)	3.09 (0.82)	3.07 (0.80)	3.12 (0.85)
Mean antenatal SBP/DBP from booking visit, mmHg (SD)	118.0 (12.6)/74.0 (9.1)	118.7 (10.0)/73.5 (9.4)	116.5 (14.7)/72.4 (8.7)
Mean SBP/DBP (readings 2+3) at baseline*[4] (SD)	128.1 (13.4)/82.3 (10.8)	128.5 (13.6)/83.0 (11.2)	127.6 (13.2)/81.5 (10.4)
Positive COVID PCR[*5], n (%)	1 (0.5%)	0 (0%)	1 (0.5%)

[1]n=213 (intervention n=109, control n=104)[2] PCR reported for those with HELLP and pre-eclampsia was the peak value obtained from time of diagnosis to time of delivery; *[3]IUGR defined as a drop in abdominal circumference (AC) of more than 40 centiles from the 20 week scan; *[4]Baseline visit was performed in the first 6 days after birth prior to discharge from the postnatal ward; *[5] included if COVID-19 PCR result was positive in the 3rd trimester or reported in the 48hrs following delivery and/or if placental histology correlated to COVID placenta. [&]3 patients in the intervention arm were pacific islanders

Abbreviations: AHT indicates antihypertensive; BMI, body mass index; DBP, diastolic blood pressure; IQR, interquartile range; PCR, protein: creatinine ratio; SVD, spontaneous vaginal delivery; EMCS, emergency caesarean-section; ELCS, elective caesarean-section; SBP, systolic blood pressure; IUGR, Intrauterine growth restriction; WHO DDD, World Health Organisation defined daily dose; and IMD, index of multiple deprivation.

Postnatal characteristics

Table 2 of Chapter 5 summarises the key postnatal characteristics of the 202 study participants who completed the trial. As this table illustrates, the final visit (V4), during which the primary and secondary outcomes were assessed, were performed at approximately the same time-point in both arms (249.8 days postpartum for the self-management arm vs 247.9 days in the usual care arm).

Postpartum characteristics were similar between groups with around 50% from each still breast-feeding (54.8% in the intervention arm vs 44% in the usual care arm), similar levels of hormonal contraception (23.1% taking progesterone only pill (POP) vs 20.4% in self-management vs usual care respectively) and with a small number taking the combined pill (COCP) despite its known link to hypertension in young females [127] (approximately 4% in each arm). The levels of adiposity remained similar between the groups too with mean BMI 29.1 vs 30.4 and mean left-arm circumference 31.4cm

vs 32.1 cm in the self-management vs usual care arms, and the mean waist: hip was the same (0.89) in both. The table below also demonstrated that the lipid and metabolic profiles of the patients were very similar. In both arms, total cholesterol was close to 5mmol/l and the LDL close to 3mmol/l.

Table 2 (Chapter 5) Postnatal characteristics of study participants at time of the final study visit[*1]			
Parameter, unit	**Overall (n=202)**	**Intervention (n =105)**	**Usual care (n=97)**
Mean time at which V4 performed, days postpartum, number of days (SD)	248.8 (16.0)	249.8 (14.6)	247.9 (17.1)
Last-menstrual period in relation to timing of MRI scan, d (SD)	8.8 (8.2)	8.6 (8.2)	9.1 (8.3)
Breast feeding at time of V4, n (%)	100 (49.5)	57 (54.8)	43 (43.9)
Contraception at re-recruitment, n (%)			
Combined oral contraceptive pill	8 (4.0)	4 (3.8)	4 (4.1)
Progesterone only contraceptive pill	44 (21.8)	24 (23.1)	20 (20.4)
Implanon® implant	7 (3.5)	2 (1.9)	5 (5.1)
Copper coil	14 (6.9)	7 (6.7)	7 (7.4)
Mean BMI, kg/m2 (SD)	29.7 (7.1)	29.1 (5.8)	30.4 (8.3)
Mean left mid-arm circumference, cm (SD)	31.8 (4.4)	31.4 (3.9)	32.1 (4.9)
Mean waist to hip ratio ± SD	0.89 (0.06)	0.89 (0.06)	0.89 (0.06)
Triglycerides (mmol/l), mean (SD)*[2]	1.43 (1.1)	1.41 (0.78)	1.45 (1.3)
Total Cholesterol (mmol/l), mean (SD) *[2]	4.85 (0.9)	4.92 (0.9)	4.77 (0.9)
HDL Cholesterol (mmol/l), mean (SD) *[2]	1.43 (0.4)	1.41 (0.4)	1.46 (0.4)
LDL Cholesterol(mmol/l), mean (SD) *[2]	2.86 (0.8)	2.91 (0.8)	2.80 (0.7)
Total/HDL ratio, mean*[2]	3.62 (1.1)	3.71 (1.0)	3.53 (1.1)
Random (semi-fasting) glucose (mmol/l), mean (SD) *[3]	4.80 (1.3)	4.83 (1.4)	4.76 (1.2)

[*1]Final study visit took place at 6-9 months for the primary outcome and BP based secondary outcome measures. Other outcomes were obtained 6-12 months postpartum as agreed by the TSC to mitigate against the impact of COVID-19 on trial follow up rates; [*2]n=186 (intervention n=100, control n=86); [*3] n=185 (intervention n=100, control n=85); [*4] n=176 (intervention n=95, control n=81). BMI indicates body mass index; EQ-VAS, EuroQol-visual analogue scale from the E5-5D-5L questionnaire; IQR, interquartile range and SD, standard deviation. Bloods were taken at a standardised 3-4 hours into the study visit so were 'semi-fasting' as per current BHF guidance

b) Primary outcome results

Table 3 (of Chapter 5), which can be found on the following page, summarises the 24hr blood pressure data, from the 24hr ABPM data obtained from the V4 visit. This final study visit took place at mean of 248.8 days postpartum with no significant time-difference between the two trial arms. 2/200 of these 24hr BP monitors included in the analysis were fitted remotely but the remaining 198 included in the analysis were fitted in person as discussed in Chapter 4 section. The table below has been split to highlight the results for the primary outcome first, followed by the 24hr-ABPM based secondary outcome measures thereafter.

The table illustrates that of the 202 women who completed the final study visit, 200/202 (99%) had valid 24hr BP data sets, which contributed to the primary and 24hr-ABPM based secondary outcomes (105 in the self-management arm vs 95 in the control arm).

These results demonstrated that postpartum, physician optimised, BP self-management led to a significant improvement in both 24hour overall average systolic and diastolic blood pressure at approximately 9 months (mean 248.8 days) postpartum. This was true when adjusting for differences in baseline (mean of 2nd and 3rd readings) systolic and diastolic readings or, for the differences in antenatal booking BP readings.

When adjusting for the differences in baseline BP (mean of 2nd and 3rd clinic BP) taken at days 1-6 postpartum on the postnatal ward, the adjusted mean DBP improvement in the intervention arm was -5.80mmHg (95% CI 07.40 to -4.20; P<0.001), and the adjusted mean SBP improvement was more than -6.5mmHg (-6.51mmHg; 95% CI -8.80 to -4.22; P<0.001). When adjusting for antenatal BP, as per the second model described in the SAP and the statistical analysis section of Chapter 4, the adjusted mean differences were even greater. The 24hr overall diastolic BP difference (DBP) was -5.87 mmHg (95% CI -7.45 to -4.29; P<0.001) and, the 24hr overall systolic BP difference (SBP) was -6.86 mmHg (95% CI -9.11 to -4.61; P<0.001). The results shown in the table below are also depicted in figures 18 and 19.

Table 3 (Chapter 5). Primary outcome and 24-hr ABPM based secondary outcome results for POP-HT

Parameter, unit	**Intervention n =112**	**Usual care n =108**	**ΔI-C, mmHg (95% CI)[*] at 6 months postpartum adjusted for baseline BP[†]**	**ΔI-C, mmHg (95% CI)[*]** at 6 months postpartum **adjusted for antenatal BP[§]**
PRIMARY OUTCOME				
No. of observations, n (%)	105 (94%)	95[*1] (88%)	-	-
AHT treatment, n (%)	16	8	-	-
Mean WHO DDD AHT treatment (SD at V4)	0.16 (0.50)	0.06 (0.26)	-	-
Number of BP related readmissions, n (%)	8 (7%)	29 (27%)		
Mean 24 hr average DBP[‡], mmHg ± SD	71.2 (5.6)	76.6 (5.7)	-5.80 (-7.40 to -4.20) P<0.0001	-5.87 (-7.45 to -4.29) P<0.0001
24 HOUR BP BASED SECONDARY OUTCOMES				
Mean 24 hr average SBP[‡], mmHg ± SD,	114.0 (7.7)	120.3 (9.1)	-6.51 (-8.80 to -4.22) P<0.0001	-6.86 (-9.11 to -4.61) P<0.0001
Mean diurnal DBP[‡], mmHg ± SD,	75.4 (5.7)	80.5 (6.1)	-5.40 (-7.15 to -3.65) P<0.0001	-5.49 (-7.21 to - 3.76) P<0.0001
Mean diurnal SBP[‡], mmHg ± SD,	118.2 (7.6)	124.8 (9.4)	-6.94 (-9.25 to -4.63) P<0.0001	-7.30 (-9.57 to -5.03) P<0.0001
Mean nocturnal DBP[‡], mmHg ± SD,	64.0 (6.7)	68.7 (7.0)	-5.16 (-7.03 to -3.28) P<0.0001	-5.26 (-7.10 to - 3.41) P<0.0001
Mean nocturnal SBP[‡], mmHg ± SD,	106.7 (9.6)	112.0 (10.3)	-5.54 (-8.23 to -2.84) P<0.0001	-5.94 (-8.56 to -3.31) P<0.0001

[*1] Two of the 24hr ABPMS had to be excluded despite being repeated in the time-window due to an inadequate number of consecutive day and night readings as per NICE NG136[128]

ΔI-C indicates difference between intervention and control groups; DBP, diastolic blood pressure; SBP, systolic blood pressure and SD, standard deviation.

[†]mean difference adjusted for baseline blood pressure values in POP-HT, day 1-6 after birth.

[‡]measured by SPACELAB® 90217 ambulatory blood pressure monitor.

[§]mean difference adjusted for antenatal booking BP recorded in clinical notes

[*]95% CI around adjusted difference does not cross zero

Figure 18: Illustration of the BP difference for 24hr overall average diastolic BP (DBP) between the intervention and control arm of the POP-HT trial adjusted for baseline postnatal DBP (mean of 2nd and 3rd postnatal DBP recorded at the baseline visit)

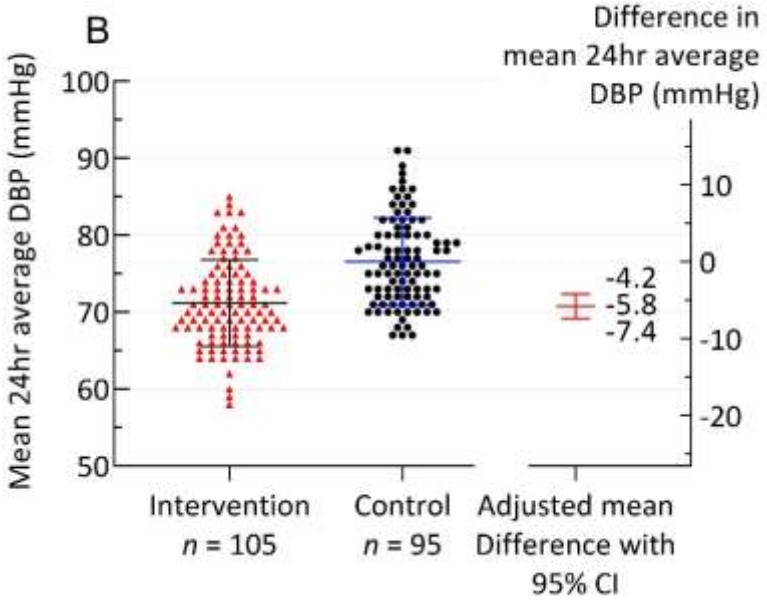
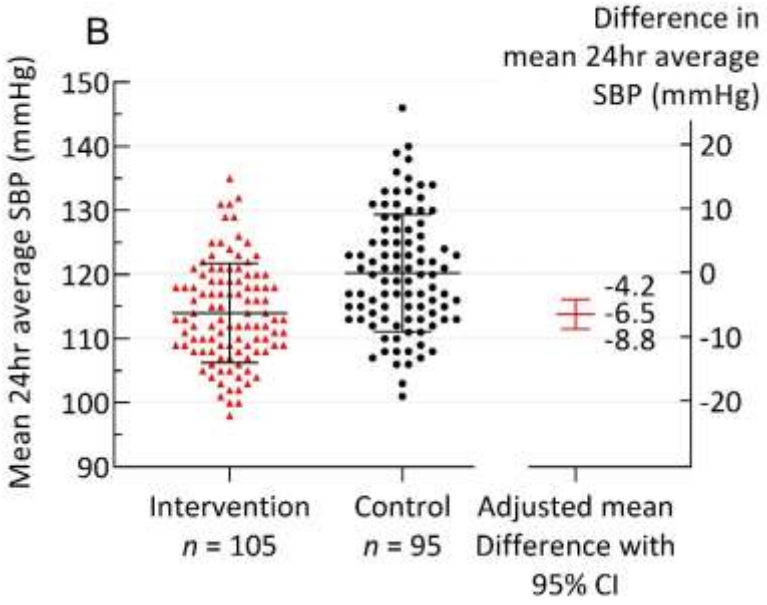


Figure 19: Illustration of the BP difference for 24hr overall average systolic BP (SBP) between the intervention and usual care control arms of the POP-HT trial adjusted for baseline postnatal systolic BP (mean of 2nd and 3rd SBP recorded at the baseline visit)



When the diurnal and nocturnal element of the 24-hr BP measurements are considered, both the daytime and night readings exhibited statistically significant lower BP values in the intervention arm vs. the usual care arm. For the systolic readings, the difference was greatest in the daytime (adjusted

mean difference -7.3 mmHg; 95% CI -9.57 to -5.03; P<0.001 vs. -5.94mmHg; 95% CI -8.56 to -3.3; P<0.001 for the night-time systolic readings.

For the diastolic readings, the situation was mirrored but the readings were more similar. The aadjusted mean difference was -5.49 mmHg; 95% CI -7.21 to -3.76; P<0.001 for the diastolic daytime readings vs. -5.26., 95% CI -7.10 to -3.41; P<0.001 for the night-time diastolic readings.

Table 3 also demonstrated that the intervention led to a significant reduction in the number of postnatal readmissions, which were attributed to blood pressure issues. Out of the 220 enrolled into the trial there were 37 (15.9%) BP related readmissions overall; eight in the intervention driven by the trial (7%) vs. twenty-nine (27%) in usual care arm brought about by community mid-wives and/or their own GP (i.e. the usual care arms participants were not readmitted by the trial team). Twenty-two patients in the intervention arm were rapidly up-titrated in the first ten days postpartum avoiding the need for readmission and without this the readmissions numbers would have been similar (8 actual + 22 avoided through medication up-titration by the trial doctors vs. 29 readmitted by the NHS care team in the usual care arm). There were also a small number of readmissions in the whole trial cohort unrelated to BP, due to wound infections, baby jaundice and similar episodes. This is detailed further in Appendix E, which is a sample of the data taken from a safety analysis done as part of the trial, on potential adverse events. The four non-blood pressure related admissions were split equally across both groups (two in each arm) and were all expected events (jaundice, sepsis, wound infection, mastitis). There were no SAES/adverse events in the trial, based on the list stipulated in the full study protocol [95].

c) Secondary BP based outcomes: Were the results for clinic readings (as was used in the original SNAP-HT trial) the same as the 24hr ABPM results presented above?

Table 4a of Chapter 5, which is shown below, details the clinic diastolic and systolic BP readings from the different time-points after study enrolment. This ran from baseline (days 1-6 postpartum), to weeks one, six and then out to the final study visit (at 6-9 months postpartum). As described in the SAP, and at the end of chapter 4, this was done using a linear mixed effects model as for the primary

outcome, which enabled a direct comparison of the BP values obtained. Incidentally, this same model was used in the original SNAP-HT trial [56], and so this also allowed a valid comparison of these readings to those obtained in SNAP-HT, albeit the intervention differed slightly between the two trials as considered in Chapter 4 and Chapters 7.

Table 4a. Unadjusted and Adjusted Linear Mixed Effects models for clinic DBP and SBP

Parameter, unit	Intervention	Control	ΔI-C, mmHg (95% CI)* at 6 months postpartum unadjusted	ΔI-C, mmHg (95% CI)* at 6 months postpartum adjusted for baseline BP†
Clinic DBP mmHg, mean (SD), [n]				
Baseline (1 - 6 days postpartum)	83 (11.2), [112]	81.5 (10.4), [108]	-	-
Week 1 (+ 5 days)	81.8 (8.0), [111]	82.2 (7.8), [106]	-0.42 (-2.56 to 1.73) P=0.7040	-0.75 (-2.81 to 1.31) P=0.4750
Week 6 (± 5 days)	80.0 (7.9), [109]	82.1 (8.0), [104]	-2.13 (-4.29 to 0.04) P=0.0540	-2.48 (-4.56 to -0.40)* P=0.0190
6 months (+ 3 months)	81.9 (8.3), [107]	85.6 (8.6), [98]	**-3.79(-5.99 to -1.59)* P=0.001**	**-4.17 (-6.28 to -2.06)* P<0.0001**
Clinic SBP mmHg, mean (SD), [n]				
Baseline (1 - 6 days postnatal)	128.5 (13.7), [112]	127.6 (13.2), [108]	-	-
Week 1 (+ 5 days)	122.4 (9.7), [111]	125.1 (9.2), [106]	-2.68 (-5.44 to 0.08) P=0.0570	-2.87 (-5.69 to -0.13) P=0.0400*
Week 6 (± 5 days)	122.1 (10.6), [109]	125.1 (10.3), [104]	-3.15 (-5.93 to -0.37) P=0.0260*	-3.34 (-6.10 to -0.59)* P=0.0170
6 months (+ 3 months)	125.6 (10.7) [107]	130.7 (11.9) [98]	**-5.44(-8.26 to -2.62) *P<0.0001**	**-5.64 (-8.43 to -2.84)* P<0.0001**

ΔI-C indicates difference between intervention and control groups; DBP, diastolic blood pressure; SBP, systolic blood pressure and SD, standard deviation. †mean difference adjusted for baseline blood pressure values (mean of 2nd and 3rd) taken day 1-6 postpartum on the postnatal ward
*95% CI around adjusted difference does not cross zero

Table 4a above highlights that there was an early separation of both systolic and diastolic BP control between the intervention and control arms from week 1, albeit non-significantly for DBP at week one. For SBP it was already marginally significant (-2.87mmHg; 95% CI -5.69 to -0.13mmhg; P=0.04) by week 1, and by week 6 there was a further separation of both DBP and SBP values between the two trial arms (-2.48mmHg adjusted diastolic BP difference; 95% CI -4.56 to -0.40, P=0.0190, and -3.34mmHg adjusted systolic BP difference; 95% CI -6.10 to -0.59, P=0.0170) with these statistically significant for DBP and SBP by this timepoint postpartum. By the final study visit at mean 248.8 days postpartum the BP differences between the intervention and control arms had widened further, and become even more significant statistically, with a mean -4.17mmHg DBP improvement (95% CI -6.28 to -2.06, P<0.0001), and a mean - 5.64mmHg SBP improvement (95% CI -8.43 to -2.84, P<0.0001) by 6-9 months postpartum, when adjusted for differences in the baseline BP.

The impact of anti-hypertensive treatment on the BP differences described between the intervention and control arms

Table 4b of Chapter 5, seen below, considers the anti-hypertensive treatment and doses recorded during each study visit in the trial from baseline (V1) to the 6-9 month final visit (V4), with the attrition rate in the number of participants, and the numbers remaining on anti-hypertensive treatment tracked over time from baseline to 6-9 months postpartum. This data showed that similar numbers remained on treatment at week 1 (100 in each arm), but that by week 6 more people had come off treatment through down-titration in the intervention arm (32) vs. 39 in the usual care arm. By 6-9 months twice as many women remained on treatment in the intervention arm vs. the usual care arm (16 vs 8 respectively). Furthermore, the amount of anti-hypertensive medication prescribed (defined by the mean WHO DDD), whilst being similar at baseline, had increased in the intervention arm by week 1 postpartum, whereby it had decreased in the usual care arm in the same period (1.86 vs 1.26 respectively). The overall value was then similar by week six (0.22 in the intervention vs 0.24 in the usual care arm), despite seven fewer women being on treatment at week six in the intervention arm. By the final study visit at 6-9 months, the mean WHO DDD was more than double (0.16 vs 0.06) in the

intervention arm for those who remained on treatment. Although the groups were randomised with the prescription of ACEi as a minimisation factor, with 27 in each arm prescribed Enalapril at the time of the baseline visit, a greater proportion of participants received enalapril over the total study duration following hospital discharge (57% in the intervention arm vs 43% in the usual care arm).

Table 4b: Number on antihypertensive treatment and mean WHO DDD at the different time-points of the POP-HT trial follow up

Variable	Baseline (1–6 d PN)	Week 1 (+ 5 days)	Week 6 (+-/ 5 days)	6 months (+ 3m)
No. of observations (I/C)	220 (112/108)	217 (111/106)	213 (109/104)	202 (105/97)
AHT treatment, n (%) (I/C)	220 (100) (112/108)	200 (92.1) (100/100)	71(33.3) (32/39)	24 (11.7) (16/8)
Mean WHO DDD AHT treatment (SD) (I/C)	1.28 (1.13) (1.21/1.35)	1.56 (1.54) (1.86/1.26)	0.23 (0.57) (0.22/0.24)	0.11 (0.41) (0.16/ 0.06)
Prescription of Enalapril in the postnatal period, n (%)				102 (49.5)
Intervention (I), n (%)				60 (57)
Control (C), n (%)				42 (43)

What was the longitudinal pattern of BP control through the trial?

The figures below illustrate an early separation of BP trajectory between the two arms of the trial as described above, and as shown in table 4a. The figures also demonstrate that the antenatal and baseline values were actually marginally higher in the intervention arm (118/73.5 mmHg antenatal and 128.5/83mmHg baseline; vs the control arm's readings of 116.5/72.4 mmHg and 127.6/81.5 mmHg respectively). Despite this, by just week 1 the intervention arm show an improvement in diastolic and systolic BP control with clearer separation visible by week 6, and out to 6-9 months, with the widest difference between the two arms evident on the 24hr ABPM values at this timepoint.

Figure 20: Longitudinal trend of diastolic BP (DBP) control from antenatal booking to 6-9 months postpartum (mean 248.8 days) in the intervention and control arms of the POP-HT trial

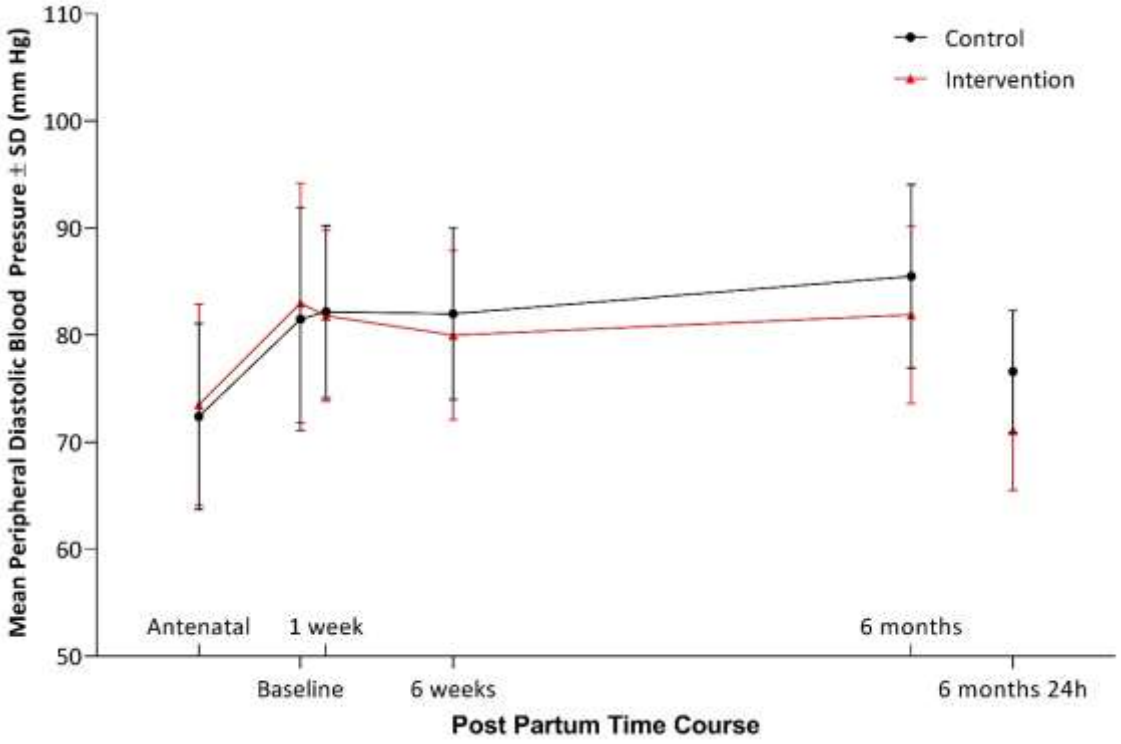
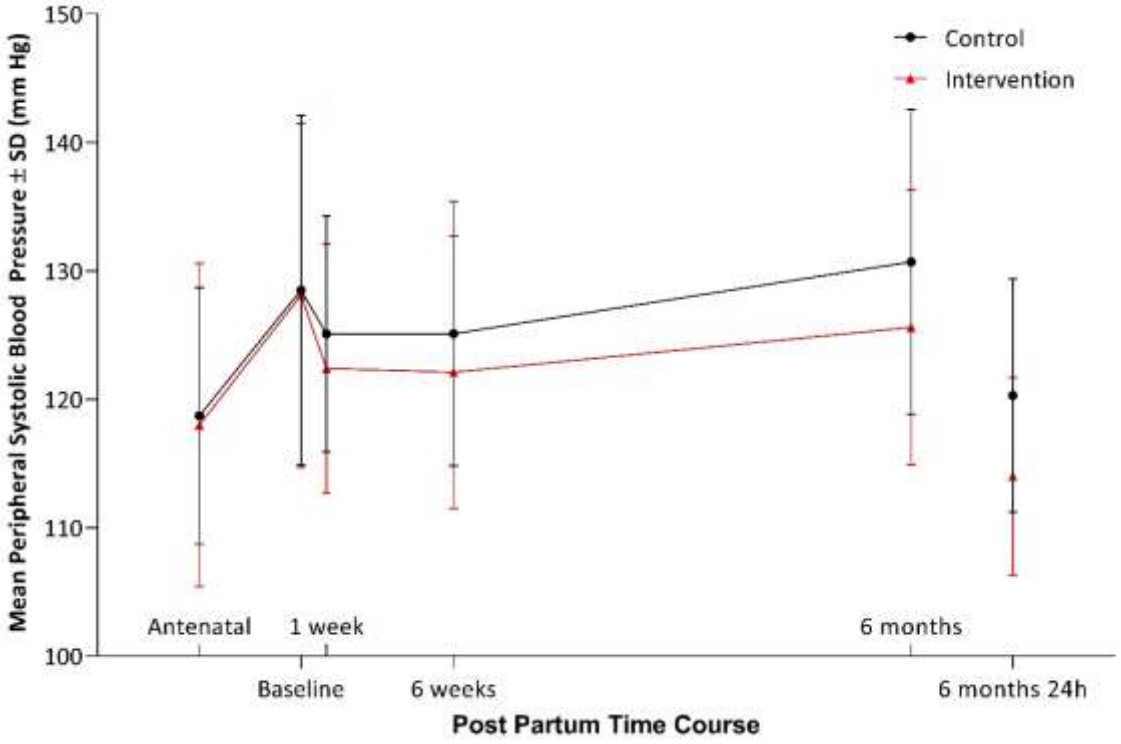


Figure 21: Longitudinal trend of systolic BP (SBP) control from the antenatal booking to 6-9 months postpartum (mean 248.8 days) in the intervention and control arms of the POP-HT trial



The impact of lifestyle differences on BP readings obtained during POP-HT

Those risk factors, which are known to influence blood pressure in the general population, as described at length in Chapter 3's discussion, were recorded in detail as part of the POP-HT trial to allow between group comparisons to be made for these 'traditional' hypertensive risk factors. At the timepoint of the final study visit at 6-9 months postpartum, levels of activity, alcohol intake and salt intake were all similar between the groups (see table 5 below). In both arms >90% of women consumed less than 7 units per week of alcohol with approximately 65% drinking no alcohol at all. Salt intake, as judged by a validated BHF diet questionnaire, was higher than anticipated in both arms with >70% from both groups self-reporting a moderate-high salt intake, with no significant difference between the groups. There were a small number of active smokers in each arm (three in intervention vs two in the control arm; each smoking <10/cigarettes per day), but with no meaningful differences in smoking or ex-smoking rates between the two arms by independent samples T-tests. Levels of activity were also similar between the groups (based on a seven-day accelerometer worn for the seven-days following the final study visit). Just under 180 women (87% of those still enrolled at the time of V4) completed the week-long period of monitoring successfully (180 valid/191 worn, and there was a fair representation from each treatment allocation (90% from the intervention arm and 87% from the usual care arm). These data showed very similar levels of activity between the two groups (9.10 vs 9.13 hours of sleep in each arm, and 8.71 vs 8.61 hours of sedentary daytime activity). Both groups were moderately active for under 5 hours a day with no vigorous activity time in either group.

Table 5 (Chapter 5). Lifestyle characteristics of study participants at the time of the final study visit

Parameter, unit	**Overall (n=202)**	**Intervention (n =105)**	**Usual care (n =97)**
Activity[*1], hours/day (IQR)			
Sleep	9.11 (11.5)	9.10 (11.48)	9.13 (11.51)
Sedentary	8.67 (11.24)	8.71 (11.26)	8.61 (11.22)
Light activity	0.59 (3.45)	0.64 (3.58)	0.55 (3.3)
Walking	0.83 (4.06)	0.89 (4.18)	0.77 (3.92)
Moderate activity	4.8 (9.24)	4.67 (9.21)	4.95 (9.28)

Smoking history*[2]			
Ex-smoker of, n (%)	53 (28.6)	25 (25.8)	28 (31.8)
Current smoker, n (%)	5 (2.7)	3 (3.1)	2 (2.3)
Alcohol consumption, units/week, n (%)*[2]			
0	121 (65.4)	64 (66.0)	57 (64.8)
1-7	54 (29.2)	26 (26.8)	28 (31.8)
8-14	7 (3.8)	6 (6.2)	1 (1.1)
15 +	3 (1.6)	1 (1.0)	2 (2.3)
Salt intake, n (%)*[2,3]			
Low	50 (27.0)	25 (25.8)	25 (28.4)
Moderate	100 (54.1)	54 (55.7)	46 (52.3)
High	35 (18.9)	18 (18.6)	17 (19.3)

*[1]As measured by Axivity AX3® accelerometers; numbers with valid recording n=176 (n=94 intervention, n= 84 control) *[2] n=185 (n=97 intervention, n=88 usual care). *[3] Salt intake at follow-up, was categorised as low, medium and high in accordance with their answers to the British Heart Foundation® validated dietary questionnaire. Low intake was classed as 0-1 positive responses to the salt intake questions, 2-3 as moderate intake and 4 or more answers to the salt questions as high intake

Table 6 of Chapter 5 (seen on the page below) considered the feasibility of the POP-HT trial, in terms of its recruitment and retention rates, trial fidelity, and adherence to the trial intervention (for those who were allocated to the intervention arm). Trial fidelity was first considered as a percentage of the entire study population (220 participants, who each had three visits following the baseline visit after enrollment on the ward i.e. there were four total visits). There was thus a total of 660 potential follow up visits after discharge from hospital, as all 220 completed the baseline visit on the postnatal ward. Fidelity was then considered as a percentage of those that completed follow up (n=202) where a possible 606 study visits could be completed after hospital discharge following their baseline visit. The predefined windows referenced in the table included five-days flexibility for the week one (V2), and week six (V3) visits (i.e. Days 7-12 for V2, and Day 51-61 postpartum for V3). The final study visit (V4) was carried out over 6-9 months for the BP based measures described in this chapter, but 6-12 months for the imaging based secondary outcomes described in chapter six. This was explained in more detail in Chapter 4.

Table 6: POP-HT Trial feasibility measures			
Recruitment			
Recruitment rate	86 % (112 randomized, 130 eligible approached) for intervention		
	88% (108 randomized, 122 eligible approached) for control arm		
Retention rate	**Whole population (n=220)**	**Intervention (n=112)**	**Control (n=108)**
6-9 months (completion)	92% (202)	93 % (104)	91 % (97)
6 weeks	97% (213)	97% (109)	96% (105)
Trial fidelity	**Whole population (n=220)**		**Population that finished follow-up (n=202)**
Study follow-up visits attended within predefined window	95% (630/660)		97% (605/606) n =1 complete after time window so data not included
Study follow-up visits attended	97% (642/660)		98% (604/606) n= 2 attended final V4 remotely
Intervention adherence	6 wks (5,847 total: 5,655 first time readings, 192 repeat readings;		6 months (16,249 total: 15,712 first time readings, 537 repeat readings)
% complying with daily/weekly readings as per the app®	76.6% (4476)		74.3 % (12,076)
% requiring the automated reminder system *	16.9 % (991)		19.5 % (3159)
% overdue requiring clinician intervention for failure to submit a reading	6.5% (380)		6.2 % (1014)

*Automated reminders were pre-programmed at set intervals as per the telemonitoring specification summarised in Appendix B with more frequents reminders and alerts for the 1st 14 days postpartum and when on treatment i.e. during the high-risk period where BP is more labile.

These results demonstrated high levels of enrolment (88% for the control arm and an 86% recruitment rates for the intervention arms) into the study. Furthermore, once enrolled, retention rates were excellent in both arms. 6-week retention was 97% in the intervention arm and 96% in the control arm. The retention remained excellent to study completion with 93% completing all visits in the intervention arm and 91% in the control arm. Almost all study visits were completed in the pre-specified time windows set out in the study protocol. Of those completing the trial (202 participants), 98% of the visits were completed in the time-windows specified in the study protocol. Admittedly, these time windows were made more 'flexible' as part of a protocol amendment during COVID-19 to allow greater flexibility for the 4th and final study visit (6-12 months was allowed for the imaging-based outcomes vs. 6-9 for the BP based outcomes, as detailed in Chapter 4 further). Furthermore, the primary outcome measurements were made more flexible so they could be done as a home visit or remote home visit, and not just a hospital visit. There was no doubt that this improved trial fidelity with thirteen of the V4 visits done as home visits, and two done as remote home visits. A number of these fifteen women (n=10) then attended at a later date, within the twelve-month window for their echocardiogram, MRI and retinal imaging etc. For the week one (V2) and week six (V3), approximately 90% of V2 visits (195/217), and 88% (188/213) of the V3s were done remotely when participants were offered the chance of home vs. remote vs. hospital based follow up visits.

For those women randomised to the intervention, adherence to daily or twice daily BP upload via the POP-HT app® was good. 76.6% of women randomised to the intervention complied with all app-based BP reading prompts during the first six-weeks (when BP is more labile), with this dropping off slightly to 74.3% compliance by six-months. Just under 17% of women required, but responded to the automated app-based reminder system in the first-six weeks with a slightly higher number requiring these weekly reminders by 6 months (19.5%). There were a small number of women who required clinician 'intervention' to chase up readings via manual SMS or phone calls; 6.5% in the first 6-weeks and 6.2% at six-months.

Did the POP-HT trial intervention impact on the participant's quality of life (QOL)?

The following table considers the results of the EQ-5D-5L analysis, which was performed at repeated time points throughout the trial. The questionnaire was first completed on the post-natal ward during the baseline visit and, then repeated at week 1, week 6 and at the final 6-month visit. On each occasion the questionnaire was e-mailed to the participant to complete in their own time. The first set of scores, reported in table 7a below, were a summary of the visual analogue scale scores, which report on the overall quality of life. The scale ran from 0 (being the worst) to 100 (being the happiest they had ever felt about their health). They also reported scores in five quality of life domains at each time point, the breakdown of which can be seen below in Tables 7a and 7b of Chapter 5.

Table 7a (Chapter 5): EQ-5D-5L Visual Analogue Scores throughout the POP-HT trial

Parameter, unit	Overall (n=202)	Intervention (n =104)	Usual care (n =98)
Baseline EQ-VAS score ± SD*[1]	75.7 (16.5)	76.6 (16.1)	74.7 (16.8)
Week 1 EQ-VAS score ± SD*[2]	81.1 (15.0)	80.8 (14.0)	81.4 (15.9)
Week 6 EQ-VAS score ± SD*[3]	85.6 (15.4)	86.2 (16.5)	84.9 (13.9)
6 month EQ-VAS score ± SD*[4]	87.0 (12.9)	88.8 (11.2)	85.1 (14.2)

*[1] overall n=179, intervention n=88, usual care n=91
*[2] overall n=180, intervention n=93, usual care n=98
*[3] overall n=168, intervention n=90, usual care n=78
*[4] overall n=156, intervention n=82, usual care n=74

Table 7b (Chapter 5): Individual Domain scores for the EQ-5D-5DL questionnaires and the derived utility scores[&]								
	Baseline (1–6 d PN)		**Week 1 (7+-5 days)**		**Week 6 (+- 5 days)**		**6 months (+ 3m)**	
	Intervention (n=89)	Usual care (n=91)	Intervention (n=93)	Usual care (n=87)	Intervention (n =91)	Usual care (n=78)	Intervention (n=82)	Usual care (n-74)
Mobility	1.5 (0.6)	1.6 (0.8)	1.3 (0.5)	1.4 (0.6)	1.1 (0.3)	1.1 (0.4)	1.0 (0.2)	1.1 (0.4)
Self-care	1.3 (0.6)	1.3 (0.6)	1.1 (0.3)	1.1 (0.4)	1.1 (0.3)	1.0 (0.2)	1.0 (0.0)	1.0 (0.2)
Usual activities	1.8 (0.9)	1.8 (0.9)	1.7 (0.8)	1.6 (0.8)	1.3 (0.6)	1.3 (0.6)	1.1 (0.3)	1.2 (0.5)
Pain/discomfort	2.1 (0.7)	2.1 (0.8)	1.8 (0.6)	1.8 (0.6)	1.5 (0.7)	1.5 (0.6)	1.2 (0.5)	1.4 (0.6)
Anxiety/depression	1.5 (0.6)	1.7 (0.9)	1.5 (0/7)	1.4 (0.6)	1.4 (0.6)	1.6 (0.8)	1.5 (0.7)	1.5 (0.8)

EQ-5D-3L derived utility scores[&]			
Parameter, unit	**Overall (n=202)**	**Self-management (n =104)**	**Usual care (n =98)**
Baseline EQ-VAS score ± SD*[1]	0.74 (0.18)	0.76 (0.16)	0.73 (0.20)
Week 1 EQ-VAS score ± SD*[2]	0.80 (0.15)	0.79 (0.15)	0.80 (0.14)
Week 6 EQ-VAS score ± SD*[3]	0.87 (0.14)	0.88 (0.14)	0.86 (0.13)
6 month EQ-VAS score ± SD*[4]	0.90 (0.12)	0.92 (0.10)	0.88 (0.14)

[&]A mapping equation was used to transform the EQ-5D-5L responses into EQ-5D-3L utility scores, which is the recommended approach and, which is well validated (https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/).

The scores in tables 7a and 7b above demonstrate that both the VAS quality of life score, individual domain scores, and the averaged derived utility scores, transformed using a standardised approach validated for use in the NHS [129], showed an improvement in both arms from the time of delivery/the first few days of postnatal life in hospital, up to the trial completion date six to nine months later. The scores were higher in the intervention arm at baseline (VAS by 1.9 points), although this failed to increase as much by week 1 in the intervention arm vs the control arm, but the scores returned to being higher in the intervention arm vs. the control/usual care arm from week six to trial completion (VAS mean 3.7 (1.8) points higher when adjusted for the baseline difference between groups).

The impact of traditional risk factors known to influence postpartum BP on the POP-HT results

The following table considers those factors that could have influenced BP control at the time it was assessed (6-9 months postpartum) in the POP-HT trial. Prior work in SNAP-HT Extension [88] had shown that the level of salt intake was associated with the BP value at a mean of 3.6 years postpartum, so all of relevant lifestyle/hypertensive risk factors were tested in univariate linear regression analysis. Obstetric factors known to influence BP control [130] in this cohort of patients were also included in this analysis i.e. age, parity, the type of hypertensive disorder (gestational hypertension vs PET vs HELLP); disease severity (as judged by gestation of delivery, and duration of antenatal anti-hypertensive treatment); and ethnicity. None of these factors was found to have a significant impact on the POP-HT results, as evidenced by the P values in the table below.

Table 8 (Chapter 5). Univariable linear regression of factors that can affect BP control to determine their relative association with the average 24-hour DBP at 6-9 months postpartum in POP-HT

Risk Factor	B coefficient (95% CI)	P value
Mean age at re-recruitment, years	0.506 (-0.09, 1.021)	P = 0.15
Parity at re-recruitment	-0.42 (-.673, 0.352)	P = 0.54
Median BMI at re-recruitment, kg/m^2	0.23 (-.363, 0.514)	P = 0.73

Hypertensive disorder*	0.078 (-1.927, 7.399)	P = 0.25
Gestation at delivery, weeks	-0.25 (-1.167, 0.802)	P= 0.71
Ethnicity†	-0.72 (-.343, 0.102)	P = 0.29
Duration of antenatal treatment, days	0.054 (-0.091, 0.216)	P = 0.42
Smoking history&, n	-0.17 (0.266, 0.209)	P = 0.81
Alcohol use, units/week	0.12 (-0.213, 0.251)	P= 0.87
Salt intake, n‡	0.51 (-0.159, 0.327)	P = 0.5
Mean arm circumference, cm	0.27 (-0.532, 0.800)	P = 0.69

BMI indicates body mass index and DBP, diastolic blood pressure

*Categorised into: gestational hypertension, pre-eclampsia and HELLP

†Categorised into: 1 white, 2 black, 3+4 South and East Asian, 5 Hispanic, 6 Other

&Categorised into: 1 – current smoker, 2 ex-smoker, 3 non-smokers

‡Categorised as low, medium and high in accordance with their answers to the British Heart Foundation dietary questionnaire. Low intake was classed as 0-1 positive responses to the salt intake questions, 2-3 as moderate intake, and >=4 answers as high intake

d) Sensitivity analyses of the Blood Pressure results

Table 9 (of Chapter 5), seen below, was a sensitivity analysis excluding those women that had to have a repeat 24hr ABPM fitted after their final study visit, due to equipment failure/a lack of valid data from their initial V4 24rh ABPM.

Table 9. Sensitivity analysis with 6 participants excluded in which the 24hr ABPM night-time data had to be repeated and merged with their first 24hr BP monitor (n=196 with these 6 removed; intervention n= 104, control n= 92)

Parameter, unit	**ΔI-C, mmHg (95% CI) adjusted for baseline BP (mean 2nd and 3rd)&**	**ΔI-C, mmHg (95% CI) adjusted for antenatal BP**
PRIMARY OUTCOME		
Mean 24 hr average DBP†, mmHg ± SD	-5.54 (-7.14 to -3.93)*; p<0.001	-5.446 (-7.04 to -3.85)*; p<0.001
SECONDARY OUTCOMES		
Mean 24 hr average SBP†, mmHg ± SD	-6.24 (-8.55 to -3.93)*; p<0.001	-6.316 (-8.6 to -4.02)*; p<0.001
Mean diurnal DBP†, mmHg ± SD	-5.08 (-6.73 to -3.42)*; p<0.001	-4.96 (-6.61 to -3.31)*; p<0.001
Mean diurnal SBP†, mmHg ± SD	-6.51 (-8.81 to -4.21)*; p<0.001	-6.62 (-8.88 to -4.37)*; p<0.001
Mean nocturnal DBP†, mmHg ± SD	-4.84 (-6.80 to -2.88)*; p<0.001	-4.85 (-6.78 to -2.94)*; p<0.001

Mean nocturnal SBP[†], mmHg ± SD	-5.29 (-8.05 to -2.52)[*]; p<0.001	-5.40 (-8.13 to -2.68)[*]; p<0.001

ΔI-C indicates difference between intervention and control groups; DBP, diastolic blood pressure; SBP, systolic blood pressure and SD, standard deviation. [&]mean difference adjusted for baseline blood pressure values in POP-HT, day 1-6 after birth. [†]measured by SPACELAB 90217 ABPM. [‡]95% CI around adjusted difference does not cross zero

These six women's first period of 24hr monitoring did not contain a valid number of daytime and/or night-time readings as per NICE NG136 [114], as was described in more detail in Chapter 4. These six were repeated within the 9-month window but at a slightly later time point. When all six sets of repeat values were excluded the 24hr BP results remain significant and largely unchanged (2/6 were excluded from the primary analysis anyway,as described in section b), due to still not containing the valid number of day and/or night readings).

Table 10 (of chapter 5), seen below, was a further sensitivity analysis in which all those women who remained on anti-hypertensive treatment at V4 were excluded (n= 24; 16 in the intervention arm vs 8 in the control arm), to determine if the BP lowering effect achieved in the intervention arm was driven by being on medication at the time of BP measurement.

Table 10 of Chapter 5. Sensitivity analysis removing those 24 participants who still remained on anti-hypertensive treatment at the time of the 24hr ABPM at 6-9 months (n= 176; n= 89 intervention vs n= 87 control)		
Parameter, unit	**ΔI-C, mmHg (95% CI) adjusted for baseline BP (mean of 2nd and 3rd)[&]**	**ΔI-C, mmHg (95% CI) adjusted for antenatal BP**
PRIMARY OUTCOME		
Mean 24 hr average DBP[†], mmHg ± SD	-6.21 (-7.87 to -4.56)[*]; p<0.001	-6.21 (-7.86 to -4.57)[*]; p<0.001
SECONDARY OUTCOME		
Mean 24 hr average SBP[†], mmHg ± SD	-6.95 (-9.41 to -4.49)[*]; p<0.001	-7.23 (-9.67 to -4.8)[*]; p<0.001

ΔI-C indicates difference between intervention and control groups; DBP, diastolic blood pressure; SBP, systolic blood pressure and SD, standard deviation. [&]mean difference adjusted for baseline blood pressure values in POP-HT, day 1-6 after birth. [†]measured by SPACELAB 90217 ABPM.
[‡]95% CI around adjusted difference does not cross zero

The results in table 10 above demonstrate an even wider difference in 24hr overall average diastolic BP difference between the intervention arm and control arm when those 24 participants who remained on treatment at the time of their final V4 assessment were excluded (-6.21mmHg; 95% CI -7.86 to -4.57mmHg, P=<0.001). The same was true for the 24hr overall average systolic BP, which was then almost 7mmHg lower in the intervention arm, when adjusted for differences in the baseline systolic BP and becomes more than 7mmHg lower when adjusted for the antenatal differences in mean booking systolic BP (-7.23mmHg; 95% CI -9.67 to -4.8mmHg, P=<0.001).

As per the other sensitivity analysis, detailed in Chapter 4 section VI: statistical analysis, and in the POP-HT formal SAP for the trial (see Appendix D); a formal analysis was done to assess the degree of missingness. No baseline variables were associated with missingness, so there was no need for multiple imputation since there were no variables associated with missing to be put in the model.

III. Discussion

The POP-HT study demonstrated that at approximately nine months after a hypertensive pregnancy, women who received the POP-HT intervention had an almost 6mmHg lower 24hr overall average diastolic blood pressure (adjusted mean difference -5.8mmHg; 95% CI -7.40 to -4.20 with P<0.001), when adjusting for baseline postpartum BP differences.

The benefits were not merely limited to DBP moreover, as there was also a >6.5 mmHg improvement in 24hr overall average systolic blood pressure , when measured by the gold standard method of 24hr ABPM [96]. The benefits were not confined to 24hr BP readings, as they had been in SNAP-HT Extension [88], but rather, the clinic readings also demonstrated a similar pattern of progressive diastolic BP improvement between the intervention and control arm, as was seen in SNAP-HT [56], with a 4.17mmHg lower clinic DBP by 6-9 months postpartum (95% CI -6.28 to -2.06 with a P<0.001). Furthermore, the improvement in clinic readings was also significant for SBP in POP-HT, rather than just trending as was seen in SNAP-HT. The adjusted clinic SBP was -5.64mmHg lower in the intervention vs usual care arms (95% CI -8.43 to -2.84mmHg with P<0.0001). All of this was achieved without any serious adverse events (as detailed in Appendix E) and in fact with a large reduction in the number of post-natal readmissions attributed to labile BP (20% absolute risk reduction in postnatal readmissions in the first 14 days after hospital discharge).

Persistently high blood pressure six weeks after a hypertensive pregnancy is associated with a greater increase in blood pressure over the next five to ten years [29]. This is independent of blood pressure levels during early pregnancy, and at time of delivery, and is evident both in those with more severe HDP, such as early onset preeclampsia, and later onset, milder disease. More recent evidence has shown that the risk of having persistent hypertension is exceptionally high shortly after giving birth in women affected by HDP. High rates of progression to persistent hypertension occur in the first year following a pregnancy complicated by HDP [131, 132]. In low- and high-resource settings, about two-thirds of women with a pregnancy complicated by HDP remained hypertensive at six months

postpartum [133, 134]. One meta-analysis quantified the risk of persistent hypertension within two years after a hypertensive pregnancy, with an OR for postpartum hypertension of 5.42 (95% CI 3.12-9.41) in the period up to one year, and an OR of 7.24 (95% CI 4.44-11.80) out to two years [135]. Therefore, if the ~6mmHg diastolic and ~ 7mmHg systolic BP improvement, achieved in POP-HT were maintained longer term, as achieved for the diastolic BP in SNAP-HT EXTENSION, this could lead to as much as a 40% reduction in life-time stroke and 20% reduction in lifetime coronary artery disease risk [40]. This is particularly important given that there have been no interventions proven to reduced disease risk in this group to date, with only the recent PICk-UP trial [100] showing any meaningful potential for BP lowering and cardiac remodelling through the use of Enalapril postpartum.

By the final study visit at a mean of almost 250 days postpartum the mean BP differences between the intervention and control arms were also significant based on the clinic readings with an ~-4.2 mmHg diastolic improvement (95% CI -6.28 to -2.06, P<0.0001), when adjusted for differences in the baseline BP readings between the two arms. This was in keeping with the findings of the original SNAP-HT trial, which described a mean 4.5mmHg lower diastolic BP at 6 months postpartum using clinic readings. The degree of diastolic BP improvement seen in POP-HT for the primary outcome, measured by 24hr ABPM, was even greater (-5.8mmHg; 95% CI -7.40 to -4.20); P=<0.001). Diastolic BP was chosen as the primary outcome in POP-HT, both due to previous results from SNAP-HT and SNAP-HT Extension, and, because in those <50 years of age DBP is a better correlate to long-term cardiovascular risk [33]. In addition, it is a driving factor in the pathophysiology of progression to the mixed, and systolic patterns of hypertension, seen in those age over 50, as proven in the long-term follow up of the FRAMINGHAM cohort [122]. It was pleasing nonetheless, that an improvement was achieved in both systolic and diastolic BP in this trial, as both play a pivotal role in long-term CV risk, and as mentioned above, few prior interventions have been shown to reduce BP or CV risk in this cohort of women [136].

The original SNAP-HT trial [56] was designed to assess feasibility, and safety of a digital intervention in the postnatal period, but was not powered to detect a difference in BP. The POP-HT trial was the

first trial powered specifically to investigate the potential for BP improvement in this study population. With 200 women having valid 24hr BP data completing the trial, it has provided adequate power to detect these differences. This holds true, even when allowing for the potential dilution of the intervention that providing a home BP monitor to the usual care arm may have had, something mandated/advised by the RCOG during the COVID-19 pandemic (see Chapter 4 sample size calculations for further explanation).

As summarised above, POP-HT not only demonstrated a significant improvement in DBP as in SNAP-HT, but it also demonstrated a significant improvement in systolic BP in the intervention arm by 24hr ABPM (adjusted mean difference -6.51 mmHg; 95% CI -8.80 to -4.42; P<0.001). There was a non-significant trend towards an improvement in clinic systolic BP in SNAP-HT of 1mmHg (95% CI -6.3 to 4.4) but in POP-HT the improvement was also significant for the clinic (mean of 2nd and 3rd) systolic readings (-5.64mmHg systolic improvement; 95% CI -8.43 to 2.84, P<0.0001). Whilst the >-4mmHg diastolic BP improvement was in keeping with the previous findings of SNAP-HT (-4.5mmHg), the detection of a clinic systolic BP improvement was new. The greater sample size in POP-HT, combined with the smaller standard deviations achieved through the use of 24hr ABPM (7.7 and 9.1 mmHg in POP-HT vs 12.9 and 14.0mmHg in SNAP-HT) may have been what allowed us to demonstrate an improvement in both systolic and diastolic BP in POP-HT using 24hr ABPM, as supported by the overlapping confidence intervals for the DBP and SBP values in each trial at each timepoint [56] e.g. at week 1 and week 6 SBP (POP-HT 122.4 (9.7) vs SNAP-HT 127.5 (10.9) mmHg at week 1 and POP-HT 122.1 (10.6) vs SNAP-HT 123.3 (10.4) mmHg. However, the SBP improvement, which is always greater in POP-HT vs SNAP-HT, may also represent the impact of more rapid/aggressive medication up titration in the first 10 days postpartum, resulting in fewer BP related admissions (8/112 (7%) in POP-HT intervention vs 5/41 (12%) in SNAP-HT intervention arm. Tighter BP control was also evident in the first 10 days (POP-HT clinic mean BP in the intervention arm was 122.4 [9.7] /81.8mmHg [8.0] vs 127.5 [10.9]/83.7 [8.6] mmHg in the SNAP-HT intervention arm at the same timepoint).

The smaller margin of improvement seen in the clinic readings vs. 24hr ABPM readings for all measures reflects the larger standard deviations seen with the clinic readings (10-12mmHg vs 8-9mmHg), together with the impact white-coat hypertension is known to have on clinic-based readings.

White-coat hypertension, defined as per NICE guidance NG136 [128] as a mean clinic SBP minus 24 hour daytime SBP >=20mmHg, and a mean clinic DBP minus 24 hour daytime DBP >=10mmHg, was present in 6/183 (3.3%) of women during V3 (2/109 in the intervention arm and 4/104 in the control arm), increasing to 15/202 (7.4%)of women at V4/the final visit. At the V4 a greater proportion of those in the intervention arm (9/105 (9%)) vs. 6/97 (6%) in the usual care arm), exhibited white-coat hypertension. The increasing prevalence of white-coat hypertension seen with repeated measuring between V3 and V4, more so in the intervention arm, is something that needs to be evaluated further for future work in this area.

The fact the both systolic and diastolic BP differences remain significant when adjusting for baseline BP differences, or adjusting for antenatal (12-week booking midwife) BP differences, and even when removing those who remained on treatment at 9 months from the analysis (as done in the sensitivity analysis described in table 10 of this chapter), suggests that the BP benefits seen in POP-HT, were not merely an alteration of an antenatal/pre-pregnancy life-time BP trajectory between the two study arms, as the HUNT studies argue [27], as discussed in Chapter 3. Rather, given the fact that the systolic BP remains almost 7mmHg lower, and the diastolic almost 6mmHg lower, in the intervention arm, when adjusting for any antenatal differences between the two arms, and the fact the BP improvements remain when removing the 24 women who were still on BP treatment at 9 months, it suggests the BP improvement resulted from the intervention itself (physician optimised self-management); and not from anti-hypertensive medication at time of BP measurement, or pre-existing differences between the cohorts. Interestingly however, and in keeping with the HUNT longitudinal follow up data [32], the mean antenatal BP for the 220 patients enrolled was 117/72mmHg, and even in the intervention arm the diastolic BP remained higher than this at 9 months postpartum at 75mmHg

i.e. 3 mmHg above the mean booking BP). It was however much higher in the control arm (80mmHg i.e. 8mmHg above booking BP), suggesting that although there was indeed a failure to 'normalise diastolic BP' after a hypertensive pregnancy, the intervention has some impact on returning the altered trajectory towards 'normal'.

What was the explanation for the BP improvement demonstrated in POP-HT?

Although more people had down-titrated in the intervention arm by week 6, 71% (77/109) vs 62% (65/104) in the usual care arm, the mean WHO DDD was higher by week 1 in the intervention arm (increasing from 1.21 to 1.86 vs a drop from 1.35 to 1.26 in the usual care arm). This indicates more aggressive up-titration in the intervention arm over the first 7-10 days, the period known to be the highest risk [136] for postpartum BP spikes . By week 6 the WHO DDD was similar, despite fewer women being on treatment in the intervention arm i.e. 32 vs. 39 in the usual care arm. This also suggests that those remaining on treatment were down-titrated more carefully/slowly. The evidence for 'more aggressive BP control and more careful down-titration' was further supported by the fact that of the 37 (15.9%) BP related readmissions during the overall trial period, only eight were in the intervention arm vs. 29 in the usual care arm.

By ~9 months twice as many women were on treatment in the intervention arm vs. the usual care arm (16 vs 8 respectively), with a small number of women actually restarting treatment (n=3) in the intervention arm due to a late recrudescence of BP at the four-five-month mark. The increased monitoring, afforded by weekly app® uploaded BP measurements in the intervention arm, allowed women to restart treatment when needed. There was also a slightly higher mean number of days of total postnatal treatment in this arm (67.7 in the intervention vs 60 days in the usual care arm), although this difference was not statistically significant (95% CI -25.5 to 9.9).

Together these results indicate that the intervention arm received a greater amount of anti-hypertensive medication over the total trial period, which may well be one element of the benefit seen through the intervention used in this trial. The longitudinal BP patterns seen in figures 20-21 of this Chapter also support the hypothesis that 'more aggressive BP control' plays a role in shaping the

primary outcome results. There was an improvement in DBP (and SBP) control evident by week one, which then increases further by week 6, and further again by 6-9 months. This mirrors the longitudinal BP pattern of results demonstrated in the SNAP-HT and SNAP-HT Extension studies described in Chapter 3. The 16 women in the intervention arm who remained on a small dose of medication at 6-9 months (WHO mean DDD 0.16 (0.50)) vs the eight in the usual care arm (WHO mean DDD 0.06 (0.26)) do not explain the magnitude of the BP difference demonstrated at 9 months postpartum. In fact, when these 24 women were excluded in the sensitivity analysis (shown in table 10), the BP difference between the groups remains, and in fact increases further, for both 24hr overall average SBP and DBP (with n= 89 in the intervention arm and n= 87 in the usual care arm the adjusted 24 hr overall average DBP difference was -6.21mmHg; 95% CI -7.86 to -4.57, P=<0.001), and the adjusted SBP difference was -7.23mmHg; 95% CI -9.67 to -4.80, P<0.001).

Were there other factors that could have influenced the BP results presented for POP-HT?

Differences in BP control were not explained by variation in contraception use between groups (with the combined pill known to influence BP in young women), parity, adiposity, age, ethnicity, or by differences in the diagnosis/disease severity (as shown in table 8 of this Chapter).

As in SNAP-HT Extension [88], to allow evaluation of the potential effect of lifestyle differences between the groups, univariable linear regression was performed for salt and alcohol intake, smoking history, objectively measured levels of exercise, and other factors that could influence BP control by 9 months postpartum (see table 5 in chapter 5). Ultimately, none of these factors listed in tables 5 and 8 were found to have any significant impact on the blood pressure differences seen at 6-9 months postpartum in POP-HT, reinforcing the conclusion that the effect seen was driven by the intervention not 'unhealthy living', although the high salt intake in both groups (>70% having >moderate intake) is something to address in future work and a target for lifestyle interventions in long-term follow-up.

The role of Enalapril

With the introduction of the new NICE guidance on hypertension in pregnancy [45] came the introduction of ACEi into the treatment algorithm (enalapril or captopril), with ACEi in fact being

recommend as a 1st line treatment in those who are White-Caucasian as of July 2019. This was thus included as one of the minimisation factors in the trial to try and minimise the potential effect this could have on assessing the benefit of the POPHT intervention. The trial began recruitment in February 2020 and recruited until March 2021. Over this time period clinicians looking after women in the postnatal period became more familiar with the drug, and the usual inertia seen following guideline change [137] started to drop off, with the result that approximately one quarter of women were discharged on Enalapril (27 in each arm) by the time the trial ceased recruiting. As table two of this chapter illustrated however, a greater proportion of participants received enalapril over the total study duration in the intervention arm (57% in the intervention arm vs 43% in the usual care arm) and of those women remaining on treatment at 6-9 months (n=24, 16 intervention (12 were on enalapril) and 8 control (5 on enalapril) with the remainder in both groups on low dose labetalol. The higher usage of enalapril in the intervention arm was likely driven by the fact the physicians guiding self-management were more familiar with ACEi, as cardiologists and obstetric physicians, than some GPs in primary care [138]. When those women on ACEi at ~9 months were removed however, the SBP and DBP benefit widen and the small difference in absolute usage between the arms, suggests this had a minimal impact on the overall results. This is explored further in the cardiovascular imaging-based sensitivity analyses described in the next Chapter (Chapter 6).

Using the 24hr APBM results from POP-HT I could start to consider the mechanism underlying the BP improvement seen, based around nocturnal dipping patterns, but these mechanisms will be explored further, and directly correlated with the results of the cardiovascular and vascular phenotyping data presented in the next chapter.

Does self-management/telemonitoring remain a feasible and attractive option?

Since SNAP-HT was published in 2018 [56], several other trials have shown telemonitoring postpartum is safe and effective when compared to standard care. In one study by Hoppe et al from 2020 [90], 428 women were randomised in a 1:1 fashion to telemonitoring with nurse-led medication titration or

standard care. The intervention group had fewer hypertension-related readmissions compared with the controls (1 [0.5%] vs 8 [3.7%]; relative risk [RR], 0.12; 95% CI, 0.01–0.96), as in POP-HT. Furthermore, significantly more women in the intervention group had a minimum of one BP measured within 10 days postpartum when compared with the controls (202 [94.4%] vs 129 [60.3%]; RR, 1.59; 95% CI, 1.36–1.77).

Another postpartum study provided further support for a role for Home BP monitoring (HBPM), showing that 10-15% of patients with hypertensive disorders had unplanned postpartum healthcare use after discharge, and that mild blood pressure elevation upon discharge was the key risk factor for unplanned health care use [139]. The readmission data from the POP-HT trial demonstrate reinforce these findings with table 3 demonstrating that the intervention led to a significant reduction in the number of postnatal readmissions attributable to blood pressure issues.

Moreover, given that ~ 90% of women approached in Oxford were willing to enrol, with 20% being non-white and with a reasonable spread of IMD scores, for a predominantly white middle-class area of the UK, it suggests telemonitoring and its variations, remains attractive in this cohort of women. Retention was also excellent with >90% retention to trial completion in both arms (91% usual care; 96% in intervention). These recruitment rates were higher than those seen in SNAP-HT (which had a 49-59% recruitment rate between the two arms), but with similar retention rates (89-91% in SNAP-HT). The high recruitment rates likely reflect changing behaviour during the pandemic [89, 90] with women more aware of the value that could be provided by telemonitoring during a global pandemic when face-face healthcare visits were restricted. Due to the RCOG guidance [140] advising that ‘all women be given a home BP monitor for the first week after a hypertensive pregnancy’ the control arm were also provided with a home monitor (but not remote physician guided self-management), and this difference may also explain the higher recruitment rates since SNAP-HT. The fact that both SNAP-HT and POP-HT demonstrated that >95% of women completed all visits was also testament to the appeal of this technology. This was further supported by the EQ-5D-5L results seen in table 7a and 7b. Interestingly the self-reported VAS score did fail to increase as much from baseline (on the ward) to

week 1 (with a 4.4-point increase in intervention vs 6.7 points in the usual care arm), which may reflect the extra-work associated with the intervention process in the first week after discharge i.e. a 'settling in period' to get used to the technology. These QOL scores needs exploring in more detailed qualitative work in future work.

CHAPTER 6 - POP-HT CARDIAC AND VASCULAR IMAGING RESULTS AND DISCUSSION

I. Introduction

As described in Chapter One Section V, significant cardiac abnormalities have been identified in the majority of pregnant women affected by HDP and these persist in the postpartum in a smaller, but significant proportion of these patients. Maternal echocardiography has shown HDP-associated increases in left ventricle mass and cardiac remodelling, especially in women with pre-eclampsia [105]. Most data suggest these changes are associated with the development of diastolic dysfunction [141], as well as a significant reduction in global longitudinal strain (GLS), a sensitive tool for subclinical myocardial dysfunction [142]. Although delivery helps to treat the acute phase of HDP by removing the placenta, persistent cardiac remodelling and dysfunction remain detectable by transthoracic echocardiography during the postpartum period out to 6 months [36, 105]. In a multicentre observational study of 321 women with preterm PE, 10% of women had a left ventricle ejection fraction <55% and/or diastolic dysfunction at six months postpartum [143]. Women with a history of HDP present with long-term cardiac complications including heart failure, valvular heart disease and atherosclerotic coronary artery disease, at a much younger age that that seen in the general population [14], as was discussed in more detail in Section I as part of the introduction to this thesis. HDP, is also a risk factor for peripartum cardiomyopathy (PPCM), which is a severe complication that occurs in ~1 in 1000 pregnancies worldwide. In a cohort of 735 women affected by PPCM, women with PPCM and PE had more severe symptoms and signs of heart failure compared to PPCM without hypertension [144]. Interestingly, Melchiorre et al. demonstrated that differences in cardiac dysfunction were also associated with later risk of hypertension [36]. Therefore, as well as demonstrating the ability to improve postpartum BP control, as has been discussed and demonstrated in Chapter 5, the purpose of the POP-HT trial was to determine if self-management could impact on the adverse cardiac remodelling, now so well described at both one year [145], and up to a decade or

more after HDP [60]. By doing so it was hoped I could start to understand the mechanisms driving these long-term CV risks and, help to refine the management strategies for this cohort to improve their long-term CV health, and ultimately reduce their long-term risk.

II. Cardiovascular imaging results

1. Echocardiography

Of the 220 people enrolled, 217/220 underwent a baseline transthoracic echocardiogram at day 0-5 postpartum on the postnatal ward of the Oxford Women's centre. One of these scans was saved as an incomplete dataset so only 216/220 were included in the baseline analysis, as outlined in the data completeness section at the opening of this Chapter. Table 1 of Chapter 6, seen below, shows the baseline and V4 parameters that were assessed, including those assessing left ventricular (LV) systolic and diastolic function, right ventricular (RV) longitudinal systolic function, LV size/volumes and remodelling, and left atrial (LA) size/volumes. As this table illustrates, there were no significant differences between the intervention and usual care arms of the trial in any of the baseline echo measures, which was confirmed statistically using independent samples T-tests. The sample sizes were also similar between the two arms with n= 109 in the intervention arm and n= 107 in the usual care arm for detailed echocardiographic baseline data. Repeat full resting transthoracic echo datasets were performed in 187 (92%) of the 202 participants who completed the trial. The repeat echo was performed at an overall mean of 258 days postpartum (258.9 days for the intervention arm and 257.4 for the usual care arm). The reason for the lower number of V4 echo scans (compared to baseline) was discussed in the data completeness section, at the opening of chapter 5. The baseline and V4 echo results were compared side by side in table 1 (of chapter 6), which is seen below, with adjusted regression coefficients performed on the measurements recorded at 6-12 months and the baseline measurements included in the model. This enabled assessment of the effect of the intervention on the echo parameters between the two time points. A similar number of follow up scans were performed in each arm of the study, albeit there was a larger sample size in the intervention arm at

the V4 follow up (n= 107 vs. n=86). This was due to a larger number of the control arm opting for home or remote home visits, where it was not possible to perform an echocardiogram.

Table 1: Comparison of echocardiographic measures of cardiac structure and function from baseline to V4 adjusted for baseline measurements[+]

	Intervention		Usual care		Adjusted regression coefficients[+]		
Haemodynamics	**Baseline mean (SD) (n=109)**	**V4 mean (SD) (n=101)**	**Baseline mean (SD) (n=107)**	**V4 mean (SD) (n=86)**	**Difference**	**95% C.I.**	**P value**
HR, bpm	79.6 (12.56)	79.3 (11.9)	78.70 (11.27)	79.1 (12)			
SV indexed, ml/m^2	45.2 (6.33)	38.7 (4.83)	44.7 (6.70)	40.77 (6.31)	-2.15	(-3.01 to -1.00)*	<0.001
CO, L/min†	6.57 (1.30)	5.58 (1.09)	6.41 (1.26)	5.78 (1.13)	-0.24	(-0.55 to 0.57)	0.111
MAP, mmHg	98.1 (11.58)	97.1 (8.09)	96.9 (10.75)	100.5 (9.07)	-3.62	(-6.05, -1.20)*	0.004
SVR, mmHg/min/ml-1	1.56 (0.39)	1.80 (0.38)	1.58 (0.37)	1.80 (0.39)	0.006	(-0.10, 0.11)	0.912
Systolic function							
LVEF, %	64.90 (3.65)	65.57 (2.82)	64.33 (3.61)	63.72 (3.77)	1.79	(0.84 to 2.75)*	<0.001
GLS, %‡	21.50 (1.72)	22.67 (1.84)	21.49 (1.63)	21.67 (1.74)	1.19	(0.65 to 1.72)*	<0.001

	Intervention		Usual care		Adjusted regression coefficients+		
TAPSE, cm	2.52 (0.39)	2.26 (0.35)	2.58 (0.41)	2.30 (0.42)	-0.02	(-0.13 to 0.09)	0.690
RV free wall S', cm/s	14.67 (2.40)	12.91 (2.14)	14.83 (2.48)	12.68 (1.96)	0.26	(-0.33 to 0.85)	0.383
Diastolic function							
E/A ratio	1.28 (0.27)	1.31 (0.29)	1.31 (0.33)	1.30 (0.36)	0.02	(-0.06 to 0.11)	0.592
E deceleration time, sec	0.16 (0.03)	0.17 (0.02)	0.16 (0.03)	0.18 (0.03)	-0.01	(-0.02 to 0.001)	0.057
Lateral E'	14.69 (2.94)	14.37 (2.83)	14.77 (2.93)	14.02 (2.98)	0.38	(-0.39 to 1.12)	0.331
Medial E'	10.51 (2.24)	10.28 (2.23)	10.59 (2.38)	9.56 (2.69)	0.76	(0.11 to 1.40) *	0.021
Average E'	12.60 (2.04)	12.33 (2.19)	12.64 (2.17)	11.79 (2.38)	0.56	(-0.03 to 1.15)	0.064
E/E' average	7.93 (1.83)	6.05 (1.38)	8.08 (2.09)	6.61 (1.86)	-0.52	(-0.97 to -0.07) *	0.024
E/E' medial	9.22 (2.45)	7.05 (1.86)	9.45 (2.61)	7.96 (2.67)	-0.84	(-1.47 to -0.20) *	0.009

Remodelling							
	Intervention		Usual care		Adjusted regression coefficients[&]		
LVIDd, cm	4.81 (0.38)	4.61 (0.32)	4.85 (0.40)	4.66 (0.36)	-0.02	(-0.09 to 0.04)	0.514
PWd, cm	0.94 (0.13)	0.62 (0.11)	0.92 (0.13)	0.76 (0.09)	-0.14	(-0.17 to -0.12) *	<0.001
SWd, cm	1.02 (0.12)	0.67 (0.10)	1.00 (0.12)	0.84 (0.09)	-0.18	(-0.21 to -0.16) *	<0.001
RWT (ASE)	0.39 (0.06)	0.27 (0.05)	0.38 (0.06)	0.33 (0.04)	-0.06	(-0.07 to -0.05) *	<0.001
LAVi, mL/m^2	31.66 (6.39)	21.74 (3.19)	31.26 (6.19)	25.98 (5.20)	-4.33	(-5.48 to -3.18) *	<0.001
EDVi, ml/m^2	69.92 (10.04)	59.03 (7.18)	69.74 (10.54)	63.68 (8.77)	-4.74	(-6.23 to -3.26) *	<0.001
ESVi, ml/m^2	24.49 (4.93)	20.31 (3.07)	25.16 (4.99)	23.26 (4.03)	-2.69	(-3.57 to -1.81) *	<0.001

Parametric: mean (SD). CO indicates cardiac output; MAP, mean arterial pressure; SVR, systemic vascular resistance calculated as MAP/CO; E/A, ratio of early to late mitral inflow velocity; E/E', ratio of early mitral inflow velocity and early mitral annular diastolic velocity; GLS, global longitudinal strain; HR, heart rate; LAV, left atrial volume; LAVi, LAV indexed to body surface area; LV, left ventricular; LVEF, left ventricular ejection fraction; LVIDd, LV internal diameter in diastole; PWd, posterior wall diameter in diastole; RWT, relative wall thickness; ASE, American society of echo model for RWT assessment (i.e. 2 x PWd/LVIDd) [118]; SV, stroke volume; SWd, septal wall diameter in diastole.

[*] 95% confidence interval does not cross zero. [&] All regressions were performed on measurements at 6 months with the baseline measurement included in the model

† Nonparametric: median (range). ‡ baseline intervention n=98, usual care n=86, V4 intervention n=96, usual care = 77 (numbers less as the image quality required for strain led to more cases being excluded)

As table 1 of this chapter illustrates, in terms of haemodynamic differences, there were no significant differences in the heart rate, systemic vascular resistance (SVR) or cardiac output (CO) in the intervention vs. usual care arms from baseline to V4. Not unsurprisingly there was a significant improvement in the MAP of -3.62mmHg (95% CI -6.05 to -1.20mmHg), in keeping with the BP findings in chapter 5.

However, there was a reduction in the stroke volumes of -2.15ml/m^2 in the intervention arm when adjusting for baseline differences (95% CI – 3.01 to -1.00; P=<0.001). This was accompanied by a greater reduction in indexed end-diastolic volumes and end-systolic volumes between the baseline and V4 scans in the intervention arm (-4.74ml/m^2; 95% CI -6.23 to -3.26, P=<0.001, and -2.69ml/m^2; 95% CI -3.57 TO -1.81, P<0.001 respectively. Both septal and posterior LV walls showed a greater reduction between baseline and V4 in the intervention arm of 1.4mm and 1.8mm respectively. Relative wall thickness (which is a composite of both septal and posterior wall thickness in relation to the LV internal diastolic diameter by BSE, or derived from 2 x PWD/LVIDd using ASE), also showed a greater improvement over the 9 months postpartum between the two interval scans (-0.06; 95% CI -0.07 to -0.05, P=<0.001 by ASE method).

This beneficial LV remodelling was also accompanied by a greater improvement in LV systolic function in the intervention arm, with an almost 2% improvement in LV ejection fraction assessed by Biplane Simpson's method (+1.79; 95% CI 0.84 to 2.75%, P=<0.001), and a significant improvement in peak global longitudinal systolic strain (GLS) (+1.19; 95% CI 0.65 to 1.72, P=<0.001). Although the EF change is small (+2%), it is reinforced by the GLS data, and given the fact women should have 'normal systolic function' at this timepoint, this change was significant. There was no significant difference evident between the two groups in RV longitudinal systolic function, as measured by RV S' or TAPSE. The cardiac MRI data explored potential RV remodelling further as it is the gold-standard means of assessing RV volumes and function [115]. This is discussed in the next sub-section, which outlines the cardiac MRI results.

There were also significant improvements seen in several markers of diastolic function for the intervention arm between the baseline and V4 scans, approximately 258 days apart. Whilst E/A ration and E deceleration time did not differ significantly, the more sensitive Tissue Doppler Imaging (TDI) did. There were notable improvements in the average E/E' (0.52; 95% CI -0.97 to -0.07, P=0.024) and the medial E/E' (-0.84; 95% ci -1.47 t 0.21, P=0.009), as well as the Average E', all of which indicate a greater improvement in myocardial relaxation/diastolic function in the intervention arm. This was accompanied by a significant reduction in the indexed left atrial volume (LAVi) of more than 4ml/m^2 (-4.33ml/m^2; 95% CI -5.48 to -3.18, P=<0.001) with lower LV filling pressures resulting in beneficial LA remodelling.

Were these improvements driven by the BP improvement described in Chapter 5?

A number of sensitivity analyses were performed to assess the the impact that various factors could have had on LV remodelling to determine if the remodelling described was a result of the intervention itself or other factors. These analyses included the following univariate multiple linear regression models, with baseline differences in echo measures adjusted for in all of these models:

1. **The impact of either; antenatal differences in diastolic BP, or; differences in 24hr overall average diastolic BP at the time of the V4 scan on LV geometry and function**

As table one of chapter 5 illustrates, there were marginal differences in the antenatal systolic and diastolic BPs, recorded by the community mid-wives at the 12-week booking visit: 118.7 (10.0)/73.5 (9.4) mmHg in the intervention arm vs 116.5 (14.7)/72.4 (8.7) mmHg in the usual care arm. Although the values were non-significantly higher in the intervention arm, to make sure this antenatal difference was not influencing the results described above, this post-hoc analysis was performed. As seen in table 2 of this Chapter (see below), the results show there was no significant impact on the degree of improvement in LV function and remodelling when this adjustment was made.

Similarly, and perhaps more importantly, when the echo findings at V4 were adjusted for the diastolic BP difference achieved in POP-HT, an almost 6mmHg lower 24hr overall average DBP in the intervention arm, the differences in LV systolic function and geometry were maintained (see table 3 of this chapter). Interestingly, the differences in diastolic function no longer remain significant when

adjusting for this 24hr BP difference between the intervention vs usual care arms, with the 95% CI now crossing zero but the indexed LAV does remains significantly lower in the intervention arm.

Table 2 of Chapter 6: Sensitivity analysis adjusting for antenatal diastolic BP differences on LV geometry and function			
	Adjusted regression coefficients[†]		
	Difference	95% C.I.[*]	P value
Systolic function			
LVEF, %	1.78	0.82 to 2.74[*]	P = <0.001
GLS†, %‡	1.20	0.67 to 1.7[*]	P = <0.001
Diastolic function			
E/E' average	-0.55	-1.00 to -0.11[*]	P=0.016
E/E' medial	-0.88	-1.51 to -0.26[*]	P=0.006
Remodelling			
LV EDVi (ml/m^2)	-4.70	-6.20 to -3.2[*]	P = <0.001
LV ESVi (ml/m^2)	-2.67	-3.55 to -1.79[*]	P = <0.001
RWT (ASE)	-0.06	-0.07 to -0.05[*]	P = <0.001
SV indexed (ml/m^2)	-2.11	-3.27 to -0.96[*]	P = <0.001
LAVI (ml/m^2)	-4.37	-5.52 to -3.21[*]	P = <0.001

LV, left ventricular; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; E/E', ratio of early mitral inflow velocity and early mitral annular diastolic velocity; LAV, left atrial volume; LAVi, LAV indexed to body surface area; RWT, relative wall thickness; ASE, American society of echo model for RWT assessment; SV, stroke volume;

*95% CI does not cross zero [†]All regressions were performed on measurements at 6 months with the baseline measurement included in the model. † Nonparametric: median (range).

‡ baseline intervention n=98, usual care n=86, V4 intervention n=96, usual care = 77

Table 3 of Chapter 6: Sensitivity analysis adjusting for the difference in 24hr overall average diastolic BP at 6-9 months postpartum between the two arms, on LV geometry and function			
	Adjusted regression coefficients[&]		
	Difference	**95% C.I.***	**P value**
Systolic function			
LVEF, %	2.24	1.19 to 3.29*	P = <0.001
GLS†, %‡	1.01	0.42 to 1.61*	P = <0.001
Diastolic function			
E/E' average	-0.20	-0.69 to 0.29	P=0.42
E/E' medial	-0.40	-1.09 to 0.28	P=0.25
Remodelling			
LV EDVi (ml/m^2)	-4.83	-6.48 to -3.18*	P = <0.001
LV ESVi (ml/m^2)	-3.19	-4.15 to -2.32*	P = <0.001
RWT (ASE)	-0.06	-0.07 to -0.04*	P = <0.001
SV indexed (ml/m^2)	-1.75	-3.02 to -0.47*	P = 0.008
LAVI (ml/m^2)	-4.28	-5.55 to -3.00*	P = <0.001

LV, left ventricular; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; E/E', ratio of early mitral inflow velocity and early mitral annular diastolic velocity; LAV, left atrial volume; LAVi, LAV indexed to body surface area; RWT, relative wall thickness; ASE, American society of echo model for RWT assessment; SV, stroke volume;

*95% CI does not cross zero [&]All regressions were performed on measurements at 6 months with the baseline measurement included in the model. † Nonparametric: median (range).

‡ baseline intervention n=98, usual care n=86, V4 intervention n=96, usual care = 77

1. **The impact of ethnic differences between the two arms on LV geometry and function**

As shown in the baseline characteristics table (table 1 of Chapter 5), the differences in the ethnic makeup of each trial arm were minimal with both arms being ~80% White-Caucasian and the remaining 20% comprised of Black (5.4% vs 3.7%), Asian (8.9% vs 7.4%) and Hispanic (3.6% vs 4.6%) ethnicities in the intervention vs. usual care arms respectively. Given there were some differences, albeit small in the ethnic minorities within each arm, Table 4 of this chapter (seen on the page below), demonstrates that even when the echo data were adjusted for marginal differences in ethnicity, the differences were maintained for LV function (systolic and diastolic), and both LV and LA remodelling.

2. **The impact of prior HDP**

Table one of Chapter 5 (Baseline characteristics) also demonstrated there was a higher percentage of women in the intervention arm who had experienced a prior HDP; 30 in the intervention (26.8%) vs. 10 in the control arm (9.3%), and thus this may have been expected to result in more prior adverse remodelling in this group, based on prior meta-analyses [142]. However, as table 5 of this chapter below demonstrates, despite this baseline difference between the randomisation groups, the intervention arm still achieved greater beneficial remodelling by approximately nine months postpartum, with no dilution of the initial remodelling benefit described in table 1 of this Chapter (see table 5 of this chapter, which can be found two pages below).

3. **The impact of prescription of an ACEi (Enalapril) for at least one month on LV remodelling**

Although there was no meaningful difference between the two arms in the percentage prescribed it for a meaningful period i.e. the percentage in each randomisation group who were still on enalapril by week 6 was 44.6% of those in the usual care arm vs 46.3% in the intervention arm, given that ACEi are known to result in beneficial cardiac remodelling, in the general population [101], as well as postpartum [100], an additional exploratory sensitivity analysis was performed to see if the benefits seen in table 1 of this chapter were affected by Enalapril. The results of this analysis seen in table 6 of this chapter (three pages below), demonstrated no significant impact from the differences in enalapril prescription between the two arms on cardiac remodelling and function, albeit the trial was not powered to be able to detect such differences. Similarly, if those participants who were still on ACEi at

6 months were excluded, the beneficial differences in LV remodelling and systolic function remain significant for the 174 participants still included. These findings are shown in Table 7 of this chapter, four pages below.

Table 4 of Chapter 6: Sensitivity analysis adjusting for differences in ethnic make-up between the groups (and baseline mean DBP) on LV geometry and systolic and diastolic function

	Adjusted regression coefficients [&]		
	Difference	**95% C.I.***	**P value**
Systolic function			
LVEF, %	1.80	0.83 to 2.76*	P = <0.001
GLS†, %‡	1.18	0.64 to 1.72*	P = <0.001
Diastolic function			
E/E' average	-0.51	-0.96 to -0.06*	P=0.028
E/E' medial	-0.83	-1.46 to -0.19*	P=0.011
Remodelling			
LV EDVi (ml/m^2)	-4.90	-6.37 to -3.43*	P = <0.001
LV ESVi (ml/m^2)	-2.77	-3.64 to -1.89*	P = <0.001
RWT (ASE)	-0.06	-0.07 to -0.05*	P = <0.001
SV indexed (ml/m^2)	-2.22	-3.37 to -1.06*	P = <0.001
LAVI (ml/m^2)	-4.41	-5.56 to -3.25*	P = <0.001

LV, left ventricular; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; E/E', ratio of early mitral inflow velocity and early mitral annular diastolic velocity; LAV, left atrial volume; LAVi, LAV indexed to body surface area; RWT, relative wall thickness; ASE, American society of echo model for RWT assessment; SV, stroke volume; *95% CI does not cross zero [&]All regressions were performed on measurements at 6 months with the baseline measurement included in the model. † Nonparametric: median (range).
‡ baseline intervention n=98, usual care n=86, V4 intervention n=96, usual care = 77

Table 5 of Chapter 6: Sensitivity analysis adjusting for differences in the % with a prior HDP in the intervention vs. usual care arms (and baseline mean DBP) to assess impact on LV geometry and function			
	Adjusted regression coefficients[&]		
	Difference	95% C.I.*	P value
Systolic function			
LVEF, %	1.88	0.89 to 2.87*	P = <0.001
GLS†, %‡	1.18	0.63 to 1.74*	P = <0.001
Diastolic function			
E/E' average	-0.51	-0.98 to -0.05*	P=0.032
E/E' medial	0.79	-1.43 to -0.13*	P=0.019
Remodelling			
LV EDVi (ml/m^2)	-4.8	-6.34 to -3.29*	P = <0.001
LV ESVi (ml/m^2)	-2.71	-3.62 to -1.81*	P = <0.001
RWT (ASE)	-0.06	-0.07 to -0.05*	P = <0.001
SV indexed (ml/m^2)	-2.10	-3.30 to -0.90*	P = <0.001
LAVI (ml/m^2)	-4.44	-5.63 to -3.25*	P = <0.001

LV, left ventricular; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; E/E', ratio of early mitral inflow velocity and early mitral annular diastolic velocity; LAV, left atrial volume; LAVi, LAV indexed to body surface area; RWT, relative wall thickness; ASE, American society of echo model for RWT assessment; SV, stroke volume; *95% CI does not cross zero [&]All regressions were performed on measurements at 6 months with the baseline measurement included in the model. † Nonparametric: median (range).
‡ baseline intervention n=98, usual care n=86, V4 intervention n=96, usual care n=77

Table 6 of Chapter 6: Sensitivity analysis adjusting for impact of taking$ an ACEi (Enalapril) for >28 days (and baseline mean DBP) on the difference in LV geometry and function			
	Difference	**95% C.I.***	**P value**
Systolic function			
LVEF, %	1.81	0.85 to 2.87*	P = <0.001
GLS†, %‡	1.16	0.62 to 1.70*	P = <0.001
Diastolic function			
E/E' average	-0.49	-0.95 to -0.04*	P=0.033
E/E' medial	-0.81	-1.45 to -0.18*	P=0.013
Remodelling			
LV EDVi (ml/m2)	-4.87	-6.36 to -3.38*	P = <0.001
LV ESVi (ml/m2)	-2.77	-3.65 to -1.89*	P = <0.001
RWT (ASE)	-0.06	-0.07 to -0.05*	P = <0.001
SV indexed (ml/m2)	-2.18	-3.34 to -1.01*	P = <0.001
LAVI (ml/m2)	-4.38	-5.54 to -3.22*	P = <0.001

LV, left ventricular; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; E/E', ratio of early mitral inflow velocity and early mitral annular diastolic velocity; LAV, left atrial volume; LAVi, LAV indexed to body surface area; RWT, relative wall thickness; ASE, American society of echo model for RWT assessment; SV, stroke volume; $Only women who received enalapril for >28 days without interruption by the time of the week 6 visit were included in this model. Prescription assumes good compliance. *95% CI does not cross zero
All regressions were performed on measurements at 6 months with the baseline measurement included in the model. † Nonparametric: median (range).
‡ Baseline intervention n=98, usual care n=86, V4 intervention n=96, usual care = 77

Table 7 of Chapter 6: Sensitivity analysis excluding those on ACEi/A2RB at 6-9 months postpartum (and adjusting for differences in baseline mean DBP) to assess the impact on LV geometry and function (n= 174; n=90 intervention and n = 84 control)

	Adjusted regression coefficients[&]		
	Difference	**95% C.I.•**	**P value**
Systolic function			
LVEF, %	1.88	0.89 to 2.87*	P = <0.001
GLS†, %‡	1.16	0.62 to 1.70*	P = <0.001
Diastolic function			
E/E' average	-0.48	-0.95 to -0.001*	P=0.050
E/E' medial	-0.83	-1.5 to -0.16*	P=0.015
Remodelling			
LV EDVi (ml/m2)	-4.77	-6.32 to -3.26*	P = <0.001
LV ESVi (ml/m2)	-2.77	-3.68 to -1.85*	P = <0.001
RWT (ASE)	-0.06	-0.08 to -0.05*	P = <0.001
SV indexed (ml/m2)	-2.11	-3.32 to -0.89*	P = <0.001
LAVI (ml/m2)	-4.20	-5.44 to -3.01*	P = <0.001

LV, left ventricular; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; E/E', ratio of early mitral inflow velocity and early mitral annular diastolic velocity; LAV, left atrial volume; LAVi, LAV indexed to body surface area; RWT, relative wall thickness; ASE, American society of echo model for RWT assessment; SV, stroke volume;

*95% CI does not cross zero [&]All regressions were performed on measurements at 6 months with the baseline measurement included in the model. † Nonparametric: median (range).

‡ baseline intervention n=98, usual care n=86, V4 intervention n=85, usual care = 72

Additional sensitivity analyses detailed below also confirmed that when adjusting for the following two factors there were also no significant differences on the benefits seen in LV remodelling, LV function and LA volume first described in table 1 of this chapter. These additional analyses included: 1. Adjusting for the differences in the duration of total post-natal anti-hypertensive treatment between the two trial arms (table 8 of this chapter, see below) and; 2. Removing those who remained on any form of anti-hypertensive treatment at the time of the V4 (n=24), shown in table 9 on the following page.

Table 8 of Chapter 6: Sensitivity analysis adjusting for the total duration of postnatal anti-hypertensive treatment (and baseline differences in the mean of the 2nd and 3rd DBP) on LV geometry and function (Baseline differences in echo measures are adjusted for in the model)

	Adjusted regression coefficients[&]		
	Difference	**95% C.I.***	**P value**
Systolic function			
LVEF, %	1.78	0.81 to 2.74	P = <0.001
GLS, %‡	1.17	0.63 to 1.71	P = <0.001
Diastolic function			
E/E' average	-0.53	-0.98 to -0.07	P = 0.023
E/E' medial	-0.85	-1.48 to -0.21	P = 0.009
Remodelling			
LV EDVi (ml/m^2)	-4.87	-6.35 to -3.39	P = <0.001
LV ESVi (ml/m^2)	-2.73	-3.61 to -1.85	P = <0.001
RWT (ASE)	-0.06	-0.07 to -0.05	P = <0.001
SV indexed (ml/m^2)	-2.21	-3.37 to -1.06	P = <0.001

LV, left ventricular; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; E/E', ratio of early mitral inflow velocity and early mitral annular diastolic velocity; LAV, left atrial volume; LAVi, LAV indexed to body surface area; RWT, relative wall thickness; ASE, American society of echo model for RWT assessment; SV, stroke volume;
*95% CI does not cross zero [&]All regressions were performed on measurements at 6 months with the baseline measurement included in the model. † Nonparametric: median (range).
‡ baseline intervention n=98, usual care n=86, V4 intervention n=85, usual care = 72

Table 9 of Chapter 6: Sensitivity analysis removing the 24 participants on anti-hypertensive treatment at 6-9 months (as well as adjusting for baseline mean DBP) (n=164; intervention n=86 vs. control n= 78)

	Adjusted regression coefficients[&]		
	Difference	**95% C.I.***	**P value**
Systolic function			
LVEF, %	1.79	0.82 to 2.76*	P = <0.001
GLS, %‡	1.36	0.80 to 1.92*	P = <0.001
Diastolic function			
E/E' average	-0.54	-1.04 to -0.04*	P = 0.034
E/E' medial	-0.91	-1.60 to -0.21*	P = 0.011
Remodelling			
LV EDVi (ml/m^2)	-4.84	-6.48 to -3.20*	P = <0.001
LV ESVi (ml/m^2)	-2.74	-3.71 to -1.78*	P = <0.001
RWT (ASE)	-0.07	-0.08 to -0.05*	P = <0.001
SV indexed (ml/m^2)	-2.13	-3.39 to -0.87*	P = 0.001
LAVI (ml/m2)	-4.21	-5.48 to -2.94*	P = <0.001

LV, left ventricular; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; E/E', ratio of early mitral inflow velocity and early mitral annular diastolic velocity; LAV, left atrial volume; LAVi, LAV indexed to body surface area; RWT, relative wall thickness; ASE, American society of echo model for RWT assessment; SV, stroke volume; *95% CI does not cross zero [&]All regressions were performed on measurements at 6 months with the baseline measurement included in the model. † Nonparametric: median (range).
‡ baseline intervention n=98, usual care n=86, V4 intervention n=85, usual care = 72

The findings shown in the two tables above were in keeping with those of the sensitivity analyses performed on the BP data itself described that were described in detail in Chapter 5 i.e. the remodelling results were also not influenced by being on treatment at the time of assessment or the total duration of treatment prior to the V4 measurements being made at a mean 258 days postpartum.

2. Cardiac MRI

As described in the data completeness section, diagnostic quality cardiac MRI data were obtained in n=174 participants (intervention n=93; usual care n=81). The MRI was performed at an overall mean of 258 days postpartum (258.9 days for the intervention arm and 257.4 for the usual care arm), as for the V4 echo data described above. This was a slightly longer than the time period postpartum than at which the primary outcome was assessed (mean 248.8 days; intervention 249.8 vs. usual care 247.9 days). As explained in section I of Chapter 4, more time had been allowed to follow up the POP-HT trial participants for imaging-based outcomes as a consequence of the disruption caused by the COVID-19 pandemic. The table below shows the results of the key Cardiac MRI parameters measured in the POP-HT trial:

Table 10: Cardiac MRI outcomes in the POP-HT trial adjusted for baseline mean (2nd and 3rd) DBP

	Intervention& n=93	Usual Care& n=81	Adjusted regression coefficients†		
	Mean (SD)	Mean (SD)	Difference	95% C.I.*	P value
Haemodynamics					
HR, bpm	72.8 (11.2)	72.1 (10.9)			
LV SV indexed (ml/m^2)	42.3 (5.65)	42.9 (6.07)	-0.638	-2.41 to 1.13	P= 0.47
RV SV indexed, (ml/m^2)	42.4 (6.2)	41.6 (6.1)	0.636	-1.22 to 2.94	P= 0.50
LV CO, L/min	5.85 (1.1)	5.90 (1.2)	-0.85	-.45 to 0.28	P= 0.65
LV CI (L/min/m^2)	3.09 (0.59)	3.07 (0.54)	0.002	-0.17 to 0.17	P = 0.97
RV CO, L/min	5.84 (1.15)	5.67 (1.29)	0.139	-0.23 to 0.50	P = 0.45
RV CI (L/min/m^2)	3.09 (0.59)	3.0 (0.54)	0.12	-0.05 to 2.90	P = 0.16

	Intervention[&] n=93	Usual Care[&] n=81	Adjusted regression coefficients[†]		
Systolic function					
LVEF, %	64.4 (4.3)	61.8 (4.38)	2.58	1.27 to 3.89[*]	P = <0.001
RVEF, %	60.9 (4.17)	58.3 (4.68)	2.73	1.41 to 4.05[*]	P = <0.001
Remodelling					
LV EDVi (ml/m^2)	66.3 (8.9)	70.0 (10.3)	-3.94	-6.8 to -1.04[*]	P= 0.008
LV ESVi (ml/m^2)	23.9 (5.05)	27.0 (5.7)	-3.25	-4.86 to – 1.63[*]	P = <0.001
LV mass indexed to BSA (g/m^2)	39.2 (5.7)	45.4 (5.1)	-6.4	-8.1 to -4.8[*]	P = <0.001
LV mass indexed to height (g/m)	44.9 (7.9)	53.1 (9.2)	-8.3	-10.89 to -5.75[*]	P = <0.001
LV mass/LVEDV	0.58 (0.06)	0.67 (0.07)	-0.09	-0.113 to -0.072[*]	P = <0.001
Mean LV wall thickness[&] (mm)	5.7 (0.6)	6.9 (0.7)	-1.26	-1.46 to -1.06[*]	P = <0.001
RV EDVi, ml/m^2	70.2 (11.7)	71.5 (10.3)	-1.59	-4.92 to 1.74	P = 0.35
RV ESVi, ml/m^2	27.9 (6.6)	30.1 (6.2)	-2.43	-4.35 to -0.51[*]	P = 0.014
Potential Mechanisms					
T1 mapping value[$]	1161.2 (26.4)	1155.1 (26.1)	6.09	-2.04 to 14.24	P=0.14
T2 mapping value[!]	41.1 (1.8)	40.9 (1.7)	0.26	-0.36 to 0.87	P=0.41

	Intervention[&] n=93	Usual Care[&] n=81	Adjusted regression coefficients[†]		
Myocardial fibrosis[^]					
Presence of LGE	7	5			
ECV	0.2662 (0.015)	0.2664 (0.179)	0.0002	-0.012 to 0.012	P=0.95

Parametric: mean (SD). HR, heart rate; SV, stroke volume;; LV, left ventricular; RV, right ventricular; CO indicates cardiac output; CI indicates cardiac output indexed to body surface area; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; EDVi, end diastolic volume indexed to BSA; ESVi, end systolic volume indexed to BSA; BSA, body surface area, calculated by the MOSTELLAR equation; ECV, extra-cellular volume; LGE, late gadolinium enhancement.
* 95% CI around adjusted difference does not cross zero [†] All regressions were performed on measurements at 6 months with adjustment for baseline DBP (mean of 2nd&3rd). [&]Wall thickness measured in the basal slice of the short axis stack in 6 segments: anterior, lateral, inferior, inferolateral, inferoseptal, septal. [$]Diagnostic T1 mapping data obtained in n=165; n= 89 intervention vs n= 76 control. [!]Diagnostic T2 mapping data obtained in n=131 as this was only added following a protocol amendment whilst the trial was running; n=73 intervention and n =58 control). [^]Diagnostic LGE images were obtained in 34 non-breast-feeding participants for this exploratory work; n=14 intervention and n=20 control. 12 had patchy RV/LV inferior insertion point enhancement and 1 participant had a faint mid-wall band.

These results, seen in the above table (table 10 of this chapter), demonstrate that whilst there was no significant difference in the haemodynamic measures, as was seen with the echo data (HR, CO and CI were all similar), there was clear evidence of left ventricular remodelling (LV) in the intervention arm, in keeping with the echo findings described previously. The parameters presented here have been indexed to BSA, and then again to height, to reduce the impact of differences in participant size on the results.

There was a significant reduction in the LV volumes (LV EDV and LV ESV when indexed to BSA; -3.94 ml/m^2 for LVEDVi (95% CI -6.8 to -1.04; P= 0.008) and a -3.25ml/m^2 reduction in LVESVi (95% CI -4.86 to – 1.63; P = <0.001). This reduction in LV diastolic and systolic volumes was accompanied by a reduction in LV mass, whether indexed to BSA or height (LVEDV/H) or the LV end diastolic volume itself (LVmass/LVEDV). All three measures of LV mass demonstrated a significantly lower LV mass in the intervention arm, providing convincing evidence of the reliability of these between group differences. The gold standard used in clinical practice (LV mass/BSA) showed a -6.4g/m^2 reduction in LV mass in the intervention arm compared to the usual care arm (95% CI -8.1 to -4.8; P = <0.001). Not

unsurprisingly, this reduction in LV mass was accompanied by a reduction in the mean LV wall thickness (mean of 6 measures taken from the basal slice of the short axis stack in 6 segments: anterior, lateral, inferior, inferolateral, inferoseptal and anteroseptal), with a 1.26 mm reduction in mean LV wall thickness in the intervention arm by 9 months postpartum (95% CI -1.46 to -1.06 P = <0.001). This was similar and supportive of the change in echo wall thickness described above. As per echo, this remodelling resulting in a significant improvement in LVEF (2.58%; 95% CI 1.27 to 3.89, P = <0.001). The degree of LV remodelling described above was not mirrored by a similar degree of RV remodelling. Whilst there was a 2.7% higher RV ejection fraction (RVEF) in the intervention arm, there was no significant difference in RV EDV when indexed to BSA (RV EDVi) with the 95% confidence intervals crossing zero; but there was still a slightly significant reduction in RV end systolic volume when indexed to BSA (-2.43 ml/m^2; 95% CI -4.35 to -0.51, P = 0.014). Further analysis will be needed to evaluate if RV mass differs between the two arms and to explore the RV remodelling further.

There was also exploratory work done as part of the POP-HT trial to start to start to explore the mechanisms behind the LV remodelling. The T1 mapping (ShMOLLI), performed in n=165, and the T2 mapping performed in n= 131, as it was introduced later as part of an amendment, showed no significant differences between the intervention and control arms. The mean T1 values were 1161.2ms (26.4) in the intervention arm and 1155.1ms (26.1) in the control arm. A 'healthy' reference range based on 16 age matched females (mean age 32.2yrs) produced a normal T1 range for our 3TESLA SIEMENS PRISMA® scanner of 1141-1195ms with a mean value of 1166ms (18.42). The mean T1 values were thus within the normal range for both arms of the trial. The mean T2 mapping value was 41.1ms (1.8) in the intervention arm vs 40.9ms (1.7) in the control arm. The normal reference range based on the 15 healthy women described above was 38.8 to 43.3ms with a mean of 40.91ms (SD 1.3). Again, both arms of the trial were well within the normal range of T2 mapping values by a mean of 258 days postpartum, suggesting there were no global myocardial inflammation/oedema at the time of their final assessment.

Optional late gadolinium imaging was also offered to those participants who were not breast-feeding at the time of the cardiac MRI scan (and a total of n=34/36 had diagnostic late gadolinium imaging

performed; n=20 intervention vs n=14 control; 2 LGE participants being of too poor quality to include). The results of these 34 participants showed patchy fibrosis at the RV/LV insertion points in 12/34 cases with one case displaying a faint mid-wall band (but no corresponding oedema/fibrosis was seen on T1/T2 or ECV calculations). The cases of insertion point fibrosis occurred in both arms (n= 7 intervention and n= 5 control.) There were also no differences in the ECV values between the two arms in this small exploratory sample size of n=34.

Additional detailed sensitivity analyses (**see tables 11-16 of appendix F**) were performed to assess the impact of the various factors that could have influenced LV remodelling, beyond the intervention itself, as described above for the echocardiography data. It is important to note the trial was not powered for such sub-analysis and so limited conclusions can be drawn from such findings. These analyses included the following multivariate linear regression models to assess:

1. **The impact of antenatal diastolic blood pressure on LV remodelling**

Two separate sensitivity analyses demonstrated that the LV remodelling (shown above in table 10 of this chapter) were reproducible when the data were adjusted for:

a) Antenatal differences in diastolic BP (DBP), as was done for the primary outcome data presented in chapter 5 and for the echo data in this chapter;

b) The 24hr overall average DBP at 6-9 months postpartum.

The LV remodelling remained significant in both of these sensitivity analyses, as seen in tables 11 and 12 of appendix F, with P values remaining at <0.001 for all parameters tested except LVEDVi, which still remained significant at P=0.012 for model a) above and P=0.023 for model b).

2. **The impact of ethnicity on LV remodelling**

Table 13 demonstrates that the indexed LV end diastolic and end systolic volumes, LV mass and LV wall thickness all remain significantly lower in the intervention vs. the usual care arm even when differences in ethnicity were adjusted for, although the baseline characteristics table (in Chapter 5; table 1) showed that the groups were well-matched anyway in this regard. Similarly, the improvement in LVEF of >2.5% also remain significant (+2.55 adjusted difference; 95% CI 1.24 to 3.86, P = <0.001)

3. **The impact of differences in the number with a prior hypertensive disorder of pregnancy (HDP) in each arm**

As table 1 in Chapter 5 illustrated, the only really difference between the two arms of the trial in baseline characteristics was in the number of women who had had a prior hypertensive pregnancy. In the intervention arm 30 (26.8%) had an HDP previously vs 10 (9.3%) in the usual care arm. A sensitivity analysis was thus performed to evaluate the impact this may have had on LV function and LV remodelling given it is now well described in the literature that prior HDPs result in long-lasting changes to the heart [105]. This sensitivity analysis (seen in table 14 of appendix F), demonstrated the beneficial effects on LV function and LV remodelling (LVEDVi, LVESVi, LV mass and LV wall thickness) became even greater when this adjustment was made i.e. the significance of the difference between the indexed LV volumes between the intervention vs control arms strengthens (P value drops to 0.005 from 0.008) when removing the legacy of prior adverse remodelling from the last HDP.

4. **The impact of prescription of an ACEi (Enalapril) for at least one month on LV remodelling, and also the impact of duration of postnatal anti-hypertensive treatment**

As explained previously, a greater number of women received Enalapril over the total study duration in the intervention arm vs the usual care arm (60 (57%) vs 42 (43%)), although there was no meaningful difference between those receiving it for at least one month postpartum (44.6% of those in the usual care arm vs 46.3% in the intervention arm). As with the echo data shown above, an additional exploratory sensitivity analysis was still run to evaluate the potential impact differences in levels of ACEi prescription may have had on the cardiac MRI results described in table 10. Table 15 of appendix F contains the results of this particular sensitivity analysis. This analysis demonstrated that when adjusted for differences in the prescription of Enalapril between the two arms of the trial, there was no significant impact on the beneficial cardiovascular remodelling in the intervention arm described in table 10. Significant improvements in LVEF remain at >2.5% (+2.51%; 95% CI 1.20 to3.82 with P<0.001). The reductions in LVEDVi, LVESVi, indexed LV mass and mean wall thickness all remain at comparable levels with all P values <0.001 except LVEDVi where -3.96 ml/m^2 is at P=0.008.

One final sensitivity analysis was performed to assess the potential impact that differences in total duration of postnatal treatment may have had on LV function and remodelling (see table 16 of appendix F). As for the echo data, this table demonstrated that the total duration of post-natal anti-hypertensive treatment which varied slightly between the two arms, albeit not significantly (mean 67.7 vs 60 days treatment in the intervention vs control respectively) had no impact on the statistical significance on the MRI measured beneficial LV remodelling.

III. Vascular remodelling results

As described in Chapter 4, Section e), a Vicorder® device was used to measure central/aortic blood pressure, aortic stiffness (augmentation index (AI%)), and pulse wave velocity (PWV m/s). As the data completeness section of this chapter describes data were obtained in 219/220 enrolled at baseline and paired Vicorder® data were obtained in 194/202 (96%) of those still enrolled at the time of their final study visit V4 with 102 remaining in the intervention arm vs 92 in the usual care arm. Augmentation index results below were adjusted for maternal heart rate in the model.

The table below (table 17 of this chapter) shows a comparison of the baseline and V4 values for the intervention vs. usual care arms. Independent samples T-test showed no significant difference between the two groups in the baseline data, but the V4 data were still adjusted for the baseline values in the adjusted regression coefficients shown, as has been done with the echo data.
Histograms and Normal P-P plots of standardised regression, were performed using IBM SPSS V28.0.0, as was done for the echocardiography and MRI data described above. These demonstrated a parametric distribution of the data for all parameters shown in the table below. Reproducibility data was not performed on the Vicorder® data due to time constraints during an already 4 hour study visit.

Table 18 of this chapter, which can be seen two pages below, shows the vascular outcomes measures that have been adjusted for the baseline differences in mean diastolic BP (mean of 2nd and 3rd) recorded day 1-6 postpartum during the baseline visit.

Table 17: Comparison of aortic (vascular) remodelling data from baseline to final study visit in POP-HT							
	Intervention		Usual care		Unadjusted regression coefficients[†]		
	Baseline‡ Mean (SD)	V4[&] mean (SD)	Baseline‡ mean (SD)	V4[&] mean (SD)	Difference	95% C.I.*	P value
Vicorder® Parameter							
Aortic SBP, mmHg	134.5 (15.4)	124 (12.5)	133.7 (13.8)	125.9 (13.6)	-1.94	-5.62 to 1.73	P=0.298
Aortic DBP, mmHg	76.4 (10.1)	70.9 (9.7)	74.5 (10)	76.05 (9.8)	**-5.21**	-8.0 to -2.41*	**P=<0.001**
Augmentation index (%)	27.6 (10)	6.72 (6.5)	26.1 (11)	7.48 (7.3)	-0.86	-2.82 to 1.10	P=0.390
PWV (m/s)	11.785 (2.1)	12.7 (2.51)	11.434 (2)	13.3 (2.6)	-0.68	-1.40 to 0.02	P=0.062

Parametric: mean (SD). Aortic SBP, aortic systolic blood pressure; Aortic DBP, aortic diastolic blood pressure, PWV (pulse wave velocity)
V4 (4^{th}) and final study visit which took place between 6-12 months postpartum (mean 258 days; 258.9 intervention and 257.4 usual care).
[†] All regressions were performed on measurements at 6 months with the baseline measurement included in the model.
‡ Baseline 219 participants; intervention n=111, usual care n=108
[&] V4 194 participants; intervention n= 102, usual care n=92
*95% CI around adjusted difference does not cross zero

Table 18: Comparison of aortic (vascular) remodelling data from baseline to final study visit in POP-HT when adjusted for baseline BP differences (mean of 2nd and 3rd baseline BP recorded day 1-6 postpartum)							
	Intervention		Usual care		Adjusted regression coefficients†		
	Baseline‡ Mean (SD)	V4& mean (SD)	Baseline‡ mean (SD)	V4& mean (SD)	Difference	95% C.I.•	P value
Vicorder® Parameter							
Aortic SBP, mmHg	134.5 (15.4)	124 (12.5)	133.7 (13.8)	125.9 (13.6)	-2.08	-5.77 to 1.66	P=0.26
Aortic DBP, mmHg	76.4 (10.1)	70.9 (9.7)	74.5 (10)	76.05 (9.8)	**-5.19**	-7.96 to -2.42•	**P=<0.001**
Augmentation index (%)	27.6 (10)	6.72 (6.5)	26.1 (11)	7.48 (7.3)	-0.74	-2.82 to 1.10	P=0.45
PWV (m/s)	11.785 (2.1)	12.7 (2.51)	11.434 (2)	13.3 (2.6)	**-0.71**	-1.42 to -0.06*	**P=0.048**

Parametric: mean (SD). Aortic SBP, aortic systolic blood pressure; Aortic DBP, aortic diastolic blood pressure, PWV (pulse wave velocity)
V4 (4th) and final study visit which took place between 6-12 months postpartum (mean 258 days; 258.9 intervention and 257.4 usual care).
† All regressions were performed on measurements at 6 months with the adjustment for baseline differences in mean DBP (mean of 2nd and 3rd included in the model) and baseline measures included in the model. ‡ Baseline 219 participants; intervention n=111, usual care n=108
& V4 194 participants; intervention n= 102, usual care n=92*95% CI around adjusted difference does not cross zero

The results in tables 17 and 18 above demonstrate a significant difference in aortic (central) diastolic blood pressure (adjusted mean difference -5.21mmHg; 95% CI -8.0 to 2.21; p=<0.001), in keeping with the findings described in Chapter 5 for peripheral blood pressure measures using both 24hour ABPM and clinic sphygmomanometry. However, the same change was not seen in aortic systolic blood pressure as was described for peripheral systolic BP. Furthermore, the augmentation index and pulse wave velocity did not show significant differences between the two arms of the trial in the unadjusted data shown in table 17 above, although there was a trend towards a lower pulse wave velocity in the intervention arm by 9 months postpartum (unadjusted difference was -0.67m/s with P=0.062). When additional adjustment was performed for the differences in baseline mean diastolic BP between the intervention and usual care arms, the difference in pulse wave velocity does become significant (adjusted difference -0.71m/s; 95% CI -1.415 to -0.006; p=0.048). The lower PWV seen in the intervention arm was in keeping with the aortic DBP being lower and suggests better aortic compliance (relaxation) in the intervention arm. The fact that the aortic SBP difference between the arms was non-significant supported the findings described above for systemic vascular resistance (SVR), derived from the echo data i.e. this suggests there has not yet been translation into widespread vascular remodelling of the small and medium sized vessels that help govern SVR [146].

IV. Discussion

Beyond the AHA recommendation of incorporating HDPs as a risk-enhancing factor to guide statin prescribing, no other specific guidelines exist to direct screening strategies or interventions for long-term cardiovascular risk reduction in these women. Consequently, despite the well-described association between HDP and CVD, pregnancy history is not incorporated into post-pregnancy preventive care consistently.

As described in the introduction (Chapter 1; section V) normal pregnancy is itself associated with substantial cardiac and vascular remodelling over a period of nine months [36]. The added burden of hypertension, in combination with the acute inflammatory, anti-angiogenic and oxidative stress of a hypertensive pregnancy, results in additional significant adverse cardiovascular changes [37, 38, 141] such as left ventricular hypertrophy (LVH) and diastolic dysfunction and reduced GLS [105]. In a proportion of those who had hypertension during pregnancy, echocardiogram-based differences can still be observed up to one year after delivery [36, 39, 145]. In fact, in 2011 Melchiorre et al demonstrated that persistent LV dysfunction and/or the presence of LV hypertrophy at one year postpartum, in women who had preterm preeclampsia, were strongly associated with the risk of development of essential hypertension within the subsequent 2 years. Such correlations were also described based on MRI based follow up of HDPs 5-10 years postpartum, which demonstrate that these adverse remodelling changes persist longer-term and may well be related to their increased life-time risk of CV disease. In a 2020 paper, Boardman et al showed that 100 women who had had a HDP had a higher left ventricular mass index (49.9±7.1 versus 46.0±6.5 g/m^2; *P*=0.001) and left atrial volume index almost a decade after the index pregnancy, when compared to 73 normotensive controls [60]. These differences remained after adjustment for blood pressure (*P*=0.01, and *P*=0.04, respectively), suggesting that the maladaptation in cardiac structure and geometry, occurs independent of blood pressure. If differences in LV geometry do occur prior to pregnancy, a relatively thicker and stiffer heart might be relevant in the development of HDP as it is less able to adapt to the physiological challenges of pregnancy, and hence this may explain the higher incidence of HDP in those with essential hypertension [136]. In normotensive pregnancy diastolic function is reduced [147,

148] with greater dysfunction found in pregnancies complicated by preeclampsia [39]. If less diastolic reserve is available prior to conception this might be a key factor in the development of an adverse cardiovascular phenotype during pregnancy.

Several studies report higher LV mass in women during pregnancy who have preeclampsia. Hamad et al [149] showed greater LV mass index compared to normotensive pregnant cohort (60 g/m^2 vs 45 g/m^2) together with reduced diastolic function. In a small echo based study, Simmons et al [150] (n=71) explored longitudinal changes in LV mass between women with normotensive and pre-eclamptic pregnancies and found that in normotensive pregnancies LV mass index increased from 66±13 g/m^2 in the first trimester to a peak of 76±16 g/m^2 in 3rd trimester before returning to 67±11 g/m^2 at 13 weeks postpartum. Interestingly the attenuation of LV mass index in the early postpartum period in women with a history of preeclampsia reported by Simmons et al [150] suggests two possible explanations. Either that the LV structural differences associated with hypertensive pregnancy are attenuated after delivery, or that there are distinct phenotypes within the group of hypertensive pregnancies, those at lower cardiovascular risk whom have resolution of LV mass after delivery vs those at higher risk who maintain elevated LV mass. The latter theory was supported by a study by Ghossein et al [57] who reported increased indexed LV mass measured at nine months postpartum, in women with initial normalisation of blood pressure after a history of preeclampsia, was predictive of developing hypertension by 6 years postpartum.

It was thus vital to look at targeted interventions in this cohort of women that can reduce long-term cardiovascular maladaptation and in turn, perhaps reduce the increased cardiovascular risk that exists. There have been some recent promising trials in the past few years. SNAP-HT [56] and SNAP-HT Extension [88] described in this thesis at length together suggest there may be a long-term BP benefit from postpartum BP intervention, but these were not adequately powered and did not assess the impact on cardiovascular remodelling/phenotype. Shortly after, the PICk-UP trial published in October 2020 [75]. This was a randomised double-blind placebo-controlled feasibility trial in early onset preeclampsia, which showed that specific pharmacological intervention (ACEi) can reverse the adverse LV remodelling seen during the pregnancy (at randomisation, 88% of women had diastolic dysfunction and 68% had

concentric remodelling/hypertrophy). After six months' treatment with enalapril (5mg once daily for 1 week, then 10mg for 2 weeks then a 20mg maintenance dose), alongside their other anti-hypertensive therapy, there was significantly better diastolic function vs. those treated with placebo alongside their normal anti-hypertensive therapy, as measured by E/E' (adjusted difference -1.07, 95% CI -2.08 - -0.06, p=0.04). Allocation to enalapril was also associated with improved LV remodelling at 6 months, compared with placebo (LVMi measured by echo showed an adjusted difference of -9.23g/m^2, 95% CI -7.73 - -0.71, p=0.03). There was no significant difference in LV or RV systolic function (measured by LVEF / GLS / S') but the sample size was small (n=19 enalapril vs. n = 21 in placebo by 6 months). The supplementary tables published along with this paper revealed a significant improvement in the diastolic BP in the intervention arm; 79.6 (10.9) mmHg in the ACEi group vs 86.9mmHg (10.6) in the placebo group. This raises the question of whether it was diastolic BP lowering in the puerperium itself, like that achieved in SNAP-HT and POP-HT, which resulted in the beneficial cardiovascular remodelling, or whether it was driven by the ACEi, which are known to be able to bring about such beneficial remodelling. The HOPE study [151], was a seminal study supporting the cardio-protective effects of ACE inhibitors. The HOPE study, during which participants at high risk of CVD were randomised to Ramipril or placebo, was stopped prematurely due to a 22% reduction in myocardial infarction/cerebrovascular accident/death from CVD, irrespective of hypertension or other confounders. Given NICE introduced Enalapril as 1st line postnatal drug for White-Caucasian women in NICE NG133 in July 2019, there were a larger number of women being prescribed it by the time of POP-HT. The POP-HT trial data presented in this chapter shows conclusively that the intervention can not only improve BP postpartum but also improve/reverse the adverse cardiovascular remodelling, described above and in the introduction. Additional sensitivity analyses described in this chapter were done to determine if the remodelling occurred independent of a prolonged period of ACEi prescription.

Cardiovascular remodelling in POP-HT

Both the echo and cardiac MRI data from POP-HT provide overwhelming evidence for the potential beneficial cardiac remodelling that can be achieved through postpartum physician optimised BP self-

management in the first 6-9 months after a hypertensive pregnancy. The detailed sensitivity analyses on both the echo and MRI data suggest the remodelling was driven by the intervention itself rather than total duration of post-natal treatment, specific use of agents such as enalapril, or by remaining on anti-hypertensive treatment at 6-9 months. The remodelling benefits described persist despite adjustment for any/all of these factors. Interestingly, the sensitivity analysis in table 15 of appendix F, which adjusted for the use of ACEi for a prolonged period (>28 days) did show some impact of the ACEi on diastolic function. There was no real dilution of the effect on the postpartum physician-guided BP self-management improvements on LV systolic function or LV remodelling (LV EDV/LV ESV/LV SV and wall thickness), but as mentioned previously limited conclusions can be drawn from this given that the trial was not powered to investigate this. One can merely hypothesise that diastolic function remains malleable for a longer period and may be more greatly influenced by ACEi. The fact that the significant diastolic differences (Medial and Average E/EI' and Average E') seen in table 1 of this chapter were lost, when adjusting for the diastolic BP differences between the groups at 6-9 months on 24hr ABPM, may also suggest that DBP is still influencing the remodelling process at the 9-month mark.

Therefore, keeping DBP low beyond 9-12 months likely remains important, even though LV geometry and systolic function appears to be remodelled earlier in the puerperium, given these particular parameters remain largely unchanged between the groups in these sensitivity analyses. The ability of the intervention to maintain a DBP improvement out to 4 years, as shown in SNAP-HT Extension may thus be vital.

Together this data suggests that combining self-management with the use of ACEi will likely achieve the maximum benefit for diastolic function, and that in PICk-UP the DBP improvement of >7mmHg at 6 months in the Enalapril arm may have been driving part of the remodelling alongside the ACEi themselves. Further work is needed to explore these particular hypotheses however.

The sensitivity analyses, which consider the impact of a prior HDP on LV remodelling (contained in table 5 of the echo sensitivity analyses of this chapter and appendix F, table 14, of the MRI sensitivity analyses), demonstrate the intervention also has the capacity to benefit those who have prior adverse

remodelling from a previous HDP. Although this cohort were excluded from POP-HT, his raises the interesting question about whether the intervention could also benefit those who have a HDP super-imposed on chronic HTN. This is something that could also be evaluated in the recently funded SNAP-HT-2 multi-centre RCT.

Vascular remodelling

The vascular remodelling data showed that the intervention also resulted in a significant improvement in aortic DBP and this was associated with an improvement in Pulse wave Velocity (PWV) when adjusting for baseline differences in mean DBP between the two arms. These data suggest that aortic compliance can be improved, although the SVR data derived from echo did not differ between the two trial arms. Together this suggests that by 9 months, beneficial changes in aortic compliance have are not accompanied by widespread improvements in vascular resistance in the small and medium sized blood vessels. Further work on the retinal data and aortic distensibility currently being analysed is needed to explore this in more detail.

V. Strengths and Limitations

Strengths of the study

The sample size was adequately powered, even when allowing for the dilution afforded by the provision of home monitoring during COVID-19 (n=18 recruited pre-pandemic with n=202 recruited after) to detect changes in BP as a result of the intervention. The trial had excellent recruitment, retention and intervention adherence rates as described in chapter 5.

It was the first study to use both CMR and echo, utilising the strengths of each modality to collect a comprehensive set of measurements encompassing structural and functional measurements of both the RV and LV in a population with a history of HDP. Although other studies have explored LV geometrical changes following HDP, this was the first to explore changes from baseline to one year postpartum using MRI and with mechanistic sequences (T1 and T2 maps and the use of late gadolinium enhancement) to try and explore the mechanisms behind the BP improvement seen in SNAP-HT and reproduced in POP-HT.

This was also a trial that evaluated the potential benefit of a postpartum intervention that was both acceptable and well tolerated and so offers the chance of making a tangible difference to real-life clinical practice in the UK and beyond.

Limitations of the study

Due to the nature of the intervention it was impossible to remain blinded to treatment allocation, particularly after COVID-19 meant that the same team member had to deliver and instruct participants on how to use the intervention for those allocated to this arm. This was the reason the study design was adapted to PROBE and not a true single blinded prospective RCT as had been planned in version 1 of the study protocol.

There was a majority (>80%), white Caucasian population, due to the nature of the local population demographic and the patient flow through the Oxford Women's centre. Therefore, extrapolating the results to predominantly Asian or Afro-Caribbean populations is difficult, although there are lessons to learn from the intervention arm data on how to increase patient engagement in populations of lower socio-economic grouping, and in BAME (British Asian and Minority Ethnicity communities), but additional follow up qualitative work is needed to further address this issue.

The provision of self-monitoring to the control/usual care arm may have diluted out some of the benefit seen in SNAP-HT and SNAP-HT Extension. This is further explained in the power calculations section of Chapter 4, but the over-recruitment to 220 and large sample size appear to have largely protected against this.

Furthermore due to time and cost restrictions I was not able to perform intra-participant variability on the echo, Vicorder® and MRI measures.

There was also no doubt that COVID-19 had an impact on the trial through increased use of remote follow up for V2 and V3 study visits, resulting in more 24hr BP data having to be excluded at V3 than it would have if done in person (comparison between the V3 and V4 24HR ABPM rejection rate supports this assumption). It also meant that fewer people attended in person for the final visit due to relocation, travel restrictions or emigration and so the numbers with imaging based secondary and tertiary outcomes were slightly lower than may have been achieved without a global pandemic.

Chapter 7 – OVERALL CONCLUSION AND FUTURE WORK

The questions I set out to answer during my DPhil and in this thesis were the following:

1. ***Do traditional hypertensive risk factors dilute out the benefit of BP self-management evident 0-6 months postpartum or could BP trajectory be reset through self-management?***

This was answered through the SNAP-HT Extension study carried out during the 1st year of my D Phil which demonstrated a long-lasting diastolic BP improvement of -7.4mmHg in the self-management arm, which persisted even after adjustment for risk factors such as BMI, inactivity, age, salt and alcohol intake. This finding suggested there was a real tangible reprogramming of BP trajectory but the sample size was small (n=62) and the original trial was under-powered to detect BP differences as its primary outcome. This led on to the planning of the POP-HT trial whilst the SNAP-HT Extension study was running, which aimed to answer questions two and three outlined below and to provide convincing evidence of whether BP self-management could be a treatment strategy that truly alters BP control and the adverse CV remodelling so well described in the HDP cohort.

2. ***Could I demonstrate reproducibility of the BP lowering benefit of self-management in this cohort in a definitive trial powered to detect differences in diastolic BP, whilst maintaining safety and feasibility?***

The results presented in Chapter 5 conclusively show that the POP-HT intervention resulted not only in diastolic BP improvement, as in SNAP-HT, but also a large systolic BP improvement, both for clinic readings and 24hr ABPM. An almost 6mmHg of DBP and 7mmgHg or SBP benefit was seen in the intervention arm when assessed by ABPM, the gold-standard method, and >4mmHg DBP and >5mmHg SBP improvements were also seen in clinic readings at the ~9-month timepoint postpartum.

Furthermore, there was a large reduction in the number of post-natal readmissions attributed to BP issues (29 in the control arm vs 8 in the usual care arm), which has huge implications in terms of cost-effectiveness, participant (future patient satisfaction/experience), and resource allocation. This was supported by E5-5D-5L data throughout the trial wither higher VAS scores (out of 100) by trial completion in the intervention arm (88.8 (11.2)) vs 85.1 in the control arm (14.2). Whilst there were a small number of readmissions in the whole trial cohort unrelated to BP, due to wound infections, baby

jaundice and similar episodes (detailed further in Appendix E), the four non-blood pressure related admissions were split equally across both groups (two in each arm) and were all expected events (jaundice, sepsis, wound infection, mastitis). There were no SAES/adverse events in the trial, based on the list stipulated in the full study protocol so safety was maintained.

With recruitment and retention rates at ~90% throughout the trial and intervention adherence at >75% trial fidelity was also maintained as in SNAP-HT.

For the first time, POP-HT has shown that self-management of BP (albeit physician/doctor guided due to MHRA safety stipulations on using a novel app), can improve both systolic and diastolic BP by 9 months postpartum in a trial definitely powered to detect DBP improvement as its primary outcome. Furthermore, the SNAP-HT Extension study showed for the first time that this BP improvement can be maintained to almost 4 years postpartum, with only marginal dilution (by salt intake) from traditional hypertensive risk factors.

Together these studies, which built upon the earlier work described in SNAP-HT, will help redefine the postpartum management of women affected by HDP. It was useful to first consider how the SNAP-HT and POP-T studies differ before considering the wider implications of this body or work and discussing future implications and future work that is needed to translate this current body of work into real-world clinical practice in the UK, and eventually beyond.

How do the SNAP-HT and POP-HT trials differ?

This is summarised most easily in the figure on the following page, which is a side: side comparison of the key trial features.

Figure 22: Comparison of the SNAP-HT and POP-HT Trials

	SNAP-HT	**POP-HT**
Study Design	Unmasked RCT	PROBE
Target population	HDP day 1-6 postpartum	The Same
Sample size, n	91 (45 intervention; 46 control)	220 (112 intervention; 108 control)

Primary outcome	Feasibility: specifically, recruitment, retention, and compliance with follow-up rates	24hr overall average DBP
Secondary outcomes	BP control and safety	All other 24hr ABPM parameters and clinic BP measures Measures of LV function and remodelling and vascular stiffness Safety
Intervention	SNAP-HT SMS based app with automated down-titration with SMS supervision for those with high BP needing readmission	POP-HT Bluetooth enabled app with physician overseen down-titration as per SNAP-HT using same BP thresholds (seen in appendix C). Novel uptitration using new BP thresholds to trigger medication adjustment. Safety net for up-titration threshold 159/109mmHg i.e. >160/110 triggered automatic admission to maternity unit (see appendix C)
Control	Usual NHS-led care by community mid-wives and GPs	As per SNAP-HT (NHS-led care) buts RCOG update advised provision of home monitoring for first week during COVID-19 – given to participant 19-220
Number completing follow up, n (%)	82 (90%)	202 (92%)
Postnatal readmission, n (%)	8 total (9%): 5 (11%) intervention; 3 (7%) control	37 total (17%): 8 (7%) intervention; 29 (27%) control
Number on AHT at trial end, n	3* (1 intervention; 2 control), which is 4% of those completing follow up	24 (16 intervention; 8 control), which was 12% of those completing follow up

Baseline Characteristics		
Age, (SD)	31.7 (5.3)	33.1 (5.0)
Mean BMI, kg/m^2 (SD)	28.5 (7.9)	28.4 (6.4)
Ethnicity (%)	82% White Caucasian	81.8% White Caucasian
Diagnosis	GH 46% PET 54%	GH 39.5% PET 60.5%
Median gestation at delivery, weeks (IQR)	37.4 (36.2-39.2)	39.1 (37.0-40.4)
% with SCBU admissions	26%	28.2%
Median duration antenatal AHT treatment, d (IQR)	9 (5-22)	4 (1-17)
Mean WHO DDD of AHT at baseline visit	1 (0.7-1.5)	1 (0.7-1.7)
Mean SBP/DBP at antenatal booking visit, mmHg (SD)	119.2 (14.1)/72.7 (9.3)	118.0 (12.6)/74.0 (9.1)
Mean SBP/DBP (readings 2+3) at baseline visit mmHg (SD)	132.9 (14.1)/86.2 (9.8)	128.1 (13.4)/82.3 (10.8)

*****4 were excluded from this analysis in SNAP-HT as they had an incomplete medication end date

This figure demonstrates that the two trial populations were actually well matched in terms of demographics, anthropometry, disease diagnosis and severity (judged by % of SCBU admissions, gestation at delivery and mean WHO DDD of anti-hypertensives (AHT)), albeit with small differences in some of these parameters. The main difference, sample size aside, was the intervention.

In SNAP-HT, which was governed by automated down-titration, rather than being physician/doctor overseen semi-automated down and up-titration, the total medication dose did not differ between the groups, and the mean duration of treatment in the intervention arm was actually less (39 vs 49

mean number of days on treatment). What was similar between SNAP-HT and POP-HT however was the fact more time was spent in the therapeutic/target BP range in POP-HT when this data presented here is compared to that published for SNAP-HT [56]). This suggested an element of 'remodelling' may be occurring during the puerperium driven by 'tighter' BP control. The POP-HT trial now allows us to confirm for the first time that this is indeed the case as shown by the Echo, MRI and vascular indices of systolic and diastolic function, LA volumes and LV wall thickness and mass described in chapter 6.

The POP-HT trial has also demonstrated the 'real-life' benefit that offering up-titration can have when compared to SNAP-HT. In SNAP-HT there were a balanced number of BP readmissions in the first few weeks postpartum (5 self-management vs 3 usual care with no significant difference when considering the adjusted incidence rate; 2·0 (0·6 – 6·2) [56]. However, during POP-HT of the 37 BP related readmissions during the entire trial period, only 8/112 were in the intervention arm (7%) vs. 29/108 (27%) in usual care, with a 20% absolute risk reduction in readmission. 22 admissions were avoided in the intervention arm by safely up-titrating during day one to ten postpartum, and then avoiding the need for admission. This was done with no adverse outcomes resulting. The 8 that were still readmitted were due to their BP straying into the red range stipulated in the telemonitoring specification (see appendix B) i.e. >160/110mmHg. This did not result in any adverse outcomes for these eight.

Another interesting difference between SNAP-HT and POP-HT were numbers on treatment by study completion. In POP-HT, by 6-9 months twice as many women were on treatment in the intervention arm vs. the usual care arm (16/112 vs 8/108 respectively), vs SNAP-HT where the supplementary published data shows there was 1/45 in the intervention vs 2/46 in the usual care remaining on treatment at 6months. This may be due to the enhanced and prolonged, self-monitoring afforded during COVID-19 in both arms, as well as fewer face-face NHS reviews to stop treatment in the usual care arm. In the intervention arm, a small number of women actually restarting treatment (n=3/16) due to a late recrudescence of the BP at the four-five month mark, perhaps driven by incomplete reversal of their adverse cardiac remodelling. Indeed these 3 women had higher BP during the first 6 weeks than the overall average of the intervention arm during week 1 (V2) and week 6 (V3), which would support this hypothesis. The increased monitoring, afforded by weekly app® uploaded BP

measurements, allowed these women to restart treatment when needed and highlights the importance of ongoing monitoring after treatment cessation. In women where there has been persistence of adverse remodelling, it is known this recrudescence occurs, as reported by Melchiorre et al and Ghossein et al [39, 57].

3. *Does improved postpartum BP control translate into reduced end organ damage in the cardiovascular system by a time-point of 6 -9 months postpartum?*

HDP and CVD share common pathophysiological pathways and markers such as endothelial dysfunction, inflammation and angiogenic factors [145]. These findings have led to the acknowledgement of HDP as a crucial female-specific risk factor for CVD and their inclusion as a risk factor in international guidelines [11, 76]. However, there is no consensus regarding clinical policies on optimal screening, prevention, and management of CVD risk after pregnancies complicated by HDP. Although further studies are necessary to elucidate the mechanisms behind HDP, postpartum preeclampsia is underdiagnosed as postpartum blood pressure monitoring is not universally recommended for women without HDP in the “fourth” trimester [152].

Moreover, due to the lack of recognition, women who develop postpartum preeclampsia are at increased risk of severe maternal morbidity, particularly eclampsia and stroke, than women with the antepartum disease, at postpartum re-admissions [153]. In addition to adverse maternal outcomes, there are other critical issues related to postpartum re-admission, such as a financial burden for the healthcare system and the family distress caused by interrupting early parenting. Risk factors for postpartum readmission for cardiovascular complications include ethnicity, age, multiple gestations, known cardiac disease, history of pregnancy complications and blood pressure levels. These are all identifiable at the time of delivery, regardless of antepartum HDP, and a predictive model based on these risk factors could guide a more tailored postnatal follow-up for these patients, with postpartum self-monitoring with physician oversight forming a pivotal role in their care.

Clinical Relevance of cardiovascular remodelling

Left ventricular hypertrophy has been shown to be strongly associated with mortality of any cause, independent of blood pressure [154] and the finding of 8% higher LV mass in women with a history of HDP may explain a proportion of the increase in cardiovascular risk seen in this population [155, 156]. In the Multi-Ethnic Study of Atherosclerosis, a large CMR based study of healthy asymptomatic men and women free of cardiovascular disease, a 10% increase in LV mass correlated with a 40% increased risk of heart failure events [157]. In 2015 Tsao et al [158] reported on the associations in a large Framingham cohort between both LV mass index and LVM: LVEDV and the future risk of cardiovascular disease over a median follow up of >8 years. They found that for every 10g/m^2 increase in LV mass index there was a 36% increase in cardiovascular disease and for every 0.2g/ml increase in LVM: LVEDV there was an increased risk of 40%. The intervention arm of the trial had a 6.4g/m^2 reduction in LV mass vs the usual care arm, ~60% of that reported in this Framingham cohort. If the relationship was linear, this suggests that the LV geometrical differences achieved would correspond to a relative reduction in cardiovascular disease burden of >20%.

The finding of higher LV ejection fraction in women both on echo (+1.79%; P=<0.001) and MRI (+2.58%; P=<0.001) may be due to differences in sympathetic activation, known to be increased during hypertensive pregnancy [159], and which persists many years later and drive the increase in LV ejection fraction. However, a more likely explanation was that the improvement in LV ejection fraction reflects a smaller concentrically remodelled LV, a hypothesis supported by the reduced RWT on echo, and reduced mean wall thickness on MRI of ~1.3mm, which was in turn accompanied by reductions in LVEDVi and LVESVi on both imaging parameters i.e. Echo and CMR.

The differences between the intervention and usual care arm across a range of Doppler diastolic measures, and longitudinal measures of systolic function (GLS) on echo, also suggest that there was 'reduced' systolic function as a result of HDP and the higher ejection fraction achieved via the intervention was likely unmasking a ventricle under strain. It is known that diastolic dysfunction predicts clinical heart failure [160] and an increased risk of death [161], and longitudinal follow up

studies such as those of Honingberg from 2019 show such a correlation with an increased risk of heart failure (RR 1.7) following HDP [14]. This cohort would need to be followed up long-term to confirm this association however.

Clinical Relevance of vascular remodelling

Blood pressure has a close and complex relationship with arterial stiffness [162] and there is controversy over the temporal relationship between arterial stiffness and blood pressure [163, 164]. Large arteries are compliant structures and serve to buffer the pressure changes resulting from intermittent ejection of blood into the aorta during systole from the left ventricle. By absorbing a proportion of the energy in systole and releasing it in diastole, peripheral blood flow is smoothed and diastolic coronary artery flow maintained. **Aortic stiffness is an independent predictor of cardiovascular risk and cardiovascular outcome in a variety of patient groups** [165-167]. Increased arterial stiffness is associated with a number of cardiovascular risk factors, including age, gender, smoking, hypertension, diabetes, hypercholesterolaemia and atherosclerosis [168]. I**ncreased stiffness may precede the onset of clinically overt atheromatous disease.** Therefore, improved detection of changes in stiffness may allow early identification of individuals at risk, at a stage when intervention might be of most benefit. **Arterial stiffness can be assessed by a variety of methods, but aortic pulse wave velocity (aortic PWV) is the current 'gold-standard' measure** [169]. PWV is defined as the time taken by a pressure or flow wave to travel a given distance and PWV can be determined from dual, non-invasive recordings of femoral and brachia artery pressure/flow waveforms, as was done in the POP-HT study using the extensively validated Vicorder ® device [170-172]. These validation studies include populations who were approximately age and sex matched in the more recent systematic reviews [173].

The fact that both the diurnal, and nocturnal, average systolic and diastolic readings were significantly lower in the intervention arm vs. the usual care arm, suggests the overall improvement was not driven merely by a lower peripheral/systemic vascular resistance (PVR/SVR), for which you would expect a drop in the nocturnal diastolic BP primarily [174]. This was further supported by formal SVR calculations

(based on the MAP and cardiac output obtained on echo and MRI), shown in the first of the results tables described in chapter 6. Traditional understanding/teaching has been that young adult systolic hypertension is driven by an increase in stroke volume, with or without elevated arterial stiffness, with the latter usually coming in later life [175]. Prior work in young adults has shown that ambulatory blood pressure during waking hours was related to left ventricular and arterial function, the strongest relations being ambulatory DBP with left ventricular function, and ambulatory SBP with arterial stiffness [176]. In POP-HT, the greatest improvement in BP actually occurred in the diurnal systolic and diastolic BPs, for which there was an approximately 7 and 5 mmHg improvement respectively. This suggests that the mechanism for BP improvement achieved in the first nine months postpartum entails an alteration in stroke volume, as well as an alteration in arterial stiffness.

With vascular stiffening, pulse wave velocity (PWV) and the amplitude of the reflected wave (augmentation index) both increase, such that the reflected wave arrives earlier and increases central systolic pressure[146]. **Aortic PWV is itself an independent predictor of cardiovascular risk [177] and is related to the elastic properties of the arterial wall.** Augmentation index is a surrogate for arterial stiffness. *Pulse wave velocity (PWV) is inversely related to aortic distensibility, which has been measured in the POP-HT trial by MRI*, but the analysis has not yet been completed on the MRI cine data of the aorta.

The results demonstrate that, in keeping with the peripheral BP improvements, the aortic diastolic BP was also significantly lower in the intervention arm (-5.21mmHg; 95% CI-8.0 to -2.41, P=<0.001). This suggests that the benefit achieved via the intervention in the medium sized brachial artery was reflected centrally within the aorta. The fact that there was a small, but non-significant trend in the PWV (-0.67m/s; 95% CI-1.37 to 0.035, P=0.062), which becomes significant (adjusted difference -0.71m/s; 95% CI -1.415 to -0.006; p=0.048) when adjusting for the baseline mean diastolic BP difference between the two arms, suggested that the improvement in aortic BP seen may be resulting in a reduction in aortic stiffness/improvement in aortic relaxation during diastole. Boardman et al showed that HDPs result in reduced aortic compliance (0.240±0.053 versus 0.258±0.063; P=0.046) and

functional capillary density (105.4±23.0 versus 115.2±20.9 capillaries/mm^2; P=0.01) i.e. HDPs lead to altered large vessel (aortic) and small vessel (capillary) function. The changes described for aortic compliance were in fact independent of the BP control at the time of the scan (5-10 yrs. postpartum) [60] suggesting that something during the pregnancy or the puerperium itself is influencing this long-term CV outcome. The aortic distensibility data (remembering that pulse wave velocity (PWV) is inversely related to aortic distensibility) is currently undergoing ongoing analysis and will provide vital complimentary evidence as to whether the intervention trialled in POP-HT can indeed improve the function of large vessels (the aorta) following a hypertensive pregnancy, which in term may alter life-time cardiovascular risk and cerebrovascular risk when taken in the context of the historical studies described above [166]. Nevertheless, taken together with the beneficial cardiac remodelling demonstrated on echo and CMR, the vascular remodelling data already described here suggests the intervention can not only improve BP control, but alter prognostically significant outcome measures in this cohort of patients.

Future work

There is extensive ongoing analysis on the POP-HT trial including processing of the retinal and brain vasculature to determine if the BP lowering seen results in beneficial small vessel remodelling. Exercise echo and CPET data will also explore the mechanistic element further. Additional echo and CMR analysis will allow further exploration of the RV remodelling process. This cohort was highly motivated and offer a chance to monitor the long term BP control, akin to SNAP-HT Extension, as well as longer-term phenotypic changes as they evolve, with the option of intervening through targeted diet and lifestyle interventions e.g. salt reduction, reduction in sedentary behaviour (both groups spent ~19 hours sleeping or sedentary at 249 days postpartum, albeit in a global pandemic and with new babies), to see the impact these have on BP and phenotype. Plans are underfoot for such a POP-HT Extension study. There is also a multi-centre RCT of self-management of BP postpartum following hypertensive pregnancy, SNAP-HT 2, which received NIHR funding at the end of December 2021, for which POP-HT will provide invaluable insight in refining the app based self-management process. In POP-HT, a small number of women required clinician 'intervention' to chase up readings via manual

SMS or phone calls; 6.5% in the first 6-weeks and 6.2% at six-months as shown in Chapter 5; table 6. There was also an increasing prevalence of white-coat hypertension seen with repeated measuring between V3 and V4, more so in the intervention arm. These are both factors that need further behavioral/psychological analysis to feed into SNAP-HT 2 prior to it starting. Moreover, further data are available to review the detailed titration medications, the timings of the titration, and subsequent decisions, which are outside of the work of this thesis, but will feed into SNAP-HT 2. Further processing and analysis of these could allow semi-automation of the up-titration process, which with the relevant safety netting could then be trialled in SNAP-HT 2 to make the process used in POP-HT even more translatable to real-world clinical practice. Lastly, further exploration of the role of ACEi on diastolic dysfunction and its role alongside self-management could be explore as a sub -arm of SNAPHT 2 as considered at the end of Chapter 6.

Conclusion

In summary, the findings in POP-HT suggest that there is a way of regressing LV mass, function and wall thickness to the 'norm' after a period of adverse remodelling caused by HDP, and this in turn may impact on future hypertensive and CV risk. This is as well as having the immediate BP lowering benefits seen in SNAP-HT, SNAP-HT Extension and POP-HT, which could potentially lead to a 40% reduction and 20% reduction in lifetime cerebrovascular and cardiovascular risks respectively.

Despite the clear shift in awareness of the links between HDPs and later cardiovascular disease, ESC and AHA guidance has continued to struggle to be able to advise on best ways to screen or manage the HDP cohort [11, 76] after delivery due to a lack of robust evidence on optimal care pathways. This problem has been compounded by the organisationally complex care arrangements needed between obstetricians, primary care teams and cardiologists to manage this period effectively. The evidence presented in this thesis, alongside previous work on self-management and use of different medications in the post-partum period, now suggests we should be preparing for a paradigm shift in how we manage cardiovascular health post-partum. Effective blood pressure management in the puerperium could have significant impact on the long term cardiovascular health of a large proportion of women.

Chapter 7 – Appendices

Appendix A: Summary of the SNAP-HT EXTENSION study protocol and study outline

Objectives	**Outcome Measures**
Primary To explore whether the SNAP-HT intervention translates into improved longer term BP control compared to the study controls at a time-point of at 36 +/- 12 months since randomisation into the SNAP-HT study	1. Diastolic BP between groups at current time- point as measured by 24hr home ambulatory BP monitor. 2. An interval comparison of BP 'now' to that recorded in the last 6 month SNAP-HT visit for each participant. The newly acquired BP data will thus be linked back to the BP readings obtained at 6 months in the original SNAP-HT database.
Secondary	
1. To assess the quality of life of participants in relation to the original intervention used in SNAP-HT in postnatal women	EQ-5D-5L standardised questionnaire
2. To explore whether variations in diet, exercise levels and estimated daily salt and alcohol intake relate to longer term differences in BP control	Lifestyle and diet questionnaire
3. To explore whether variation in daily activity between the intervention and control arms of the original study relate to longer term BP control	Objective measure of physical activity (7 day wrist worn activity monitor)

Outline of the SNAP-HT Extension study visit

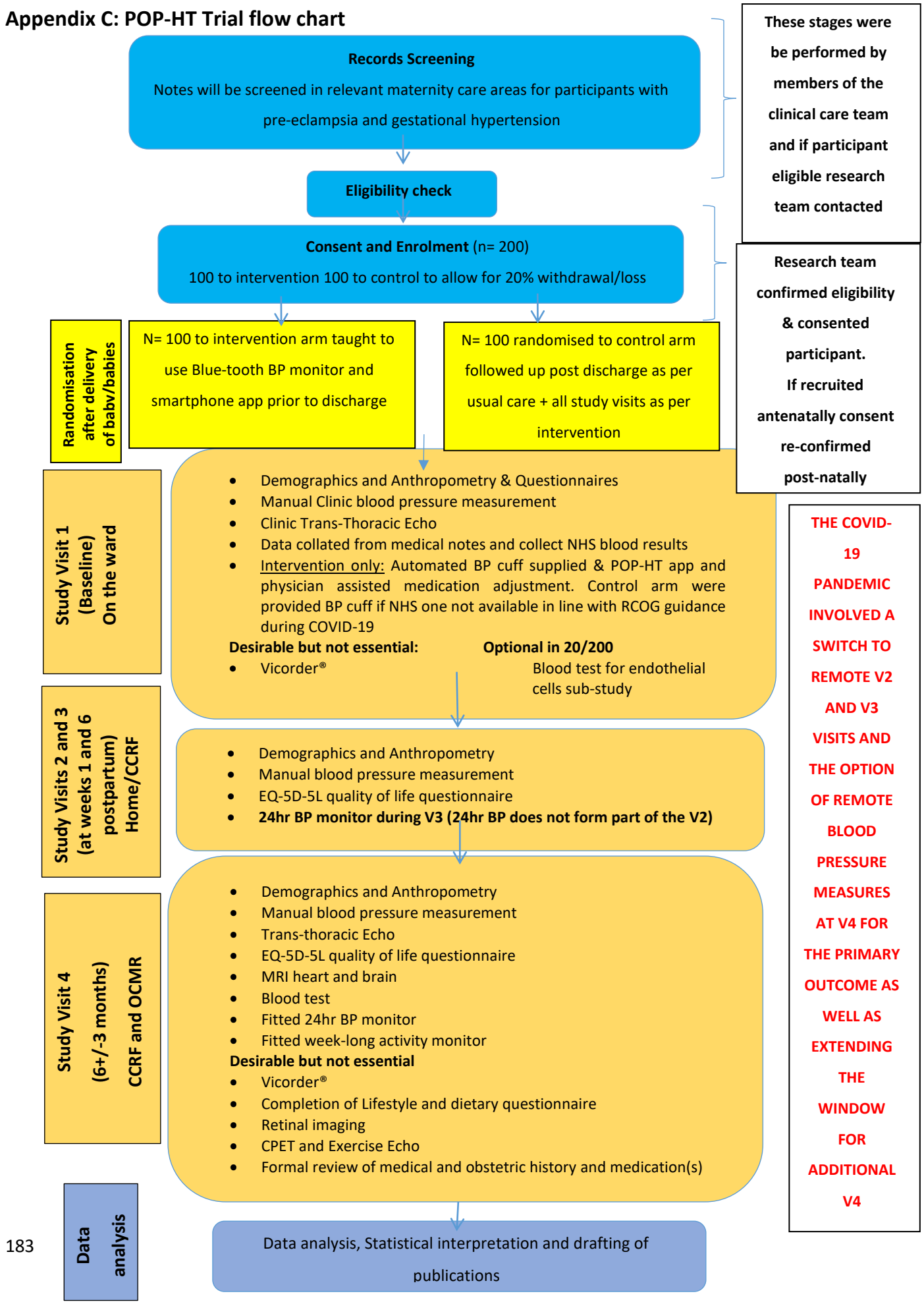
Study Visit	Study Measure	Time (minutes)
	Brief re-explanation of study and opportunity to address any questions participants may have	10
	Eligibility check	5
	Consent	10
	Anthropometry and demographics	10
	Manual BP x 6	10
	Review of medical and obstetric history and any medication side effects	15
	EQ-5D-5L quality of life questionnaire	10
	Lifestyle and diet questionnaire	25
	24 hour ABPM fitting	5
	Activity monitor fitting	5
Total time		**105 mins.**

Appendix B: Tele-monitoring specification for POP-HT

This is written in the present tense as the document was drafted, revised and locked prior to the trial starting in February 2020. The template was based on SNAP-HT and then refined over a 12-month process including several rounds of PPI consultation, expert panel feedback, simulated testing for 3 months and 2 months of real-world testing on the investigators themselves to reflect the version presented here.

This was uploaded separately due to the file size and complexity.

Appendix C: POP-HT Trial flow chart



Appendix D: Statistical analysis plan for POP-HT study

This is uploaded separately due to its size.

Appendix E: Sample data from postnatal readmissions audit for the POP-HT trial (yellow = non BP related readmission)

Study ID	Study allocation	Readmission	Readmission due to BP
POP-HT 01-001	Control	Yes- readmitted few days after discharge as BP high with CMW	Yes
POP-HT 01-006	Control	Yes 07/03- wound infection. Re-admitted 7/3/20 with Fevers and wound infection. WBCs and CRP high - BP low so medication stopped. Given Co-amoxiclav	No
POP-HT 01-008	Control	BP high with CMW	Yes
POP-HT 01-014	Control	Detected at V1 home visit. Emergency admission via the GP to RBH	
POP-HT 01-023	Intervention	Yes-sent by us 06/06 as BP 180/110. D/C 9/6/2020 on higher doses	
POP-HT 01-026	Control	Yes 04/06- UTI	No
POP-HT 01-029	Control	Yes 15/06- CMW high BP	Yes
POP-HT 01-032	Intervention	Yes- 28/06- due to sepsis, BP ok. Re-admitted 29/6/20 due to ongoing fevers and malaise. Seen on level 7 in isolation room. PUO.	No
POP-HT 01-033	Intervention	Yes 16/06 as headaches and BP high	Yes
POP-HT 01-034	Control	Yes 18/06 CMW referral to MAU	Yes
POP-HT 01-038	Intervention	CMW admitted on day 5 check and did not consult app/us. BP 150/110mmHg	Yes
POP-HT 01-041	Control	Yes - Re-admitted at day 6 due to high BP and baby having high Bilirubin level for phototherapy and medications had to be increased for BP. Seen on the ward	Yes
POP-HT 01-046	Control	Yes- 05/07 CMW	Yes
POP-HT 01-056	Intervention	Yes 19/07 - sent in by CMW. I were happy to uptitrate @ home	Yes
POP-HT 01-057	Control	Yes- 19/07	Yes
POP-HT 01-061	Intervention	Yes 26/06 on day 6 postpartum by us. Had trialled uptitration to 10mg bd enalapril	Yes
POP-HT 01-062	Control	Yes -22/07	Yes
POP-HT 01-069	Intervention	Yes 09/08- baby had jaundice causing the admission	No

POP-HT 01-077	Intervention	Yes - 15/08 - CMW asked her to go in not us as BP 155/105. Confusion over pathways	Yes
POP-HT 01-078	Control	Yes 15/08 via her CMW	Yes
POP-HT 01-085	Control	back in hospital for high BP (D/C 04/09/20)	Yes
POP-HT 01-098	Control	PNRA Day 4 as BP >200/100 so called 999	Yes
POP-HT 01-107	Control	PNRA Day 10 as BP high and then d/c on tds enalapril	Yes
POP-HT 01-108	Control	Unable to contact GP. Sent to MAU by 111	Yes
POP-HT 01-111	Intervention	PNRA 5/10.20. Sudden spike (lack of sleep & argument with brother only real trigger). D/C 7/10	Yes
POP-HT 01-115	Control	Readmiited in Poole with high BP and a wound infection	Yes
POP-HT 01-126	Control	Control arm - readmitted due to high BP	
POP-HT 01-132	Control	Control - readmitted with high BP over weekend	Yes
POP-HT 01-137	Control	Control: BP high - CMW came out and sent in to MAU	Yes
POP-HT 01-141	Intervention	CMW came out and sent in to MAU day 7. No app advice sought	Yes
POP-HT 01-156	Control	PNRA on 4/12/2020 - was taking the wrong dose - control arm x 2 admissions	Yes
POP-HT 01-156	Control	2nd re-admission 3 days later	Yes
POP-HT 01-157	Control	PNRA day 5	Yes
POP-HT 01-162	Control	PNRA control arm 9/12/2020 for PP. 2nd admission on 12th with wound dehiscence	Yes
POP-HT 01-170	Control	PNRA 22/12 TO WEXHAM - D/C BACK WITH ADVICE - CONTROL ARM	Yes
POP-HT 01-172	Control	PNRA 29/12 - control	Yes
POP-HT 01-177	Control	PNRA 8/1 - control arm -reviewed and meds increased by us 8/1 pm and back home tonight	Yes
POP-HT 01-188	Control	PNRA 29/01 - home same day - control arm	Yes
POP-HT 01-193	Control	PNRA control arm	Yes
POP-HT 01-199	Control	PNRA control arm	Yes
POP-HT 01-207	Control	PNRA MAU 24/2 by CMW	Yes

Appendix F: Sensitivity analyses on the Cardiac MRI data

Table 11: Sensitivity analysis adjusting LV function and LV remodelling for antenatal diastolic BP			
	Adjusted regression coefficients[†]		
	Difference	95% C.I.*	P value
Systolic function			
LVEF, %	2.50	1.20 to 3.81*	P = <0.001
Remodelling			
LV EDVi (ml/m^2)	-3.68	-6.56 to -0.81*	P= 0.012
LV ESVi (ml/m^2)	-3.06	-4.67 to – 1.45*	P = <0.001
LV mass indexed to BSA (g/m^2)	-6.30	-7.94 to -4.66*	P = <0.001
Mean LV wall thickness[&] (mm)	-1.27	-1.46 to -1.08*	P = <0.001

LV, left ventricular; RV, right ventricular; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; EDVi, end diastolic volume indexed to BSA; ESVi, end systolic volume indexed to BSA; BSA, body surface area, calculated by the MOSTELLAR equation;).

* 95% CI around adjusted difference does not cross zero.

[†] Regressions were performed on MRI measurements at mean 258 days postpartum with adjustment for antenatal mid-wife booking DBP.

[&]Wall thickness measured in the basal slice of the short axis stack in 6 segments: anterior, lateral, inferior, inferolateral, inferoseptal, septal

Table 12: Sensitivity analysis adjusting CMR derived LV function and remodelling for differences between groups in the 24hr overall average diastolic BP at 6-9 months postpartum			
	Adjusted regression coefficients†		
	Difference	95% C.I.*	P value
Systolic function			
LVEF, %	2.99	1.55 to 4.43*	P = <0.001
Remodelling			
LV EDVi (ml/m²)	-3.73	-6.94 to -0.52*	P= 0.023
LV ESVi (ml/m²)	-3.45	-5.24 to – 1.66*	P = <0.001
LV mass indexed to BSA (g/m²)	-5.83	-7.65 to -4.02*	P = <0.001
Mean LV wall thickness& (mm)	-1.16	-1.38 to -0.95*	P = <0.001

LV, left ventricular; RV, right ventricular; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; EDVi, end diastolic volume indexed to BSA; ESVi, end systolic volume indexed to BSA; BSA, body surface area, calculated by the MOSTELLAR equation;).

* 95% CI around adjusted difference does not cross zero.

† All regressions were performed on measurements at 6 months with adjustment for 24hr overall average DBP measured by SPACELAB 90217 ABPM at 6-9 months postpartum (mean 248.8 days).

&Wall thickness measured in the basal slice of the short axis stack in 6 segments: anterior, lateral, inferior, inferolateral, inferoseptal, septal.

Table 13: Sensitivity analysis adjusting CMR derived LV function and remodelling for ethnicity and baseline mean DBP			
	Adjusted regression coefficients†		
	Difference	95% C.I.*	P value
Systolic function			
LVEF, %	2.55	1.24 to 3.86*	P = <0.001
Remodelling			
LV EDVi (ml/m^2)	-3.95	-6.83 to -1.06*	P= 0.008
LV ESVi (ml/m^2)	-3.21	-4.82 to – 1.59*	P = <0.001
LV mass indexed to BSA (g/m^2)	-6.37	-8.01 to -4.73*	P = <0.001
Mean LV wall thickness& (mm)	-1.26	-1.46 to -1.06*	P = <0.001

LV, left ventricular; RV, right ventricular; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; EDVi, end diastolic volume indexed to BSA; ESVi, end systolic volume indexed to BSA; BSA, body surface area, calculated by the MOSTELLAR equation;).

* 95% CI around adjusted difference does not cross zero.

† All regressions were performed on measurements at 6 months with adjustment for ethnicity and the baseline mean (mean of 2nd and 3rd) diastolic BP.

&Wall thickness measured in the basal slice of the short axis stack in 6 segments: anterior, lateral, inferior, inferolateral, inferoseptal, septal.

Table 14: Sensitivity analysis adjusting CMR dervied LV function and remodelling for those affected by a prior HDP and baseline mean DBP			
	Adjusted regression coefficients†		
	Difference	95% C.I.*	P value
Systolic function			
LVEF, %	2.64	1.30 to 3.99*	P = <0.001
Remodelling			
LV EDVi (ml/m^2)	-4.24	-7.20 to -1.27*	P= 0.005
LV ESVi (ml/m^2)	-3.39	-5.05 to – 1.74*	P = <0.001
LV mass indexed to BSA (g/m^2)	-6.51	-8.19 to -4.83*	P = <0.001
Mean LV wall thickness& (mm)	-1.29	-1.49 to -1.09*	P = <0.001

LV, left ventricular; HDP, Hypertensive disorder of pregnancy; RV, right ventricular; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; EDVi, end diastolic volume indexed to BSA; ESVi, end systolic volume indexed to BSA; BSA, body surface area, calculated by the MOSTELLAR equation;).

* 95% CI around adjusted difference does not cross zero.

† All regressions were performed on measurements at 6 months with adjustment for a history of hypertensive disorder in a prior pregnancy and the baseline mean (mean of 2nd and 3rd) diastolic BP

&Wall thickness measured in the basal slice of the short axis stack in 6 segments: anterior, lateral, inferior, inferolateral, inferoseptal, septal.

Table 15: Sensitivity analysis adjusting CMR derived LV function and remodelling for prescription of an ACEi (Enalapril) for >28days duration			
	Adjusted regression coefficients†		
	Difference	95% C.I.*	P value
Systolic function			
LVEF, %	2.51	1.20 to 3.82*	P = <0.001
Remodelling			
LV EDVi (ml/m^2)	-3.96	-6.86 to -1.06*	P= 0.008
LV ESVi (ml/m^2)	-3.18	-4.80 to – 1.56*	P = <0.001
LV mass indexed to BSA (g/m^2)	-6.41	-8.05 to -4.77*	P = <0.001
Mean LV wall thickness& (mm)	-1.27	-1.47 to -1.07*	P = <0.001

LV, left ventricular; HDP, Hypertensive disorder of pregnancy; RV, right ventricular; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; EDVi, end diastolic volume indexed to BSA; ESVi, end systolic volume indexed to BSA; BSA, body surface area, calculated by the MOSTELLAR equation;).

* 95% CI around adjusted difference does not cross zero.

† All regressions were performed on measurements at 6-9 months with adjustment for the prescription of an ACEi for >28 days postpartum, as well as the baseline mean (mean of 2nd and 3rd) diastolic BP

&Wall thickness measured in the basal slice of the short axis stack in 6 segments: anterior, lateral, inferior, inferolateral, inferoseptal, septal.

Table 16: Sensitivity analysis adjusting CMR derived LV function and remodelling for total duration of post-natal anti-hypertensive treatment			
	Adjusted regression coefficients†		
	Difference	95% C.I.*	P value
Systolic function			
LVEF, %	2.55	1.24 to 3.86*	P = <0.001
Remodelling			
LV EDVi (ml/m^2)	-3.95	-6.84 to -1.07*	P= 0.008
LV ESVi (ml/m^2)	-3.22	-4.84 to – 1.61*	P = <0.001
LV mass indexed to BSA (g/m^2)	-6.43	-8.05 to -4.80*	P = <0.001
Mean LV wall thickness& (mm)	-1.27	-1.46 to -1.07*	P = <0.001

LV, left ventricular; HDP, Hypertensive disorder of pregnancy; RV, right ventricular; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; EDVi, end diastolic volume indexed to BSA; ESVi, end systolic volume indexed to BSA; BSA, body surface area, calculated by the MOSTELLAR equation;).

* 95% CI around adjusted difference does not cross zero.

† All regressions were performed on measurements at 6-9 months with adjustment for duration of postnatal anti-hypertensive treatment, as well as the baseline mean (mean of 2nd and 3rd) diastolic BP

&Wall thickness measured in the basal slice of the short axis stack in 6 segments: anterior, lateral, inferior, inferolateral, inferoseptal, septal.

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