

## ORIGINAL RESEARCH ARTICLE



# Cardiac Remodeling After Hypertensive Pregnancy Following Physician-Optimized Blood Pressure Self-Management: The POP-HT Randomized Clinical Trial Imaging Substudy

Jamie Kitt<sup>1</sup>, DPhil; Samuel Krasner<sup>2</sup>, BA; Logan Barr<sup>3</sup>, PhD; Annabelle Frost, MBBS; Katherine Tucker<sup>4</sup>, PhD; Paul A. Bateman<sup>5</sup>, PhD; Katie Suriano, PhD; Yvonne Kenworthy, BSc; Winok Lapidaire<sup>6</sup>, PhD; Miriam Lacharie<sup>7</sup>, MSc; Rebecca Mills, MSc; Cristian Roman, PhD; Lucy Mackillop<sup>8</sup>, MA; Alexandra Cairns<sup>9</sup>, DPhil; Christina Aye<sup>10</sup>, DPhil; Vanessa Ferreira<sup>11</sup>, DPhil; Stefan Piechnik<sup>12</sup>, DPhil; Elena Lukaschuk<sup>13</sup>, MSc; Basky Thilaganathan<sup>14</sup>, PhD; Lucy C. Chappell<sup>15</sup>, PhD; Adam J. Lewandowski<sup>16</sup>, DPhil; Richard J. McManus<sup>17</sup>, PhD; Paul Leeson<sup>18</sup>, PhD

**BACKGROUND:** Hypertensive pregnancy disorders are associated with adverse cardiac remodeling, which can fail to reverse in the postpartum period in some women. The Physician-Optimized Postpartum Hypertension Treatment trial demonstrated that improved blood pressure control while the cardiovascular system recovers postpartum associates with persistently reduced blood pressure. We now report the effect on cardiac remodeling.

**METHODS:** In this prospective, randomized, open-label, blinded end point trial, in a single UK hospital, 220 women were randomly assigned 1:1 to self-monitoring with research physician-optimized antihypertensive titration or usual postnatal care from a primary care physician and midwife. Participants were 18 years of age or older, with preeclampsia or gestational hypertension, requiring antihypertensives on hospital discharge postnatally. Prespecified secondary cardiac imaging outcomes were recorded by echocardiography around delivery, and again at blood pressure primary outcome assessment, around 9 months postpartum, when cardiovascular magnetic resonance was also performed.

**RESULTS:** A total of 187 women (101 intervention; 86 usual care) underwent echocardiography at baseline and follow-up, at a mean  $258 \pm 14.6$  days postpartum, of which 174 (93 intervention; 81 usual care) also had cardiovascular magnetic resonance at follow-up. Relative wall thickness by echocardiography was 0.06 (95% CI, 0.07–0.05;  $P < 0.001$ ) lower in the intervention group between baseline and follow-up, and cardiovascular magnetic resonance at follow-up demonstrated a lower left ventricular mass ( $-6.37$  g/m<sup>2</sup>; 95% CI,  $-7.99$  to  $-4.74$ ;  $P < 0.001$ ), end-diastolic volume ( $-3.87$  mL/m<sup>2</sup>; 95% CI,  $-6.77$  to  $-0.98$ ;  $P = 0.009$ ), and end-systolic volume ( $-3.25$  mL/m<sup>2</sup>; 95% CI,  $4.87$  to  $-1.63$ ;  $P < 0.001$ ) and higher left and right ventricular ejection fraction by 2.6% (95% CI, 1.3–3.9;  $P < 0.001$ ) and 2.8% (95% CI, 1.4–4.1;  $P < 0.001$ ), respectively. Echocardiography-assessed left ventricular diastolic function demonstrated a mean difference in average E/E' of 0.52 (95% CI,  $-0.97$  to  $-0.07$ ;  $P = 0.024$ ) and a reduction in left atrial volumes of  $-4.33$  mL/m<sup>2</sup> (95% CI,  $-5.52$  to  $-3.21$ ;  $P < 0.001$ ) between baseline and follow-up when adjusted for baseline differences in measures.

**CONCLUSIONS:** Short-term postnatal optimization of blood pressure control after hypertensive pregnancy, through self-monitoring and physician-guided antihypertensive titration, associates with long-term changes in cardiovascular structure and function, in a pattern associated with more favorable cardiovascular outcomes.

Correspondence to: Paul Leeson, PhD, Oxford Cardiovascular Clinical Research Facility, Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, John Radcliffe Hospital, Oxford, OX3 9DU, United Kingdom. Email paul.leeson@cardiov.ox.ac.uk  
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### Clinical Perspective

#### What Is New?

- The POP-HT trial (Physician-Optimized Postpartum Hypertension Treatment), a randomized clinical trial of 220 participants, showed that blood pressure improvements in those who received physician-guided self-management of blood pressure postnatally are also associated with beneficial left ventricular and left atrial remodeling by 9 months postpartum.
- Clinically significant increases in left and right ventricular systolic function as well as improvements in left ventricular diastolic function were evident in the intervention group when assessed by multimodality imaging, including transthoracic echocardiogram and cardiac magnetic resonance.

#### What Are the Clinical Implications?

- These multimodality imaging findings suggest that improved blood pressure control postnatally may help reverse the adverse remodeling known to occur during a hypertensive pregnancy, and that these benefits persist for at least 9 months postpartum.
- The early postpartum period may represent a critical window for intervention to improve long-term maternal cardiovascular health after hypertensive pregnancy.

### Nonstandard Abbreviations and Acronyms

<b>CMR</b>	cardiac magnetic resonance
<b>COVID-19</b>	coronavirus disease 2019
<b>POP-HT</b>	Physician-Optimized Postpartum Hypertension Treatment
<b>V</b>	visit

Blood pressure levels immediately postpartum are unpredictable after a hypertensive pregnancy,<sup>10</sup> and there is limited evidence to guide optimal blood pressure management.<sup>11</sup> We hypothesized that “poor” blood pressure control after a hypertensive pregnancy might limit normal postpartum reverse remodeling.<sup>12–15</sup> In the POP-HT (Physician-Optimized Postpartum Hypertension Treatment) randomized clinical trial, we demonstrated physician-guided antihypertensive self-management after hypertensive pregnancy results in lower blood pressure for at least 9 months postpartum.<sup>16</sup> Participants were also invited for multimodality imaging to investigate prespecified secondary imaging outcomes. These were included to test the underlying mechanistic hypothesis that better postpartum blood pressure control induces differences in cardiac structure and function, in parameters of potential relevance to long-term blood pressure control and future cardiovascular disorders, including heart failure.

## METHODS

### Study Design and Participants

POP-HT was a single-center, 2-group parallel, prospectively randomized, open, blinded end point study. The primary article reporting blood pressure outcomes has been published and includes a detailed description of recruitment, patient characteristics, and statistical analysis.<sup>16</sup> A protocol article reporting the detailed methodology and prespecified outcome measures, including the secondary imaging outcomes, has previously been published.<sup>17</sup> In brief, all participants were recruited from the Women's Centre at Oxford University Hospitals National Health Service Foundation Trust in the United Kingdom. Participants were 18 years of age or older, with a clinician-confirmed diagnosis of either gestational hypertension or preeclampsia according to the UK National Institute of Clinical Excellence guidance,<sup>13</sup> and still requiring antihypertensive medication at the time of hospital discharge. Participants with chronic/essential hypertension, defined as a blood pressure  $>140/90$  mm Hg at their 12-week

**H**emodynamic demands during pregnancy result in substantial cardiac and vascular remodeling,<sup>1</sup> which, during the 6 weeks after pregnancy, known as the puerperium, rapidly reverses in normotensive pregnancy.<sup>2</sup> When the pregnancy is complicated by hypertension, the cardiac changes during pregnancy are more pronounced, and adverse features develop,<sup>3–5</sup> such as reduced left ventricular systolic and diastolic function<sup>6</sup> and concentric remodeling. Several studies have demonstrated that adverse cardiac phenotypes can remain evident for several years after a hypertensive pregnancy.<sup>1,7–9</sup> Furthermore, persistence of adverse cardiac phenotypes predicts worse longer-term outcomes, including risk of hypertension<sup>1,6</sup> and an increased incidence of earlier-onset heart failure.<sup>9</sup> These findings suggest the postpartum “reverse remodeling” seen in normotensive pregnancy may not be occurring in all women who have a hypertensive pregnancy.

booking assessment, or those already on antihypertensive treatment before pregnancy, were excluded. Participant information on race and ethnicity were self-reported using the UK Office of National statistics prespecified categories. Individuals with hypertension before pregnancy; those with medical conditions that made self-monitoring impractical or unsafe, eg, severe postpartum anxiety or depression; those unable to follow the English app-based instructions; and those unable to provide written consent were excluded. The trial was prospectively registered at [clinicaltrials.gov](https://www.clinicaltrials.gov) (URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT04273854) and supervised by a trial steering and data safety monitoring committee. Ethical and research governance approval was gained from the London-Surrey Research Ethics Committee (reference no. 19/LO/1901; Integrated Research Application System Project ID No. 273353).

## Randomization and Blinding

After a baseline visit, eligible participants were randomized 1:1 to either telemonitored home blood pressure monitoring with physician-assisted self-management or standard National Health Service-led care from their primary care practitioner and midwives. Randomization was conducted with secure web-based software (Castor Electronic Data Capture) with minimization for gestational age, whether the patient had a diagnosis of preeclampsia or gestational hypertension, and prescription of an angiotensin-converting inhibitor at time of randomization. Because of the nature of the intervention, neither participants nor investigators assigning trial groups were blinded to group assignment.

## Procedures

Participants assigned to the usual care arm were discharged from the hospital for ongoing management according to local standard care. National UK guidance recommends standard care as a minimum of a blood pressure review with a family physician or community midwife at day 1 to 14 postpartum, a 2-week review with their family physician, and a 6- to 8-weeks review with their family physician or specialist.<sup>13</sup> Titration of antihypertensive treatment was conducted at the discretion of their supervising health care professionals (primary care physician and midwife). As previously reported,<sup>16</sup> participants in the intervention group had initial discharge medications decided by their clinical care team,<sup>13</sup> and then dose titration after hospital discharge was guided remotely by the research team physicians, including cardiologists and obstetricians, in response to daily self-monitored blood pressure measurements (increased to twice daily if out of target range; see published protocol article for further details).<sup>17</sup> Choice of medication and titration regimens were standardized on the basis of recommendations from the 2019 UK National Institute of Clinical Excellence guidance.<sup>13</sup>

There were 4 study visits, after prescreening enrollment, occurring at days 1 to 6 postpartum (visit [V] 1; baseline), 1 week (V2), 6 weeks (V3), and 6 to 9 months (V4). Participants in both groups had research measurements of "clinic blood pressure" at each study visit, and all participants were invited to have an echocardiogram (CX50 or EPIQ 7, Philips, Amsterdam, The Netherlands) at baseline (V1) with data collection based on a British Society of Echocardiography minimum dataset.<sup>18</sup> All baseline visits took place on the postnatal ward. Participants

were invited for the same echocardiography protocol when attending in person for their final study visit (V4) along with a cardiac magnetic resonance (CMR) scan (3T PRISMA, Siemens Healthineers, Erlangen, Germany) in the Oxford Centre for Clinical Magnetic Resonance Research. This was performed with an 18-channel body coil and a spine array. Images were retrospectively ECG-gated with a precordial 4-lead ECG. CMR images were acquired using a standard previously reported protocol<sup>19</sup> that allows assessment of cardiac structure, function, and myocardial characteristics, and full technical details are provided in the supplementary information based on the magnetic resonance vendor protocol file.

## Outcomes

The primary outcome has been previously reported, and was 24-hour mean diastolic blood pressure, measured by ambulatory blood pressure monitoring (model 90217; Spacelabs Healthcare, Snoqualmie, Washington) at the time of V4.<sup>20</sup> Herein, we report the prespecified secondary cardiovascular imaging outcomes including transthoracic echocardiographic assessment at V1 and V4 and CMR assessment of cardiac structure and function at V4. Full details of these prespecified outcomes of cardiac structure and function using echocardiogram and CMR were reported in the protocol article.<sup>17</sup>

Echocardiograms were performed using a Philips CX50 portable echocardiography machine for all baseline visits at V1. All follow-up echocardiograms at V4 were done using a Philips EPIQ 7 or IE33. All echocardiography machines were equipped with a 2-dimensional phased array transducer, and scans were performed in the left lateral decubitus position. All echocardiography measurements followed standard society guidelines,<sup>18,21</sup> and the modality was primarily performed to assess diastolic function including pulsed wave Doppler assessment of the mitral valve inflow and pulmonary vein inflow, tissue Doppler imaging of lateral and septal walls of the left ventricle, and assessment of left atrial volumes. In addition, standard 2-dimensional measures of left ventricular wall thickness as well as volumes based on Simpson biplane measures were used to assess cardiac structure and function. Relative wall thickness as a measure of concentric hypertrophy was calculated as  $2 \times$  posterior wall diameter/left ventricular internal diastolic diameter.<sup>21</sup> Left ventricular global longitudinal strain was assessed by speckle tracking using semiautomated 2-dimensional Cardiac Performance Analysis Software (TomTec, Munich, Germany). Apical 4, 2 and 3 chamber 2-dimensional images were processed, and the endocardial border was delineated in end-diastole. The endocardial border was tracked through a single cardiac cycle, and the tracking was then inspected and manually corrected if poorly correlated with myocardial margin. Peak global values of longitudinal strain in systole are reported. Intra- and interobserver coefficients of variation for echocardiographic measurements are reported in the [Supplementary Material \(Table S1\)](#).

For the CMR, balanced steady-state free precession images were acquired during breath hold at end expiration. Using 2-, 3-, and 4-chamber views to plan images in line with the atrioventricular valves, a stack of short-axis images was acquired at 1-cm intervals to include the entire left and right ventricles. Image analysis was performed using CVI42 version 5.12.1 (Circle Cardiovascular Imaging Inc, Calgary, Canada). The short-axis stack of images was analyzed for left and right

ventricular volumes, ejection fractions, and left ventricular mass. 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 myocardial mass in line with standard guidance.<sup>22</sup> Myocardial mass was calculated from the sum of the myocardial area in the stack of images multiplied by 1.05 g/cm<sup>3</sup> (specific gravity of myocardium per cubic centimeter). End-diastolic and end-systolic volumes were calculated from the sum of ventricular areas in the stack of images. Stroke volume was calculated as the difference between the end-diastolic and the end-systolic volume. Ejection fraction was calculated as stroke volume divided by end-diastolic volume. Wall thickness was measured at midventricular level in 6 segments (anterior, lateral, inferior, inferolateral, inferoseptal, and antero-septal).<sup>23</sup> Mean wall thickness values were calculated from these 6 measures. Myocardial T1 values were measured from short modified look locker inversion sequences using standardized protocols published previously.<sup>24</sup> A single-slice T2 map was performed using Siemens MYOMAPS product sequences. All T1 and T2 map analyses were performed blinded to the clinical information. T1 maps were analyzed using in-house software Mc-Roi (programmed by S. Piechnik in IDL, v8.8; Exelis Visual Information Solutions, Inc, Boulder, Colorado). T2 maps were analyzed using CVI42 version 5.12.1. Normal values for comparison were obtained on the same 3T PRISMA scanner in 16 age-matched female subjects using the same protocol. Extracellular volume was calculated using hematocrit obtained at time of scan and using T1 values before and after gadolinium administration.<sup>19</sup> Late gadolinium administration and sequences were performed using standard Siemens acquisitions.

## Statistical Analysis

Analysis was based on principles of intention-to-treat, including all participants with at least 1 postrandomization outcome. Mean differences between groups with 95% CI and *P* value were estimated from adjusted linear regression models at a single time point (V4) with adjustment for the prespecified minimization factors stated in the statistical analysis plan. The level of statistical significance was tested as a 5% 2-tailed significance level (*P* < 0.05). Differences in imaging-based secondary outcomes between groups were evaluated using an adjusted linear regression model, including V1 measures for echocardiography. For CMR measures, no V1 measures were available, so linear models were adjusted for baseline blood pressure readings. Where measures did not satisfy the model assumptions for linear regression, nonparametric tests/regressions were used.

Sensitivity analyses were performed using antenatal booking blood pressure in place of baseline postpartum blood pressure, and further post hoc analyses were done removing those remaining on antihypertensive treatment at V4. No adjustment was made for multiple testing. Analysis was done using R version 4.3.1 and SPSS version 28.0.0. Analysis of intra and inter-operator variation is displayed in [Table S1](#).

## Data Sharing

The data that support the findings of this study are available from the chief investigator (P.L.), upon reasonable request subject to the approval of the sponsor (University of Oxford) and the trial steering committee.

## RESULTS

### Demographics

Between February 21, 2020, and March 21, 2021, a total of 220 participants were enrolled, with 112 assigned to the intervention arm and 108 to the usual care (control) arm. Of these participants, 216 underwent a complete baseline transthoracic echocardiogram, of whom 101 in the intervention group and 86 in the usual care group underwent repeat imaging at V4. The repeat scan was performed at an overall mean of 258 days postpartum (259±7 days for the intervention arm and 257±8 days for the usual care arm). The demographics of those undergoing repeat imaging, as a whole and according to randomization group, are presented in [Table 1](#). Demographics of all those randomized and the subgroup who had CMR are presented in [Tables S2 and S3](#), respectively, and are similar to those presented in [Table 1](#). Approximately 40% had gestational hypertension and ~60% preeclampsia, which is consistent with the inclusion criteria of the trial requiring on ongoing medication requirement at hospital discharge. The 2 groups were similar in obstetric and pregnancy characteristics at baseline, except a higher proportion of participants had a previous hypertensive pregnancy in the intervention arm. Diet and lifestyle characteristics of participants at the time of V4 echocardiogram and CMR were also statistically similar by  $\chi^2$  analysis with the exception of a higher proportion breastfeeding at time of V4 in the intervention arm (*P*=0.04) ([Table S4](#)).

### Antihypertensive Treatment

Antihypertensive prescription by classes was similar in each group (enalapril 57%, nifedipine 27%, and labetalol 30% for intervention versus enalapril 43%, nifedipine 30%, and labetalol 27% for usual care). At 6 weeks, ~30% of participants in each group were still on medication, which reduced to ~12% by V4. Participants in the intervention group were medicated for a median of 39 days (interquartile range, 13.9–41.5 days). Amount of antihypertensives prescribed, defined by median World Health Organization–defined daily dose,<sup>25</sup> was similar between groups at V1 and V4. However, at V2 (week 1), more antihypertensives were prescribed (World Health Organization–defined daily dose, 1.5 versus 0.7; *P*=0.01) in the intervention group.

### Echocardiography

Echocardiography measures of left and right ventricular structure and function at V4, adjusted for baseline measures at V1, are reported in [Table 2](#) and [Figure 1](#). Relative wall thickness showed a greater reduction between V1 and V4 in the intervention arm by −0.06 (95% CI, −0.07 to −0.05; *P*<0.001). Both septal and posterior left



**Table 1. Characteristics of Participants Who Underwent Echocardiographic Imaging**

Parameter	Intervention (n=110)	Usual care (n=107)
<b>Patient characteristics</b>		
Mean age, y (SD)	33.7 (5.1)	32.8 (5.0)
Mean booking BMI, kg/m <sup>2</sup> (SD)	28.1 (5.1)	28.7 (7.6)
Mean booking height, cm (SD)	165.5 (6.4)	164.7 (6.9)
Mean booking BSA, m <sup>2</sup> (SD)	1.9 (0.2)	1.9 (0.2)
Mean systolic blood pressure at first antenatal visit, mmHg (SD)	118.5 (10.7)	117.5 (10.6)
Mean diastolic blood pressure at first antenatal visit, mmHg (SD)	72.1 (8.7)	72.5 (8.7)
Prepregnancy smoking reported*, n (%)	24 (21.8)	31 (29.0)
IMD quintile†, median (IQR)	2 (1, 3)	1 (1, 2)
<b>Race and ethnicity‡, n (%)</b>		
Asian	10 (9.1)	8 (7.5)
Hispanic or Latino	4 (3.6)	4 (3.7)
Non-Hispanic Black	6 (5.5)	4 (3.7)
Non-Hispanic White	90 (81.8)	88 (82.2)
Pacific Islander	0 (0.0)	3 (2.8)
<b>Pregnancy characteristics</b>		
Preeclampsia§, n (%)	67 (60.9)	64 (59.8)
Gestational hypertension§, n (%)	43 (39.1)	43 (40.2)
HELLP syndrome subset of preeclampsia§, n (%)	5 (4.5)	1 (0.9)
Median duration of antenatal antihypertensive treatment, d (IQR)	4.0 (2.0, 15.8)	5.0 (1.0, 18.8)
Early diagnosis of preeclampsia or gestational hypertension ≤33 wk and 6 d gestation, n (%)	24 (21.8)	23 (21.5)
Median gestation at delivery, wk (IQR)	39.2 (37.0, 40.3)	39.1 (37.0, 40.6)
Primiparous, No. (%)	67 (60.9)	75 (70.1)
Previous hypertensive pregnancy, n (%)	30 (27.3)	10 (9.3)
Assisted reproduction pregnancy, n (%)	7 (6.4)	11 (10.3)
Multifetal pregnancy, n (%)	6 (5.5)	8 (7.5)
Spontaneous vaginal birth (%)	42 (38.2)	33 (30.8)
Assisted vaginal birth (%)	16 (14.5)	28 (26.2)
Emergency cesarean section¶ (%)	47 (42.7)	40 (37.4)
Elective cesarean section¶ (%)	5 (4.5)	6 (5.6)
Fetal growth restriction##, n (%)	25 (22.7)	28 (26.2)
Neonatal unit admission**, n (%)	29 (26.4)	33 (30.8)
Mean birthweight, kg (SD)	3.1 (0.8)	3.1 (2.9)

BMI indicates body mass index; BSA, body surface area; HELLP, hemolysis, elevated liver enzymes, and low platelets; IQR, interquartile range.

\*Smoking before pregnancy for a >12-month period.

†IMD refers to the Index of Multiple Deprivation, a measure of socioeconomic disadvantage defined in quintiles with 1 describing the least deprived and 5 the most deprived. Data from n=213 (intervention n=109, usual care n=104).

‡In accordance with UK recommendations, self-reported ethnicity was recorded using standard descriptions derived from those used by the UK Office for National Statistics.

§Classification as gestational hypertension, preeclampsia, and HELLP syndrome were based on definitions provided in the National Institute of Clinical Excellence guideline (NG 133) "Hypertension in Pregnancy; Diagnosis and Management," definitions for which can be found in the protocol provided in the [Supplemental Material](#).

¶DDD refers to the defined daily doses as per the World Health Organization<sup>25</sup>, described as the assumed average maintenance dose per day for a drug used for its main indication in adults. Here the total DDD includes the sum of the total of the individual DDD for each prescribed antihypertensive.

¶Category of cesarean section was defined as per National Institute of Clinical Excellence guidance on cesarean birth (NG 192). The term "elective cesarean" refers to an electively scheduled cesarean timed to suit the patient or health care provider. "Emergency cesarean" spans the categories of "no maternal or fetal compromise but needs early birth" to "immediate threat to the life of the patient or fetus."

#Intrauterine growth restriction defined as a fetus whose weight was <10th percentile for its gestational age postpartum.

\*\*A neonatal unit is a part of a hospital that provides care for babies who are born prematurely (before 37 weeks' gestation) and is used as an umbrella term here to includes the neonatal intensive care unit, high-dependency unit, and special care baby unit.

**Table 2. Echocardiographic Measures of Cardiac Structure and Function From Baseline to V4 Adjusted for Baseline Echocardiographic Measurements\***

Hemodynamics	Intervention		Usual care		Adjusted regression coefficients*		
	Baseline mean (SD) (n=109)	V4 mean (SD) (n=101)	Baseline mean (SD) (n=107)	V4 mean (SD) (n=86)	Difference	95% CI	P value
HR, bpm	79.6 (12.56)	79.3 (11.9)	78.70 (11.27)	79.1 (12)			
SV indexed, mL/m <sup>2</sup>	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‡ (IQR)	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
SVR, mm Hg/min/mL <sup>−1</sup>	1.56 (0.39)	1.80 (0.38)	1.58 (0.37)	1.80 (0.39)	0.006	(−0.10, 0.11)	0.912
Left and right ventricular 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†
LV GLS, % (IQR)‡§	−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†
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
Left ventricular 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, s	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
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
Average E/E'	7.93 (1.83)	6.05 (1.38)	8.08 (2.09)	6.61 (1.86)	−0.52	(−0.97 to −0.06)	0.024†
Medial E/E'	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†
Cardiac remodeling							
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 <sup>2</sup>	31.66 (6.39)	21.74 (3.19)	31.26 (6.19)	25.98 (5.20)	−4.36	(−5.52 to −3.21)	<0.001†
EDVi, mL/m <sup>2</sup>	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 <sup>2</sup>	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). ASE indicates American Society of Echocardiography model for RWT assessment (ie,  $2 \times \text{PWd}/\text{LVIDd}$ )<sup>21</sup>; CO, cardiac output; E/A, ratio of early to late mitral inflow velocity; EDVi, end diastolic volume indexed to body surface area; E/E', ratio of early mitral inflow velocity and early mitral annular diastolic velocity; ESVi, end systolic volume indexed to body surface area; GLS, global longitudinal strain; HR, heart rate; IQR, interquartile range; LAVi, left atrial volume indexed to body surface area; LV, left ventricular; LVEF, LV ejection fraction; LVIDd, LV internal diameter in diastole; PWd, posterior wall diameter in diastole; RV, right ventricle; RWT, relative wall thickness; SV, stroke volume; SVR, systemic vascular resistance calculated as mean arterial pressure/CO; SWd, septal wall diameter in diastole; TAPSE, tricuspid annular plane systolic excursion; and V, visit.

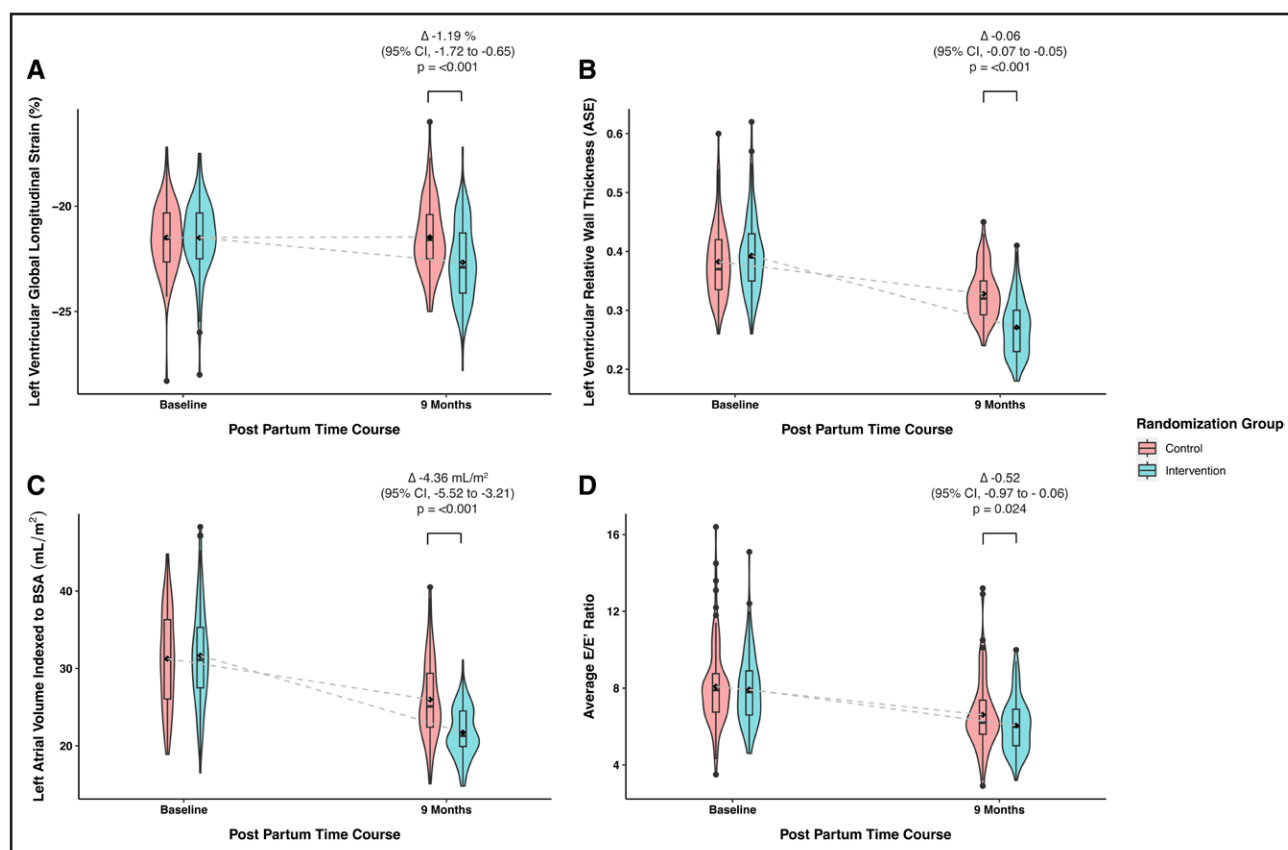
\*All regressions were performed on measurements at 9 months with the baseline measurement included in the model.  
†95% CI does not cross 0.  
‡Nonparametric: median (IQR). The nonparametric GLS and CO were analyzed by Mann-Whitney U test.  
§Baseline intervention n=98, usual care n=86, V4 intervention n=96, usual care = 77 (numbers for GLS less because the image quality required for strain led to more cases being excluded).

ventricular wall thickness were reduced in the intervention group by −0.18 mm (95% CI, −0.21 to −0.16 mm;  $P<0.001$ ) and −0.14 mm (95% CI, −0.17 to −0.12 mm;  $P<0.001$ ), respectively. Left ventricular stroke volume was 2.15 mL/m<sup>2</sup> (95% CI, 3.01–1.00 mL/m<sup>2</sup>;  $P<0.001$ ) lower in the intervention group at V4 with reductions in indexed end-diastolic (−4.74 mL/m<sup>2</sup>; 95% CI, −6.23 to −3.26;  $P<0.001$ ) and end-systolic volumes (−2.69 mL/m<sup>2</sup>; 95% CI, −3.57 to −1.81 mL/m<sup>2</sup>;  $P<0.001$ ). Left ventricular remodeling was accompanied by higher left ventricular systolic function in the intervention group, assessed by the Simpson biplane method (+1.79%; 95% CI, 0.84%–2.75%;  $P<0.001$ ), and improved peak global

longitudinal systolic strain (−1.19%; 95% CI, −0.65 to −1.72;  $P<0.001$ ). Left ventricular diastolic function was also improved in the intervention group. Average E/E' was 0.52 (95% CI, −0.97 to −0.07;  $P=0.024$ ) lower in the intervention group, which was accompanied by a significant reduction in indexed left atrial volume of 4.33 mL/m<sup>2</sup> (95% CI, −5.52 to −3.21;  $P<0.001$ ).

Cardiovascular Magnetic Resonance

CMR scans were obtained in 174 participants at V4, of whom 93 were in the intervention group and 81 in the usual care group. Cardiac measures (reported in Table 3



**Figure 1. Echocardiographic measures of cardiac structure and function at baseline\* and 9 months postpartum by randomization group.**

**A**, Changes in LV global longitudinal strain† from baseline† to 9 months by randomization group. **B**, Changes in LV relative wall thickness (RWT)§ from baseline† to 9 months by randomization group. **C**, Changes in indexed left atrial (LA)¶ volumes from baseline† to 9 months by randomization group. **D**, Changes in diastolic function¶ from baseline† to 9 months by randomization group. Violin plots with overlaid box plots. Tukey box plots represent median and interquartile range (IQR), whiskers represent largest value within 1.5 times IQR >75th percentile and smallest value within 1.5 times IQR <25th percentile, and data points beyond the whiskers represent values >1.5 times and <3 times the IQR. Diamond-shaped data points represent mean values for each group at each time point. Adjusted mean difference†, 95% CI, and P values are provided above each plot, representing the significance between control and intervention groups at 9 months. LV indicates left ventricular. \*Baseline echocardiogram performed days 1 to 6 on postnatal ward. †All measurements adjusted for mean baseline postnatal blood pressure in the model. ‡Assessment of strain by speckle tracking was undertaken offline using semiautomated 2-dimensional Cardiac Performance Analysis Software (TomTec, Munich, Germany). §RWT calculated as per American Society of Echocardiography recommended methodology, ie, 2xposterior wall diameter in diastole/LV internal diameter in diastole.¶LA volumes measured by the Simpson biplane method. LA volumes were indexed to body surface area (BSA), calculated using the Mosteller formula. ¶¶Diastolic function assessed by E/E' average (ratio of early mitral inflow velocity and averaged early mitral annular lateral and septal diastolic velocity).

and Figure 2) confirmed the differences identified with echocardiography. Left ventricular mass, both absolute and indexed to body size, was lower in the intervention group by 6.37 g/m<sup>2</sup> (95% CI, -7.99 to -4.74;  $P<0.001$ ). Left ventricular wall thickness was a mean -1.26 mm lower in the intervention arm (95% CI, -1.49 to -1.06;  $P<0.001$ ). Left ventricular end diastolic and systolic volumes were also lower by 3.87 mL/m<sup>2</sup> (95% CI, -6.77 to -0.98;  $P=0.009$ ) and 3.25 mL/m<sup>2</sup> (95% CI, -4.87 to -1.63;  $P<0.001$ ), respectively. These changes were consistent with greater concentric remodeling, demonstrated by a lower left ventricular mass to left ventricular end diastolic volume in the intervention arm of -0.09 g/mL/m<sup>2</sup> (95% CI, -0.11 to -0.07;  $P<0.001$ ). Left ventricular systolic function assessed as ejection fraction was higher in the intervention group by 2.61% (95% CI, 1.31 to

3.92;  $P<0.001$ ). In addition, CMR identified an increased right ventricular systolic function by 2.76% (95% CI, 1.44 to 4.09;  $P<0.001$ ).

Additional CMR sequences were added as an amendment during the trial to test for myocardial changes. T1 mapping (short modified look locker inversion) sequences were obtained in 165 participants, and T2 mapping in 131. No significant differences were evident between the intervention and usual care groups in T1 or T2 maps. Mean T1 value in the intervention arm was 1161.2±26.4 ms, and in the usual care group was 1155.1±26.1 ms. Mean T2 value was 41.1±1.8 ms in the intervention group and 40.9±1.7 ms in the usual care group. Late gadolinium imaging was offered as an optional addition to the protocol to participants who were not breastfeeding at the time of cardiovascular magnetic resonance. A

**Table 3. Cardiac Magnetic Resonance Data Adjusted for Baseline Mean\* Blood Pressure**

	Intervention n=93	Usual care n=81	Adjusted regression coefficients†		
	Mean (SD)	Mean (SD)	Difference	95% CI‡	P value
Hemodynamics					
HR, bpm	72.8 (11.2)	72.1 (10.9)			
LV SV indexed (mL/m²)	42.31 (5.65)	42.93 (6.07)	−0.58	−2.34 to 1.19	0.52
RV SV indexed, (mL/m²)	42.36 (6.22)	41.64 (6.07)	0.71	−1.14 to 2.55	0.45
LV CO, L/min	5.85 (1.1)	5.90 (1.2)	−0.85	−0.45 to 0.28	0.65
RV CO, L/min	5.84 (1.15)	5.67 (1.29)	0.14	−0.23 to 0.50	0.45
Left and right ventricular systolic function					
LVEF, %	64.37 (4.30)	61.85 (4.39)	2.61	1.31 to 3.92	<0.001*
RVEF, %	60.93 (4.17)	58.32 (4.68)	2.76	1.44 to 4.09	<0.001*
Cardiac remodeling					
LV EDVi (mL/m²)	66.27 (8.95)	70.07 (10.31)	−3.87	−6.77 to −0.98	0.009*
LV ESVi (mL/m²)	23.05 (5.05)	27.04 (5.72)	−3.25	−4.87 to −1.63	<0.001*
RV EDVi, mL/m²	70.22 (11.73)	71.53 (10.34)	−1.50	−4.83 to 1.83	0.37
RV ESVi, mL/m²	27.92 (6.61)	30.14 (6.27)	−2.43	−4.35 to −0.51	0.014*
LV mass indexed to BSA (g/m²)	39.18 (5.76)	45.48 (5.07)	−6.37	−7.99 to −4.74	<0.001*
LV mass indexed to height (g/m)	44.91 (7.91)	53.10 (9.22)	−8.31	−10.89 to −5.75	<0.001*
LV mass/LVEDV	0.58 (0.06)	0.67 (0.07)	−0.09	−0.113 to −0.072	<0.001*
Mean LV wall thickness§ (mm)	5.73 (0.60)	6.99 (0.72)	−1.26	−1.49 to −1.06	<0.001*

Parametric: mean (SD). BSA indicates body surface area, calculated by the Mostellar equation; CO, cardiac output; EDVi, end diastolic volume indexed to BSA; ESVi, end systolic volume indexed to BSA; HR, heart rate; LV, left ventricular; LVEDV, left ventricular end diastolic volume; LVEF, LV ejection fraction; RV, right ventricular; RVEF, RV ejection fraction; and SV, stroke volume.  
\*Mean of second and third bedside blood pressures obtained during visit 1 (baseline visit) on the postnatal ward.  
†All regressions were performed on measurements at 6 months with adjustment for baseline diastolic blood pressure (mean of second and third).  
‡95% CI around adjusted difference does not cross 0.  
§Wall thickness measured in the basal slice of the short axis stack in 6 segments: anterior, lateral, inferior, inferolateral, inferoseptal, and septal.

total of 36 women agreed, with analyzable data available for 34, of whom 20 were in the intervention group and 14 in the usual care group. Patchy fibrosis was evident at the right and left ventricular insertion points in 12 participants, of whom 7 were in the intervention group and 5 in the usual care group. One participant had a faint midwall band, but this did not correspond to edema or fibrosis on T1 and T2 mapping or extracellular volume calculations. There were also no significant differences in extracellular volume between the intervention and usual care arms.

Additional Analyses

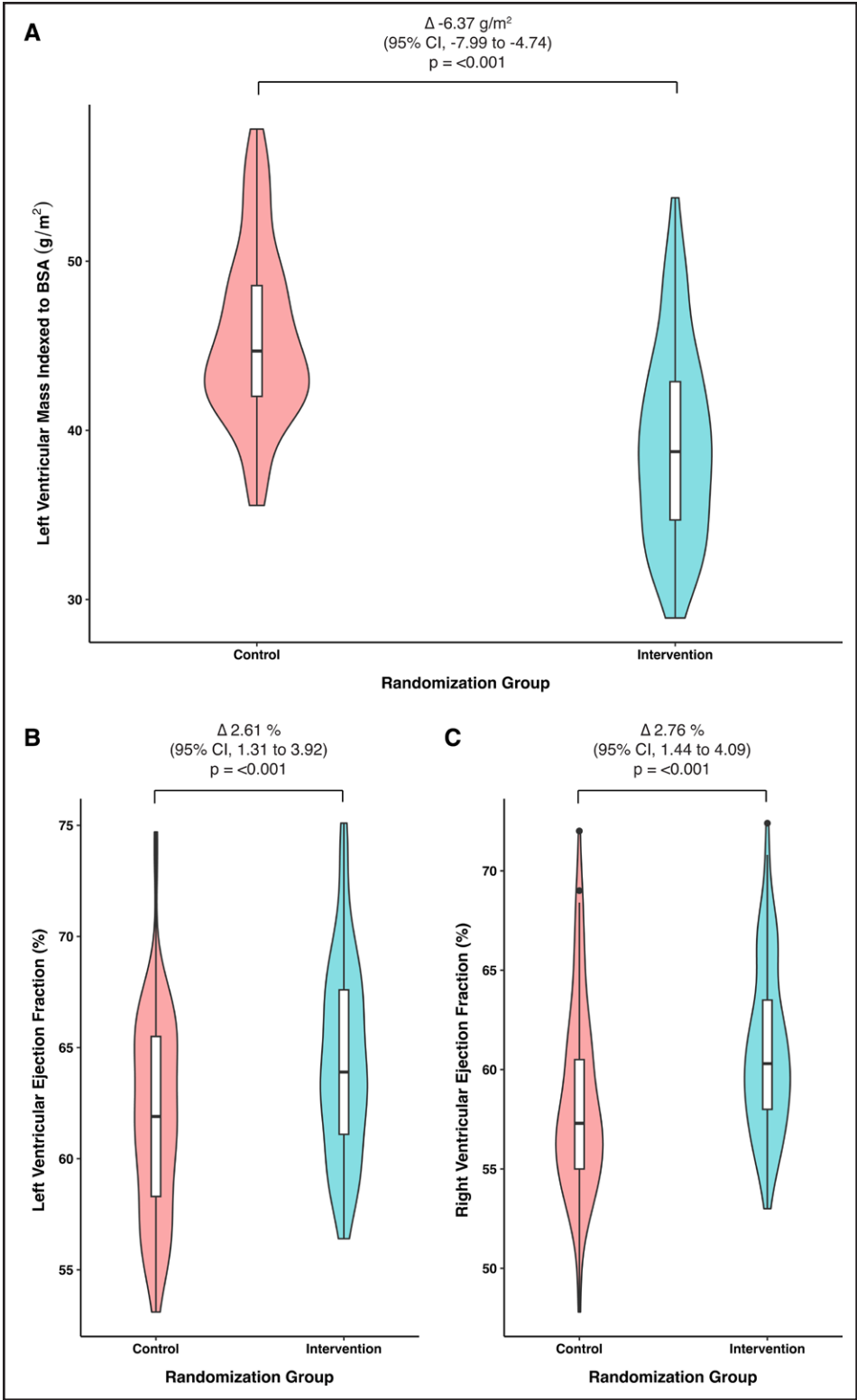
Prespecified sensitivity analyses were performed, adjusting for antenatal blood pressure differences rather than baseline postnatal blood pressure values, and are reported in Tables S5 and S6. No significant differences in the results were evident. Additional post hoc sensitivity analyses were performed to investigate the relevance of antihypertensive treatment at the time of V4. Results after exclusion of the 24 participants still on medication are shown in Tables S7 and S8, which also demonstrate no

significant effect on the differences in cardiac structure and function between the intervention and usual care arms described in Table 2 and 3.

DISCUSSION

This trial shows that women with persistently elevated blood pressure after a hypertensive pregnancy have more favorable remodeling of the left ventricle, right ventricle, and atrium if they receive physician-guided antihypertensive medication titration, in response to self-monitored blood pressure measurements, during the immediate postpartum period. These benefits are evident 9 months after pregnancy, although the blood pressure intervention is only required for the first 40 days, on average. Exploratory T1 and T2 mapping and extracellular volume values, in conjunction with late gadolinium images, show no significant residual edema or inflammation at 9 months postpartum. Furthermore, the changes in myocardial wall thickness do not appear to be caused by excess fibrosis, suggesting the primary benefit is driven by change in myocyte size and function.





**Figure 2. Cardiac magnetic resonance measures of cardiac structure and function at 9 months postpartum by randomization group.****A**, Left ventricular (LV) mass† indexed to BSA at 9 months postpartum per randomization group, either control (left, pink) or intervention (right, blue). **B**, LV ejection fraction‡ and **(C)** right ventricular ejection fraction‡ at 9 months postpartum per randomization group, either control (left, pink) or intervention (right, blue). Violin plots with overlaid box plots. Tukey box plots represent median and interquartile range (IQR), whiskers represent largest value within 1.5 times IQR >75th percentile and smallest value within 1.5 times IQR <25th percentile, and data points beyond the whiskers represent values >1.5 times and <3 times the IQR. Adjusted mean difference, 95% CI, and *P* values are provided above each plot. \*All measurements were adjusted for mean baseline postnatal blood pressure in the model. †Myocardial mass was calculated from the sum of the myocardial area in the stack of images multiplied by 1.05 g/cm³ (specific gravity of myocardium per cubic centimeter). (Continued)

**Figure 2 Continued.** †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 as stroke volume divided by end-diastolic volume. ASE indicates American Society of Echocardiography.

During a normotensive pregnancy, Simmons et al reported that left ventricular mass index increases from  $66 \pm 13$  g/m<sup>2</sup> in the first trimester to a peak of  $76 \pm 16$  g/m<sup>2</sup> in the third trimester, before returning to  $67 \pm 11$  g/m<sup>2</sup> at 13 weeks postpartum.<sup>26</sup> Rafik Hamad et al<sup>27</sup> found preeclampsia was associated with an average 15 g/m<sup>2</sup> higher left ventricular mass index during pregnancy as well as reduced diastolic function. Melchiorre et al have reported that changes in left ventricular systolic function assessed by global longitudinal strain are also evident proportional to the severity of the hypertensive disease.<sup>9</sup> The degree to which this adverse left ventricular remodeling recovers postpartum, and whether all women recover similarly after hypertensive pregnancy, has been under investigation. Simmons et al<sup>30</sup> reported similar mean differences in left ventricular measures in those who had preeclampsia by 13 weeks postpartum, suggesting that normalization of cardiac parameters after hypertensive pregnancy is possible. However, in larger studies, such as those by Ghossein-Doha et al,<sup>28</sup> a significant proportion of women continue to have persistent changes in indexed left ventricular mass at 9 months postpartum, and McCarthy et al found that 50% of a cohort with early-onset preeclampsia had significant cardiac structural changes by the end of the first year postpartum.<sup>29</sup> Women with persistent abnormalities of left ventricular structure appear to have a higher risk profile because they are more likely to develop hypertension within the next few years after pregnancy.<sup>1,6</sup>

Why some women continue to display an adverse cardiac phenotype, whereas patterns normalize in others, had been unclear. We hypothesized this may relate to the hemodynamic status of the women during the first few weeks after pregnancy, when the majority of postpregnancy remodeling occurs. After a hypertensive pregnancy, there can be significant blood pressure variability,<sup>10,30,31</sup> but in the SNAP-HT<sup>32,33</sup> randomized study (Self-Management of Raised Blood Pressure in Women After Childbirth), we demonstrated the feasibility of blood pressure optimization postpartum using self-monitoring and management. Women who received the intervention appeared to have improved blood pressure control during the first year postpartum, and the POP-HT trial has now demonstrated that physician-optimized blood pressure self-management leads to more controlled and lower blood pressures during the first few weeks after a hypertensive pregnancy. This was also demonstrated by the significantly lower rates of hospital readmissions for hypertension seen in the intervention arm.<sup>16</sup>

It is striking that these reductions in postpartum blood pressure with self-monitoring persist for at least 9 months, even after the women have stopped taking medication, and in SNAP-HT were still evident 4 years later.<sup>33</sup> This persistent effect on blood pressure is consistent with our hypothesis that early postpartum interventions may lead to underlying structural cardiovascular changes, which has now been supported by the current imaging study. An effect on cardiac remodeling of a postpartum intervention, in particular left ventricular mass, was reported in the PICK-UP trial (Postnatal Enalapril to Improve Cardiovascular Function Following Preterm Preeclampsia),<sup>34</sup> which randomized women to receive enalapril on top of standard antihypertensive medication postnatally. Diastolic blood pressure was around 7 mmHg lower in the intervention arm of PICK-UP, and whether the benefit on cardiovascular remodeling related to the lower blood pressure or a specific effect of the enalapril<sup>35</sup> was not clear. Around 50% of women in POP-HT received enalapril postpartum, in line with recent 2019 UK national guidance on first-choice postnatal drugs.<sup>13</sup> Use of the medication was similar in both arms, and 90% of participants were off treatment completely by 6 weeks. Furthermore, few participants in the SNAP-HT pilot study were on enalapril because this trial preceded the 2019 guidance and was based on National Institute of Clinical Excellence CG107.<sup>36</sup> Together this suggests an independent effect of the self-management process, rather than specific medication, on cardiac remodeling.

Ejection fraction, global longitudinal systolic strain, and E/E' can be influenced by differences in blood pressure at time of measurement. Therefore, some of the functional differences in POP-HT may be a result of the antihypertensive effect of the intervention and not just changes in cardiac structure. Nevertheless, the intervention group had a 6.4 g/m<sup>2</sup> reduction in left ventricular mass compared with usual care, which equates to around 8% reduction. If sustained longer-term, this would be expected to have a significant effect on later cardiovascular risk. Tsao et al<sup>37</sup> observed in the Framingham cohort that for every 10 g/m<sup>2</sup> lower left ventricular mass index, there was an ~40% lower incidence of cardiovascular disease over the subsequent eight years. Similarly, in the MESA study (Multi-Ethnic Study of Atherosclerosis) of healthy asymptomatic men and women free of cardiovascular disease, a 10% lower left ventricular mass correlated with a 40% lower risk of heart failure.<sup>38</sup>

We consider several limitations to this study. First, because of the nature of the intervention, the study was unblinded. However, for the imaging study, it was

possible to perform all image processing and analysis of cardiac outcomes with operators blinded to study allocation. Cardiac structural measures are also not likely to be influenced by awareness of participants, or research team members of allocation. Second, the study was affected by COVID-19, and amendments to the protocol were required to allow for remote study visits. Although in-person visits for imaging remained possible, these were undertaken under COVID-19 regulations, and some participants were not able, or willing, to attend imaging follow-up. However, the loss to imaging follow-up remained small, at <10%, and there were no significant differences between the full cohort and those who had imaging performed. Third, the majority of participants were of White British ethnicity because of the nature of local population demographics.<sup>39</sup> Additional work is required to understand whether similar patterns of remodeling in response to the intervention are seen in other ethnic and geographic groups, but a recent observational study in a large multiethnic cohort showed similar longitudinal echocardiographic changes to that seen in our control cohort,<sup>14</sup> as did other work on self-monitoring antenatally.<sup>40</sup> Fourth, participants with chronic hypertension were excluded.<sup>17</sup> Therefore, the effect of preexisting hypertensive cardiac remodeling on both the pregnancy response and postpartum remodeling has not been explored. There were more women in the intervention arm affected by previous hypertensive pregnancy. Therefore, on the basis of our findings in this study, we might expect these women to be more likely to have adverse blood pressure and cardiac changes prepregnancy. If anything, this is expected to dilute the effect of the subsequent intervention on postnatal remodeling. However, overall, there remained a relatively small number of women affected by a previous hypertensive pregnancy, and so any dilution effect is probably small. Further work will be required to understand the interactions between chronic hypertension and pregnancy induced disease on longer-term cardiac phenotypes. Last, models of care delivery that provide the close day-to-day supervision that the research physicians offered needs to be explored to effectively translate this intervention into widespread clinical practice.

Previous imaging studies have demonstrated that hypertensive pregnancy is associated with significant adverse cardiovascular changes, and during the first year after pregnancy, ~40% of affected women continue to fulfill criteria for stage B heart failure because of structural cardiac changes.<sup>6,7,18,41</sup> Yet, there is no consensus on optimal policies for screening, prevention, or management of this higher cardiovascular risk. This trial suggests that optimized blood pressure control during the first 6 weeks after pregnancy can regress the adverse cardiovascular changes known to occur during a hypertensive pregnancy. A paradigm shift toward improving health care

for women in the first few weeks after a hypertensive pregnancy may have significant long-term cardiovascular benefits for the 10% of women affected by hypertensive disorders of pregnancy.

## ARTICLE INFORMATION

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### Affiliations

Division of Cardiovascular Medicine, Radcliffe Department of Medicine (J.K., S.K., A.F., K.S., Y.K., W.L., A.J.L., P.L.), Nuffield Department of Primary Care Health Sciences (J.K., K.T., P.A.B., R.J.M.), Oxford Centre for Clinical Magnetic Resonance Research, Division of Cardiovascular Medicine, Radcliffe Department of Medicine (M.L., R.M., S.P.), Institute of Biomedical Engineering, Department of Engineering Science (C.R.), Nuffield Department of Women's and Reproductive Health (A.F., L.M., A.C., C.A.), Oxford Centre for Clinical Magnetic Resonance Research (V.F., E.L.), University of Oxford, United Kingdom. Queen's University School of Medicine, Kingston, Canada (L.B.). Fetal Medicine Unit, Oxford University Hospitals National Health Service Foundation Trust, United Kingdom (C.A.). Fetal Medicine Unit, St George's University Hospitals National Health Service Foundation Trust, London, United Kingdom (B.T.). Molecular and Clinical Sciences Research Institute, St George's University of London, United Kingdom (B.T.). King's College London and Guy's and St Thomas' National Health Service Foundation Trust, United Kingdom (L.C.C.).

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L.M. and P.L. are supported by the National Institute for Health and Care Research Oxford Biomedical Research Centre. L.M. is a part-time employee of EMIS Group plc. P.L. is a founder and shareholder of a health care imaging company and a named inventor on patents related to cardiovascular imaging. R.M. has received blood pressure monitors for research from Omron and has worked with Omron and Sensyne on telemonitoring interventions for which licensing and consultancy fees have been paid to the University of Oxford. C.R. has received consultancy fees from Sensyne Health for work on telemonitoring products. J.K. is an executive committee member of the British Society of Cardiac Imaging and Cardiac Computed Tomography. The other authors report no conflicts.

## Supplemental Material

Tables S1–S8

Figure S1

Vendor Protocol for 3T PRISMA, Siemens Healthineers, Erlangen, Germany

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