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

Running title: *Kitt et al.; The POP-HT Cardiac Imaging Sub-study*

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Abstract

Background: Hypertensive pregnancy disorders are associated with adverse cardiac remodeling, which can fail to reverse postpartum in some women. The Physician Optimized Postpartum Hypertension Treatment trial demonstrated improved blood pressure control, while the cardiovascular system recovers postpartum, associates with persistently reduced blood pressure. We now report the impact on cardiac remodeling.
Methods: In this prospective, randomized, open-label, blinded endpoint 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 primary care physician and midwife. Participants were aged 18 years or over, with pre-eclampsia or gestational hypertension, requiring antihypertensives on hospital discharge postnatally. Pre-specified secondary cardiac imaging outcomes were recorded by echocardiography around delivery, and again at blood pressure primary outcome assessment, around nine months postpartum, when cardiovascular magnetic resonance was also performed.
Results: 187 women (101 intervention; 86 usual care) underwent echocardiography at baseline and follow up, at a mean 258+/-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% CI0.07 to 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 (-6.37g/m^2 (95% CI -7.99 to -4.74, P<0.001), end diastolic volume (-3.87ml/m^2, 95% CI -6.77 to -0.98, P=0.009) and end systolic volume (-3.25ml/m^2, 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 to 3.9, P<0.001) and 2.8% (95% CI 1.4 to 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 -4.33ml/m^2 (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 following 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.
Clinical Trial Registration: https://clinicaltrials.gov/ct2/show/NCT04273854

Key Words: Pre-eclampsia, Gestational hypertension, Postpartum, Self-monitoring, Cardiac remodeling

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Non-standard Acronyms and Abbreviations

ABPM	Ambulatory blood pressure monitory
ASE	American Society of Echocardiography
BMI	Body mass index
BSA	Body surface area
bSSFP	Balanced steady-state free precession
CMR	Cardiac magnetic resonance
CO	Cardiac output
DDD	Defined daily dose
ECG	Electrocardiogram
ECV	Extra-cellular volume
EDC	Electronic data capture
EDV	End diastolic volume
EDVi	End diastolic volume indexed to BSA
ESVi	End systolic volume indexed to BSA
GLS	Global longitudinal strain
HELLP	Hemolysis, Elevated Liver enzymes and Low Platelets
HR	Heart rate
IMD	Indices of multiple deprivation
IQR	Interquartile range
LA	Left atrium
LAV	Left atrial volume
LAVi	Indexed left atrial volume
LGE	Late gadolinium enhancement
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVIDd	Left ventricular internal diameter in diastole
MAP	Mean arterial pressure
NHS	National Health Service
NICE	National Institute of Clinical Excellence
POP-HT	Physician Optimized Postpartum Hypertension Treatment
PROBE	Prosprospectively randomized, open, blinded end-point
PW	Pulsed wave
PWd	Posterior wall diameter in diastole
RV	Right ventricular
RVEF	Right ventricular ejection fraction
RWT	Relative wall thickness
ShMOLLI	Short Modified Look-Locker Inversion
SV	Stroke volume
SVR	Systemic vascular resistance
SWd	Septal wall diameter in diastole
TDI	Tissue Doppler imaging
WHO	World Health Organization

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Clinical Perspective

What is new?

- The Physician Optimized Postpartum Hypertension Treatment (POP-HT) trial, 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.
- Notably, 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 multi-modality imaging, including transthoracic echocardiogram and cardiac magnetic resonance.

What are the clinical implications?

- These multi-modality imaging findings suggest 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 nine months postpartum.
- The early postpartum period may represent a critical window for intervention to improve long term maternal cardiovascular health after hypertensive pregnancy.

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Introduction

Haemodynamic demands during pregnancy result in substantial cardiac and vascular remodeling,[1] which during the six weeks after pregnancy, known as the puerperium, rapidly reverse in normotensive pregnancy.[2] When the pregnancy is complicated by hypertension the cardiac changes during pregnancy are more pronounced and adverse features develop[3-5], such as reduced left ventricular systolic and diastolic function[6] and concentric remodeling. Several studies have demonstrated adverse cardiac phenotypes can remain evident for several years after a hypertensive pregnancy.[1, 7, 8 9] Furthermore, persistence of adverse cardiac phenotypes predicts worse longer term outcomes, including risk of hypertension[1,6] and an increased incidence of earlier onset heart failure.[9] These findings suggest the postpartum 'reverse remodeling' seen in normotensive pregnancy may not be occurring in all women who have a hypertensive pregnancy.

Blood pressure levels immediately postpartum are unpredictable after a hypertensive pregnancy[10] and there is limited evidence to guide optimal blood pressure management.[11] We hypothesized that 'poor' blood pressure control following hypertensive pregnancy might limit normal postpartum reverse remodeling.[12-15] In the Physician Optimized Postpartum Hypertension Treatment (POP-HT) randomized clinical trial we demonstrated physician guided antihypertensive self-management after hypertensive pregnancy results in lower blood pressure for at least nine months postpartum.[16] Participants were also invited for multi-modality imaging to investigate pre-specified 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.

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Methods

Study design and participants

POP-HT was a single center, two-group parallel, prospectively randomized, open, blinded end-point (PROBE) study. The primary paper reporting blood pressure outcomes has been published and includes a detailed description of recruitment, patient characteristics and statistical analysis.[16] A protocol paper reporting the detailed methodology and pre-specified outcome measures, including the secondary imaging outcomes, has previously been published.[17] In brief, all participants were recruited from the Women's Centre at Oxford University Hospitals NHS Foundation Trust in the UK. Participants were aged 18 years or over, with a clinician confirmed diagnosis of either gestational hypertension or pre-eclampsia according to UK National Institute of Clinical Excellence (NICE) guidance,[13] and still requiring antihypertensive medication at the time of hospital discharge. Participants with chronic/essential hypertension, defined as a blood pressure >140/90mmHg at their twelve-week booking assessment, or those already on anti-hypertensive treatment prior to pregnancy, were excluded. Participant information on race and ethnicity were self-reported using UK Office of National statistics pre-specified categories. Individuals with hypertension prior to pregnancy, medical conditions that made self-monitoring impractical or unsafe, e.g. 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 (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 19/L0/1901, IRAS Project ID: 273353).

Randomization and blinding

Following a baseline visit, eligible participants were randomized 1:1 to either telemonitored

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home blood pressure monitoring with physician-assisted self-management, or standard NHS-led care from their primary care practitioner and midwives. Randomization was conducted with secure web-based software (Castor® EDC) with minimization for gestational age, whether the patient had a diagnosis of pre-eclampsia or gestational hypertension, and prescription of an angiotensin converting inhibitor at time of randomization. Due to 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 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 6-8 weeks review with their family physician or specialist.[13] Titration of antihypertensive treatment was at the discretion of their supervising health-care professionals (primary care physician and midwife). As previously reported[16] participants in the intervention group had initial discharge medications decided by their clinical care team[13], 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 paper for further details).[17] Choice of medication and titration regimes were standardized based on recommendations from the 2019 UK National Institute of Clinical Excellence guidance.[13]

There were four study visits, after pre-screening enrolment, occurring at days 1-6 postpartum (Visit (V) 1; Baseline), 1 week (V2), 6 weeks (V3) and 6-9 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®

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Philips, Amsterdam, Netherlands) at baseline (V1) with data collection based on a British Society of Echocardiography minimum dataset[18]. 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 electrocardiogram (ECG) gated with a precordial four lead ECG. Images were retrospectively ECG gated with a precordial four lead ECG. CMR images were acquired using a standard previously reported protocol[19] 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 (ABPM; model 90217, Spacelabs Healthcare, Snoqualmie, USA) at the time of V4.[20] Herein we report the pre-specified 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 pre-specified outcomes of cardiac structure and function using echocardiogram and CMR were reported in the protocol paper.[17]

Echocardiograms were performed using a Philips CX50® portable echo machine for all baseline visits at V1. All follow up echo scans at the V4 were done using a Philips EPIQ 7® or IE33®. All echo machines were equipped with a 2D phased array transducer and scans were performed in the left lateral decubitus position. All echocardiography measurements followed standard society guidelines [18, 21] and the modality was primarily performed to assess

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diastolic function including pulsed wave (PW) Doppler assessment of the mitral valve inflow and pulmonary vein inflow, tissue Doppler imaging (TDI) of lateral and septal walls of the left ventricle and assessment of left atrial volumes. In addition, standard 2D measures of left ventricular wall thickness as well as volumes based on Simpsons biplane measures were used to assess cardiac structure and function. Relative wall thickness as a measure of concentric hypertrophy was calculated as 2 x posterior wall diameter/left ventricular internal diastolic diameter[21]. Left ventricular global longitudinal strain was assessed by speckle tracking 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 are reported. Intra- and Inter-observer coefficients of variation for echo measurements are reported in the supplementary material (Table S1).

For the CMR, balanced steady-state free precession (bSSFP) images were acquired during breath hold at end expiration. Using two, three and four chamber views to plan images in line with the atrio-ventricular valves, a stack of short-axis images were acquired at 1 cm intervals to include the entire left and right ventricles. Image analysis was performed using CVI42 versions 5.12.1 (Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada). The short-axis stack of images was analysed 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[22] 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 cm3). End-

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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 end-diastolic and end-systolic volume. Ejection fraction was calculated as stroke volume divided by end-diastolic volume. Wall thickness was measured at mid-ventricular level in six segments (anterior, lateral, inferior, inferolateral, inferoseptal and anteroseptal).[23] Mean wall thickness values were calculated from these six measures. Myocardial T1 values were measured from short modified look locker inversion sequences (ShMOLLI) using standardized protocols published previously.[24] A single slice T2 map was performed using Siemens MYOMAPS product sequences. 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 using CVI42 version 5.12.1. Normal values for comparison were obtained on the same 3T PRISMA scanner in 16 age matched females using the same protocol. Extra-cellular volume (ECV) was calculated using haematocrit obtained at time of scan and using T1 values pre- and post-gadolinium administration.[19] 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 one post-randomization 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 pre-specified minimisation factors stated in the statistical analysis plan. The level of statistical significance was tested as a 5% two-tailed significant 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

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pressure readings. Where measures did not satisfy the model assumptions for linear regression, non-parametric 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.

Data Sharing

The data that support the findings of this study are available from the chief investigator, [PL], upon reasonable request subject to the approval of the Sponsor [University of Oxford] and the Trial steering committee.

Results

Demographics

Between February 21st 2020 and March 21st 2021, 220 participants were enrolled with 112 assigned to the intervention arm and 108 to the usual care (control) arm. 216 of these participants 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 randomisation group, are presented in Table 1. Demographics of all those randomised and the subgroup who had CMR are presented in Tables S2 and S3, respectively, and are similar to those presented in Table 1. ~40% had gestational hypertension and ~60% pre-eclampsia, which is consistent with the inclusion criteria of the trial requiring on ongoing medication requirement at hospital discharge. The two groups were similar in obstetric and pregnancy characteristics at baseline,

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except a higher proportion of participants had a prior 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 X^2 analysis with the exception of a higher proportion breast-feeding 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%, labetalol 30% for intervention vs enalapril 43%, nifedipine 30% and labetalol 27% for usual care). At six 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 (IQR 13.9 to 41.5 days). Amount of antihypertensives prescribed, defined by median World Health Organization (WHO) defined daily dose (DDD)[25], was similar between groups at V1 and V4. However, at V2 (week 1), more antihypertensives were prescribed (WHO DDD 1.5 vs 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 ventricular wall thickness 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^2 (95% CI 3.01 to 1.00 ml/m^2; P=<0.001) lower in the intervention group at V4 with reductions in indexed end-diastolic (-4.74 ml/m^2; 95% CI -6.23 to -3.26, P=<0.001) and end-systolic volumes (-2.69 ml/m^2; 95% CI -3.57 to -1.81 ml/m^2, P<0.001). Left ventricular remodeling was accompanied by higher left ventricular systolic function in the intervention group, assessed by Biplane Simpson's method (+1.79%; 95% CI 0.84 to 2.75%, P=<0.001),

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and improved peak global longitudinal systolic strain (GLS) (-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 (LAVi) of 4.33 ml/m^2 (95% CI -5.52 to -3.21, P=<0.001).

Cardiovascular magnetic resonance

CMR scans were obtained in 174 participants at V4, of which 93 were in the intervention group and 81 in the usual care group. Cardiac measures (reported in Table 3 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^2 (95% CI -7.99 to -4.74, P<0.001). LV 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^2 (95% CI -6.77 to -0.98 at P=0.009) and 3.25 ml/m^2 (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^2 (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 (ShMOLLI) 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 values in the intervention arm was 1161.2+/-26.4 ms, and in the usual care group 1155.1+/-26.1 ms. Mean T2 values were 41.1+/-1.8 ms in the intervention group and 40.9+/-1.7 ms in the usual care group. Late gadolinium imaging

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was offered as an optional addition to the protocol to participants who were not breastfeeding at the time of cardiovascular magnetic resonance. 36 women agreed, with analysable data available for 34, of which 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 which 7 were in the intervention group and 5 in the usual care group. One participant has a faint mid-wall band but this did not correspond to oedema 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

Pre-specified sensitivity analyses were performed adjusting for antenatal blood pressure differences, rather than baseline postnatal blood pressure values, and are reported in the supplementary 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 following exclusion of the 24 participants still on medication are shown in the supplementary Tables S7 and S8, which also demonstrate no significant impact on the differences in cardiac structure and function between the intervention and usual care arms described in Table 2 and 3.

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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 nine months after pregnancy even though the blood pressure intervention is only required for the first 40 days, on average. Exploratory T1 and T2 mapping and ECV

values, in conjunction with late gadolinium images, show no significant residual edema or inflammation at nine months postpartum. Furthermore, the changes in myocardial wall thickness do not appear to be due to excess fibrosis, suggesting the primary benefit is driven by change in myocyte size and function.

During a normotensive pregnancy, Simmons et al reported that left ventricular mass index increases from 66±13 g/m^2 in the first trimester to a peak of 76±16 g/m^2 in the third trimester, before returning to 67±11 g/m^2 at 13 weeks postpartum [26]. Hamad et al [27] found preeclampsia was associated with an average 15 g/m^2 higher left ventricular mass index during pregnancy as well as reduced diastolic function. Melchiorre et al have reported changes in left ventricular systolic function assessed by global longitudinal strain are also evident proportional to the severity of the hypertensive disease.[9] 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 reported similar mean differences in left ventricular measures in those who had preeclampsia by 13 weeks postpartum suggesting normalisation of cardiac parameters after hypertensive pregnancy is possible. However, in larger studies, such as those by Ghossein et al,[28] a significant proportion of women continue to have persistent changes in indexed left ventricular mass at nine months postpartum and McCarthy et al found 50% of a cohort with early onset preeclampsia had significant cardiac structural changes by the end of the first year postpartum.[29] Indeed, women with persistent abnormalities of left ventricular structure appear to have a higher risk profile as they are more likely to develop hypertension within the next few years after pregnancy.[1, 6]

Why some women continue to display an adverse cardiac phenotype, whereas patterns normalise in others, had been unclear. We hypothesised this may relate to the haemodynamic status of the women during the first few weeks after pregnancy when the

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majority of post-pregnancy remodeling occurs. After a hypertensive pregnancy there can be significant blood pressure variability[10,30, 31] but in the SNAP-HT[32,33] randomised study we demonstrated the feasibility of blood pressure optimisation postpartum using self-monitoring and management. Women who received the intervention appeared to have improved blood pressure control during the first year post-partum, and the POP-HT trial has now demonstrated that physician optimised blood pressure self-management does lead 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.[16]

Strikingly, these reductions in postpartum blood pressure with self-monitoring persist for at least nine months, even after the women have stopped taking medication and, in SNAP-HT, were still evident four years later.[33] 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 post-partum intervention, in particular left ventricular mass, was reported in the PICk-UP trial[34], which randomised women to receive enalapril on top of standard antihypertensive medication postnatally. Diastolic blood pressure was around 7mmHg 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[35] was not clear. Around 50% of women in POP-HT received enalapril postpartum, in line with recent 2019 UK national guidance regarding first choice postnatal drugs[13]. Use of the medication was similar in both arms and 90% of participants were off treatment completely by 6 weeks. Furthermore, very few participants in the SNAP-HT pilot study were on enalapril as this trial preceded the 2019 guidance and was based on NICE CG107.[36] Together this suggests an

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independent effect of the self-management process, rather than specific medication, on cardiac remodeling.

Ejection fraction, GLS 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 anti-hypertensive effect of the intervention and not just changes in cardiac structure. Nevertheless, the intervention group had a 6.4 g/m^2 reduction in left ventricular mass compared to 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 [37] observed in the Framingham cohort that for every 10 g/m^2 lower left ventricular mass index there was an around 40% lower incidence of cardiovascular disease over the subsequent eight years. Similarly, in the MESA study 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.[38]

There are several limitations to consider. Firstly, due to 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. Secondly, the study was impacted 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 less than 10%, and there were no significant differences between the full cohort, and those who had imaging performed. Thirdly, the majority of participants were of white British ethnicity, due to the nature of local population demographics.[39] Additional work is required to understand whether similar patterns of remodeling in response to the intervention are seen in other ethnic and geographic

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groups, but a recent observational study in a large multi-ethnic cohort showed similar longitudinal echo changes to that seen in our control cohort[14], as did other work on self-monitoring ante-natally.[40] Fourthly, participants with chronic hypertension were excluded.[17] Therefore the impact of pre-existing 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 prior hypertensive pregnancy. Therefore, based on our findings in this study, we might expect these women to be more likely to have adverse blood pressure and cardiac changes pre-pregnancy. If anything, this be expected to dilute the impact of the subsequent intervention on postnatal remodeling. However, overall there remained a relatively small number of women affected by a prior 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. Finally, models of care delivery that provide the close day-day supervision that the research physicians offered needs to be explored to effectively translate this intervention into widespread clinical practice

Prior 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 fulfil criteria for stage B heart failure due to structural cardiac changes.[7,6,18,41] Yet there remains no consensus on optimal policies for screening, prevention, or management of this higher cardiovascular risk. This trial suggests that optimised blood pressure control during the first six weeks after pregnancy can regress the adverse cardiovascular changes known to occur during a hypertensive pregnancy. A paradigm shift towards improving healthcare 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.

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LM and PL are supported by the NIHR Oxford Biomedical Research Centre. LM is a part-time employee of EMIS Group plc. PL is a founder and shareholder of a healthcare imaging company and a named inventor on patents related to cardiovascular imaging. RM has received BP 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. CR has received consultancy fees from Sensyne Health for work on telemonitoring products. JK is an executive committee member of the British Society of Cardiac imaging and Cardiac CT (BSCI/BSCCT).

Supplemental Materials

Tables S1-8

Figure S1

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

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Circulation

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Table 1: Characteristics of participants who underwent echocardiographic imaging.

Parameter, *Unit*	Intervention (n = 110)	Usual Care (n = 107)
Patient characteristics		
Mean age, y (SD)	33.7 (5.1)	32.8 (5.0)
Mean booking BMI, kg/m² (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, m² (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)
Pre-pregnancy smoking reported[a], No. (%)	24 (21.8)	31 (29.0)
IMD quintile[b], median (IQR)	2 (1, 3)	1 (1, 2)
Race and ethnicity[*], n (%)		
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)
Pregnancy characteristics		
Pre-eclampsia[c], No. (%)	67 (60.9)	64 (59.8)
Gestational hypertension[c], No. (%)	43 (39.1)	43 (40.2)
HELLP syndrome subset of pre-eclampsia[c], No. (%)	5 (4.5)	1 (0.9)
Median duration of ante-natal antihypertensive treatment, days (IQR)	4.0 (2.0, 15.8)	5.0 (1.0, 18.8)
Early diagnosis of pre-eclampsia or gestational hypertension ≤ 33 weeks and 6 days gestation, No. (%)	24 (21.8)	23 (21.5)
Median gestation at delivery, wks (IQR)	39.2 (37.0, 40.3)	39.1 (37.0, 40.6)
Primiparous, No. (%)	67 (60.9)	75 (70.1)
Previous hypertensive pregnancy, No. (%)	30 (27.3)	10 (9.3)
Assisted reproduction pregnancy, No. (%)	7 (6.4)	11 (10.3)
Multi-fetal pregnancy, No. (%)	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 Caesarean section[e] (%)	47 (42.7)	40 (37.4)
Elective Caesarean section[e] (%)	5 (4.5)	6 (5.6)
Fetal growth restriction[*f], No. (%)	25 (22.7)	28 (26.2)

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Neonatal unit admission[g], No. (%)	29 (26.4)	33 (30.8)
Mean birthweight, kg (SD)	3.1 (0.8)	3.1 (2.9)

[a]Smoking prior to pregnancy for a > 12-month period
[b]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); [c]Classification as gestational hypertension, pre-eclampsia and HELLP syndrome were based on definitions provided in the NICE guideline (NG 133) "Hypertension in pregnancy; diagnosis and management", definitions for which can be found in the protocol provided in the supplementary material
[d]DDD refers to the defined daily doses as per World Health Organization (WHO)[31], 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.
[e]Category of caesarean section was defined as per NICE guidance on Caesarean birth (NG 192). The term "Elective Caesarean" refers to an electively scheduled caesarean timed to suit the patient or health care provider. "Emergency Caesarean" spans the categories of "no maternal or fetal compromise but needs early birth" to "immediate threat to the life of the patient or fetus".
[f]IUGR defined as a fetus whose weight was <10th percentile for its gestational age postpartum;
[g] A Neonatal Unit is a part of a hospital which 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.
[*]In accordance with UK recommendations, self-reported ethnicity was recorded using standard descriptions derived from those used by UK Office for National Statistics

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Table 2: Echocardiographic measures of cardiac structure and function from baseline to V4 adjusted for baseline echo 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† (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, 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
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							

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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
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^2	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^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*

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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; LV GLS, left ventricular 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) [21]; SV, stroke volume; SWd, septal wall diameter in diastole. * 95% confidence interval does not cross zero.
† Nonparametric: median (IQR). The nonparametric GLS and CO were analysed by Mann-Whitney U test
‡ baseline intervention n=98, usual care n=86, V4 intervention n=96, usual care = 77 (numbers for GLS less as the image quality required for strain led to more cases being excluded)
&All regressions were performed on measurements at 9 months with the baseline measurement included in the model

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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% C.I.*	P value
Haemodynamics					
HR, bpm	72.8 (11.2)	72.1 (10.9)			
LV SV indexed (ml/m^2)	42.31 (5.65)	42.93 (6.07)	-0.58	-2.34 to 1.19	0.52
RV SV indexed, (ml/m^2)	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	-.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/m^2)	66.27 (8.95)	70.07 (10.31)	-3.87	-6.77 to -0.98	0.009*
LV ESVi (ml/m^2)	23.05 (5.05)	27.04 (5.72)	-3.25	-4.87 to – 1.63	<0.001*
RV EDVi, ml/m^2	70.22 (11.73)	71.53 (10.34)	-1.50	-4.83 to 1.83	0.37
RV ESVi, ml/m^2	27.92 (6.61)	30.14 (6.27)	-2.43	-4.35 to -0.51	0.014*
LV mass indexed to BSA (g/m^2)	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*

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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*

*mean of 2nd and 3rd bed-side blood pressures obtained during V1 (Baseline visit) on the postnatal ward
Parametric: mean (SD). HR, heart rate; SV, stroke volume;; LV, left ventricular; RV, right ventricular; CO indicates cardiac output; 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 baseline diastolic blood pressure (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.

Circulation

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Figure Legends

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† (GLS) from baseline¥ to 9 months by randomization group.

† Assessment of strain by speckle tracking was undertaken offline using semi-automated 2D Cardiac Performance Analysis Software (TomTec®, Munich, Germany).

¥ Baseline echo performed day 1-6 on postnatal ward.

B) Changes in LV Relative Wall Thickness (RWT)§ from baseline¥ to 9 months by randomization group.

§ RWT calculated as per American Society of Echocardiography (ASE) recommended methodology i.e., (2 x PWd/LVIDd).[21]

C) Changes in indexed Left Atrial (LA)# Volumes from baseline¥ to 9 months by randomization group.

LA volumes measured by Biplane Simpson's method. LA volumes were indexed to body surface area (BSA), calculated using the Mosteller formula.

D) Changes in diastolic function‡ from baseline¥ to 9 months by randomization group.

‡ Diastolic function assessed by E/E' average (ratio of early mitral inflow velocity and averaged early mitral annular lateral and septal diastolic velocity).

Violin plots with overlayed box plots. Tukey box plots represent median and interquartile range (IQR), whiskers represent largest value within 1.5 times IQR above 75th percentile and smallest value within 1.5 times IQR below 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%

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confidence interval and p-values are provided above each plot, representing the significance between control and intervention groups at 9 months.

*All measurements adjusted for mean baseline postnatal blood pressure in the model

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).

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).

B) LV Ejection Fraction (LVEF)‡ and (C) Right Ventricular Ejection Fraction (RVEF)‡ at 9 months postpartum per randomization group, either control (left, pink) or intervention (right, blue).

‡ 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.

Violin plots with overlayed box plots. Tukey box plots represent median and interquartile range (IQR), whiskers represent largest value within 1.5 times IQR above 75th percentile and smallest value within 1.5 times IQR below 25th percentile, and data points beyond the whiskers represent values >1.5 times and <3 times the IQR. Adjusted mean difference*, 95% confidence interval and p-values are provided above each plot.

*All measurements adjusted for mean baseline postnatal blood pressure in the model.

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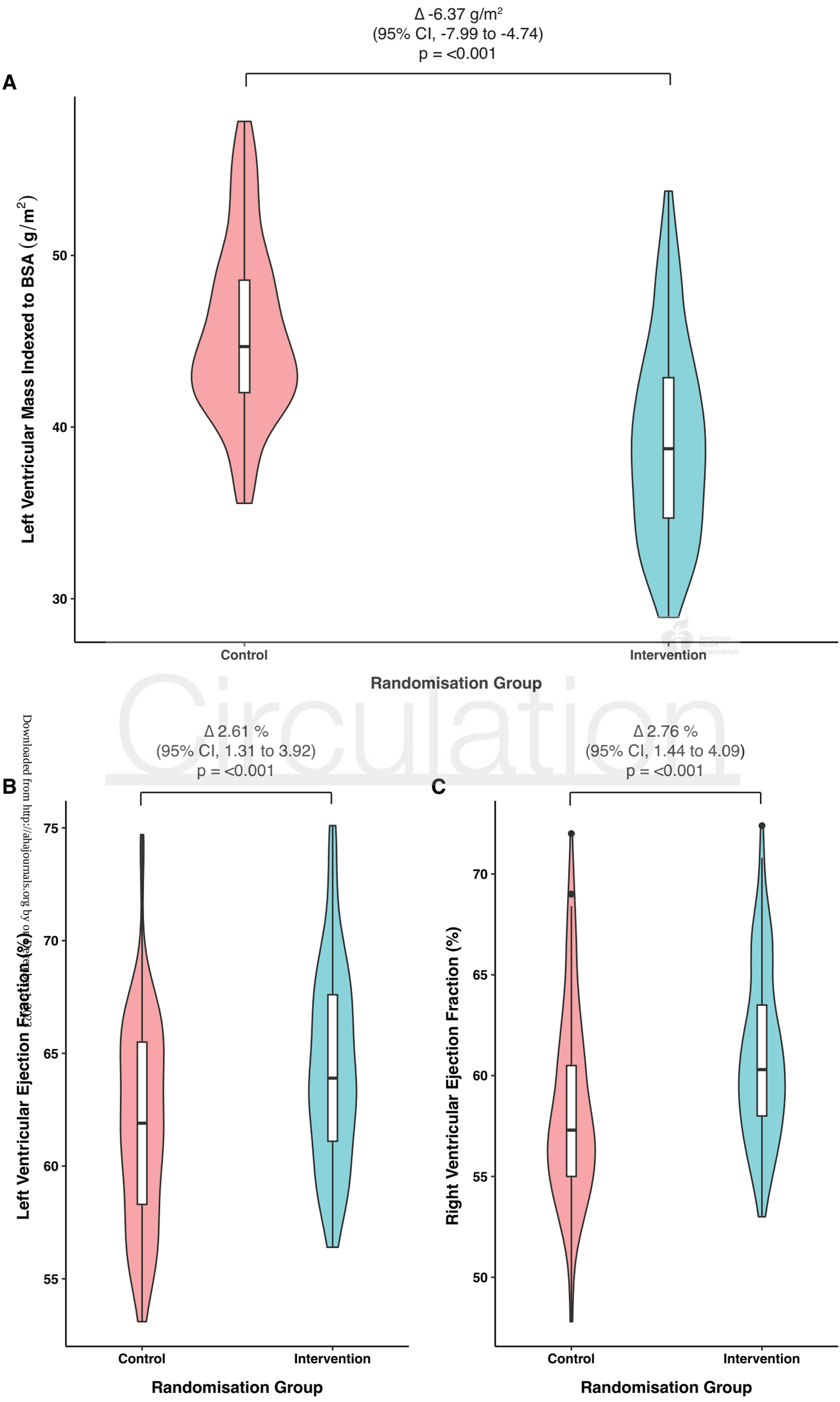

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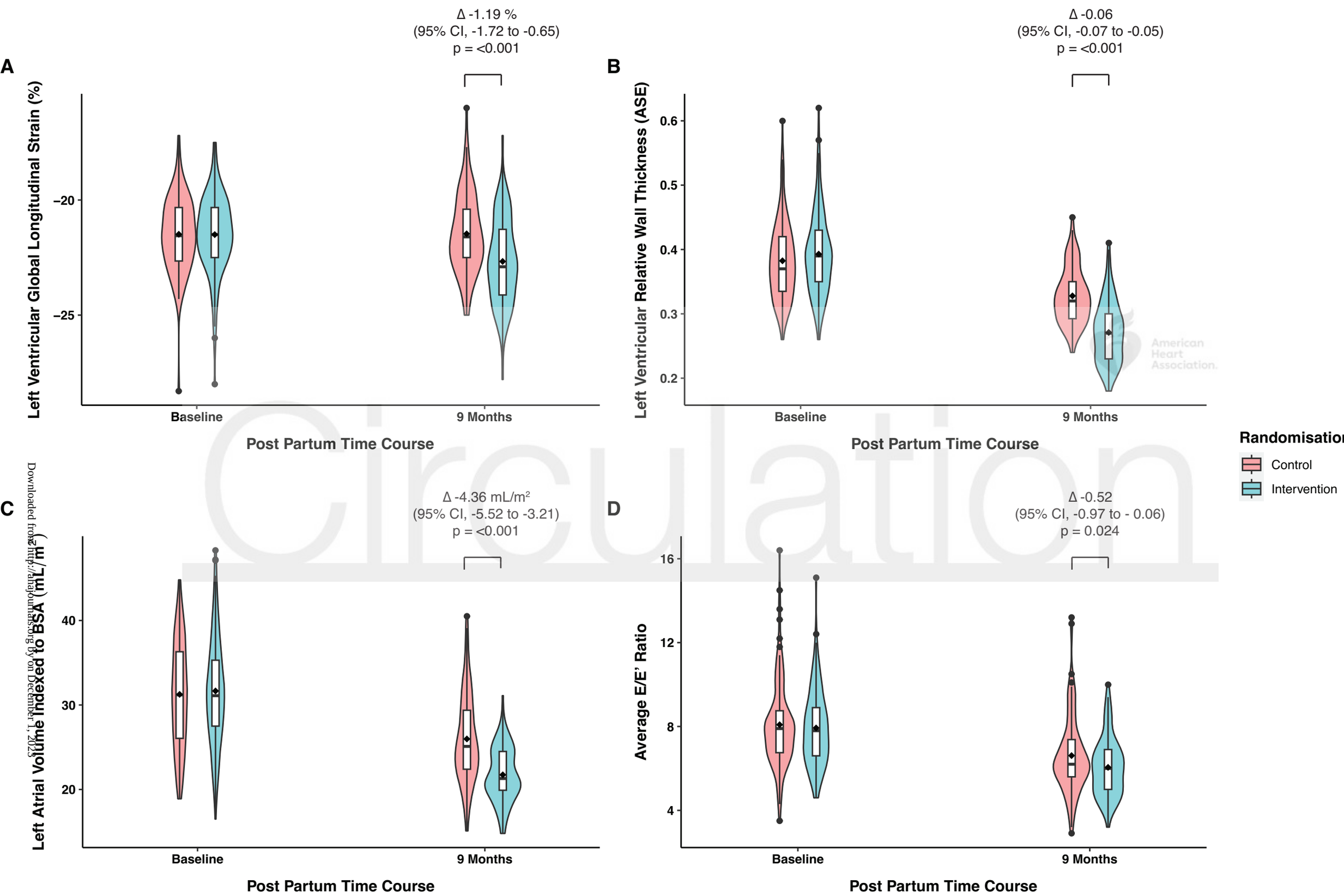

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