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Postnatal enalapril to Improve Cardiovascular fUnction following preterm Preeclampsia (PICk-UP): a randomised double-blind placebo-controlled feasibility trial

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Abstract

Hypertensive disease in pregnancy is associated with future cardiovascular disease (CVD) and therefore provides an opportunity to identify women who could benefit from targeted interventions aimed at reducing cardiovascular morbidity. This study focused on the highest-risk group, women with preterm preeclampsia, who have an 8-fold risk of death from future CVD. We performed a single-centre feasibility randomised controlled trial (RCT) of 6 months' treatment with enalapril to improve postnatal cardiovascular function. Echocardiography and haemodynamic measurements were performed at baseline (< 3 days), 6 weeks and 6 months post-delivery on 60 women. At randomisation, 88% of women had diastolic dysfunction and 68% had concentric remodelling/ hypertrophy. No difference was seen in total vascular resistance (p=0.59) or systolic function (global longitudinal strain: p=0.14) between groups at 6 months. However, women treated with enalapril had echocardiographic measurements consistent with improved diastolic function (E/E': p=0.04) and left ventricular (LV) remodelling (relative wall thickness: p=0.01; LV mass index: p=0.03) at 6 months, compared with placebo. Urinary enalapril was detectable in 85% and 63% of women in the enalapril arm at 6 weeks and 6 months, respectively. All women responded positively to taking enalapril in the future. Our study confirmed acceptability and feasibility of the study protocol with a recruitment to completion rate of 2.2 women per month. Importantly, postnatal enalapril treatment was associated with improved echocardiographic measurements;

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Disclosure
None.

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these early improvements have the potential to reduce long-term CVD risk. A definitive, multi-centre RCT is now required to confirm these findings.

Keywords

pregnancy and postpartum; preeclampsia/pregnancy; echocardiography; angiotensin-converting enzyme inhibitor; cardiovascular disease prevention

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality worldwide, accounting for more than 300,000 deaths in women in the UK per annum(1). It is increasingly recognised that primary prevention is more effective than treating established CVD(2); however this requires identification of at-risk individuals prior to the onset of disease.

For many asymptomatic women, antenatal care is their first adult engagement with the healthcare system. Consequently, pregnancy and the early postnatal period provide an ideal window for risk screening and primary prevention. Preeclampsia is a pregnancy-specific condition, affecting 3-5% of pregnant women(3). It is defined by the presence of the following clinical end-points: new or worsening hypertension after 20 weeks' gestation with proteinuria or other features suggestive of preeclampsia (including multi-organ and placental dysfunction)(4). Preeclampsia is thought to derive from placental malperfusion(5), oxidative stress, release of inflammatory factors into the maternal circulation(6) and subsequent maternal endothelial dysfunction(7). Despite the cure for preeclampsia being delivery of the infant, maternal health implications persist well beyond the pregnancy(8–14). In particular, preeclampsia is associated with maternal postnatal cardiovascular dysfunction(8,9) and long-term CVD risk(10–14) including a twofold risk of ischaemic heart disease and stroke and fourfold risk of hypertension in later life(11). The association between preeclampsia and future CVD persists despite accounting for mutual risk factors, including age, obesity and pre-pregnancy hypertension(11). Women with preterm preeclampsia (delivery before 37 weeks) are at particular risk; they are 8 times more likely to die from CVD(13).

Not only is CVD more common in women with preeclampsia, but it tends to occur earlier and with a higher fatality rate(12). Most recent studies demonstrating increased CVD risk following preeclampsia, had a median follow-up less than 20 years, with some presenting as early as 1 year postpartum(10,13,15–19). Despite cardiovascular impairment likely being a consequence as well as a trigger of preeclampsia, research to date has mainly focused on antenatal screening and treatment. (20)(21)(22) However, the early postnatal period provides an ideal window for intervention to improve long-term cardiovascular health and future pregnancy outcomes, with less pharmacological restrictions than the antenatal period. For example, angiotensin-converting enzyme (ACE) inhibitors are contraindicated in pregnancy, due to associated fetopathy(23), yet they are considered safe first-line antihypertensives postpartum, irrespective of breastfeeding status(24–26).

Women identified as having cardiovascular dysfunction in the interval between pregnancies are at an increased risk of preeclampsia recurrence(27). A postnatal case-control study of

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women with previous preterm preeclampsia found a significant difference in cardiovascular function between those who went on to develop recurrent preeclampsia and those who did not(27). Total vascular resistance (TVR) was the best independent predictive factor of recurrent preeclampsia (27). Given these data, it is plausible that the risk of preeclampsia recurrence could be reduced by correcting postnatal cardiovascular dysfunction, in particular, TVR. There is also some evidence supporting the association between raised TVR and long-term CVD risk(28), indicating the potential to reduce long-term risk in the early postnatal period.

There is extensive evidence to support the cardioprotective effects of ACE inhibitors(29,30). The HOPE study(29), during which participants at high risk of CVD were randomised to ramipril or placebo, was stopped prematurely due to the 22% reduction in myocardial infarction/cerebrovascular accident/death from CVD. This was irrespective of hypertension or other confounders(29). ACE inhibitors provide cardioprotection through a variety of mechanisms, including anti-inflammatory effects(31), increased nitric oxide bioavailability(32) and diminished fibrosis(33). These are all relevant to preeclampsia which has an inflammatory component(7) and is associated with reduced nitric oxide bioavailability(34) and vascular fibrosis(35).

To our knowledge, the potential of a postnatal intervention to correct cardiovascular impairment, and thereby influence long-term CVD risk following preterm preeclampsia, has not yet been investigated. This study aimed to assess the feasibility of an early postnatal intervention in women who have had preterm preeclampsia to improve cardiovascular function and remodelling.

Methods

Trial design

The PICk-UP study was a single-centre feasibility randomised double-blind placebo-controlled trial of 6 months' treatment with enalapril to improve postnatal cardiovascular function in women with preterm preeclampsia. Enalapril was the chosen intervention in this study since most of the safety data relating to ACE inhibitors when breastfeeding relates to enalapril and captopril(24,26). Given associated fetopathy, women were advised not to conceive during the trial, and to stop taking the study medication if found to be pregnant. The trial was funded by the Medical Research Council and prospectively registered at clinicaltrials.gov (study identifier: NCT03466333). The protocol and all participant-facing information were approved by the local research ethics committee (18/NW/0253), Health Research Authority (HRA) and Medicines and Healthcare products Regulatory Agency (MHRA). All study procedures were carried out at St Mary's Hospital, Manchester, UK, in accordance with institutional guidelines. All participants gave written informed consent prior to randomisation. The data that support the findings of this study are available upon request.

Eligibility criteria

Postnatal women aged 18 and over, with no known cardiac disease and creatinine<100μmol/L, who had preterm preeclampsia (requiring delivery before 37 weeks' gestation) were eligible for enrolment (see supplementary for definition). Women were excluded if they were unable to consent; had known cardiac disease; had a contraindication to ACE inhibitors; were currently taking ACE inhibitor / Angiotensin II Receptor Blocker (ARB) or had known renal artery stenosis.

Randomisation and study procedures

Participants were allocated to enalapril or placebo using block randomisation in a 1:1 ratio. Following consent and randomisation, postnatal baseline investigations were performed within 3 days of delivery. These included echocardiography (to measure left ventricular (LV) remodelling, systolic and diastolic function), arteriography (to measure arterial stiffness using pulse wave velocity [PWV] and augmentation index [AI]), BP(36) and cardiovascular and placental biomarkers (high-sensitivity troponin T [hs-cTnT], N-terminal pro b-type natriuretic peptide [NTproBNP], PlGF and sFlt; see supplementary material). Enalapril dose was titrated as follows: 5mg once daily for 1 week, then 10mg for 2 weeks then 20mg maintenance dose(37). Dose titration visits (at 1 week ±3 days and 3 weeks ±3 days) comprised of BP measurement, renal function and verbal check of side effects. Baseline cardiovascular measurements were then repeated at visits 4 and 5 (6 ±1 weeks and 6 months ±2 weeks, respectively). Figure 1 provides an overview of the study design.

Postnatal hypertension was treated as per NICE guidance (with calcium channel blockers, beta blockers and/or alpha blockers)(25), irrespective of treatment allocation. Changes to antihypertensive medication were made based on standard measurements of BP, using targets defined by the clinical team.

Adherence was measured using three different methodologies: verbal recall during each visit and phone call; pill counts by pharmacy and high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS)(38) of urine samples from visits 4 and 5.

Details of the investigational medicinal product (IMP) and clinical measurements are included in the supplementary material.

Reproducibility

A subset of 20 participants had echocardiography exams performed by two observers to assess interobserver agreement (IOA). Both observers analysed their own scans, blinded to the other's results. MAP was not repeated for assessment of TVR reproducibility; therefore this was assessed using repeat measurements of CO alone. Intraclass correlation coefficients (ICC) were calculated using a two-way mixed effects model. Reproducibility was classified as poor (ICC < 0.4), fair-to-good (ICC = 0.4 - 0.75) and excellent (ICC ≥ 0.75)(39).

Primary and secondary outcomes

The primary process outcome was recruitment rate (number of women eligible, recruited and completing study per month). The primary clinical outcome was reduction in TVR from

baseline to 6 months post randomisation following treatment with enalapril, compared with placebo.

The secondary process outcome was the acceptability of the intervention in postnatal women, which was based on treatment adherence and questionnaire feedback(40,41). Prespecified secondary clinical outcomes included a change in measures of cardiac structure and function and biomarkers from baseline to 6 months post randomisation following treatment with enalapril, compared with placebo. The echocardiography measures of cardiac structure and function comprised of E/E' and E/A ratios, tricuspid valve (TV) regurgitation, left atrial volume index (LAVi), LVEF, CO, stroke volume (SV), RWT, LVMi, concentric/eccentric remodelling, global longitudinal strain (GLS), LV basal, mid and apical strain, and $SR_{E/A}$. The measured biomarkers were hs-cTnT, PlGF, sFlt and NTproBNP. Pre-specified normal cut-offs were defined for each of the echocardiography measures, as described In the supplementary material(42–48).

Statistical analysis

A statistical analysis plan was agreed by the Trial Management Team and trial statistician prior to analysis. The principle of intention-to-treat was adopted for the primary and secondary outcomes. These analyses included all randomised participants as allocated, for whom the outcome(s) of interest (and any covariates) were available. Categorical data was presented using counts and percentages. Continuous data were presented as mean (standard deviation) and median (range) for parametric and non-parametric variables, accordingly.

Continuous variables were compared between the two groups at 6 weeks and 6 months, using standard Analysis of Covariance with the baseline measurement included as a covariate. At the same time points, categorical data were compared between groups using logistic regression (adjusted for baseline) and Chi-squared test.

Sample size calculation

Previous studies investigating baseline 6-month changes in echocardiographic measurements were not available at the time of study development; this study was therefore powered to identify a reduction in TVR of 255 $dyne.s^{-1}cm^{-5}$ in the enalapril group compared with placebo at 6 months postpartum. This outcome was selected as a previous study had demonstrated this magnitude of difference between postnatal women with preeclampsia recurrence and those with non-recurrence(27). Using a mean of 1638±261 $dyne.s^{-1}cm^{-5}$ with a between group difference of 255 $dyne.s^{-1}cm^{-5}$, a sample size calculation determined a minimum sample size of 36 women in total (1:1 allocation). Following review of the non-completion rate, the original target sample size of 40 was increased to 60 to ensure complete data sets on a minimum of 36 women.

Results

Process outcomes

Recruitment to completion rate was 2.2 eligible women per month. The proportion of eligible women that recruited to PICk-UP was 60/84 (71%). The proportion of eligible

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women who completed the study was 40/84 (48%; see figure 2). Five women were lost to follow-up (8%) and one conceived before the end of study (2%). The most common reason for non-completion was postnatal life stressors (8/60, 13%), including neonatal transfers and readmissions. Other reasons included maternal death from acute coronary syndrome (1/60, 2%); severe cardiomyopathy and subsequent watershed stroke preventing further treatment (1/60, 2%); development of a rash (1/60, 2%); health anxieties (1/60, 2%); moving out of area (1/60, 2%) and allocated treatment capsules being “too big” (1/60, 2%).

Of those who completed the study, verbal recall of missed doses was comparable between the two groups (at 6 weeks: enalapril median 0 [0-6], placebo 0 [0-3]; at 6 months: enalapril median 4 [0-55], placebo median 6 [0-75]). Only 12/60 (20%) women returned all of their drug bottles; therefore, pharmacy pill counting was not considered a reliable measure of adherence. Urinary enalapril and enalaprilat were detectable in 17/20 (85%) women in the enalapril arm at 6 weeks and 12/19 (63%) at 6 months. Verbal recall of missed doses was higher in those without detectable urinary enalapril compared to those with (median missed doses at 6 months: 24 [4-55] Vs. 4 [0-18] respectively; $p<0.01$). Two of the women, in whom urinary enalapril was undetectable at 6 months, postponed their final appointment, reportedly causing them to run out of medication in the preceding week.

All of the women who completed the study completed the acceptability questionnaire. The majority of women (33/40, 83%) found it easy to take the allocated treatment; 6/40 (15%) women found it neither easy nor difficult and 1/40 (3%) found it difficult (table S1). In the last month, 20/40 (50%) women recalled missing 1 to 5 doses and 2/40 (5%) recalled missing more than 20 doses. Of those that missed 10 or more doses in the last month (6/40, 15%), the most common reasons for missing doses included a change in daily routine (3/6, 50% attributed it to this sometimes/often), being busy with other things (4/6, 67% attributed it to this sometimes/often) and simply forgetting (4/6, 67% attributed it to this sometimes/often). In terms of overall acceptability, all women said they would be interested in taking it in the future if it was found to be effective.

Demographics & pregnancy outcome

Baseline characteristics and pregnancy outcome data are summarised in table 1 and table S2. At randomisation, 52/59 (88%) had diastolic dysfunction, 14/59 (24%) had systolic dysfunction and 47/59 (68%) had concentric remodelling or hypertrophy (RWT ≥ 0.42)(43–45).

Clinical outcomes

As shown in table 2, there was no difference in the primary outcome (TVR) between groups at 6 months postpartum. Similarly, there was no difference in systolic function (measured by LVEF / GLS / S’). However, women who were treated with enalapril had significantly better diastolic function at 6 months than those treated with placebo, as measured by E/E’ (adjusted difference -1.07, 95% CI -2.08 - -0.06, p=0.04). Allocation to enalapril was also associated with improved LV remodelling at 6 months, compared with placebo (LVMi adjusted difference -9.23g/m^2, 95% CI -7.73 - -0.71, p=0.03). Twelve women in the placebo arm had persistent concentric remodelling / hypertrophy (RWT ≥ 0.42) at 6 months (57%),

compared with 5/19 (26%) in the enalapril arm (adjusted OR 0.26, 95% CI 0.07-1.01, p=0.05). The association between enalapril and E/E' and LVMi persisted after adjustment for the presence of underlying risk factors (table S3).

There was no difference in clinic systolic blood pressure (sBP) between groups at 6 months, however, allocation to enalapril was associated with a significant reduction in diastolic BP (dBP) at 6 weeks and 6 months (table S4). Conversely, arteriography demonstrated a significant difference between groups in peripheral and central sBP at 6 months, but not dBP (table S5). Fewer women were taking antihypertensive medication at 6 months in the enalapril group, but this difference did not reach statistical significance (table S4).

Biomarkers

All women had hs-cTnT and NTproBNP levels within the normal range at 6 months. Four women (7%) had raised hs-cTnT and 4 different women had raised NTproBNP at baseline. There was no difference in hs-cTnT, NTproBNP, sFlt or PlGF between the two groups at 6 weeks or 6 months (table 3).

Safety & tolerability

There was a 10% dry cough rate in the enalapril arm; all women reported resolution of symptoms, despite continuing the study treatment (table 4). No serious adverse events were deemed related to the allocated treatment. Two women in each group (7%) required treatment dose reduction due to a rise in creatinine by > 20%. All of these women later tolerated titration to the maximum dose (20mg enalapril / placebo), with stable renal function. Renal function was comparable between the two groups at 6 weeks (63 [39-103] μmol/L and 64[43-81] μmol/L in the enalapril and placebo groups, respectively).

Reproducibility

Interobserver reproducibility of the primary outcome, TVR, was excellent (ICC: 0.86 (0.65 - 0.95). Interobserver reproducibility of LVM and E/E' were 0.92 (0.81 - 0.97) and 0.82 (0.55 - 9.93) respectively. Interobserver reproducibility of other echocardiography measures was comparable with previous studies, as summarized in table S6(49,50).

Discussion

To our knowledge, this is the first study to investigate whether postnatal cardiovascular dysfunction in women with preterm preeclampsia is modifiable using a postnatal intervention. This feasibility study, of 6 months treatment with enalapril, has confirmed that the study protocol is feasible and the intervention is acceptable to women. Recruitment was achieved 12 months ahead of target and uptake to the study was good (71% of eligible women were recruited). Nevertheless, there was a high non-completion rate (33% of those recruited), largely attributable to unmodifiable postnatal factors. This led to a completion rate of 48% of eligible women. Whilst there was no difference seen in the primary clinical outcome (change in TVR between treatment and placebo at 6 months), significant differences were observed in several secondary clinical outcomes related to cardiac remodelling and diastolic dysfunction.

TVR has previously been identified as predictive of preeclampsia recurrence(20,27); for this reason it was selected as the primary clinical outcome for this study given the absence of other studies which have compared baseline (at the time of birth) to 6 month echocardiography changes. TVR is derived from CO and MAP. No difference was seen between the groups, despite there being a trend towards a difference in MAP. This could be due to a) a lack of effect of enalapril on CO, b) confounding factors affecting TVR (e.g. intrapartum events at baseline, timing of intervention/other antihypertensives), or c) high level biological variability of the MAP/CO measurement and therefore insufficient power in this small feasibility study. Both diastolic function and LV remodelling have been identified as predictors of long-term CVD risk(51–54) and therefore these echocardiography parameters were prespecified as secondary endpoints, although it was not possible to perform formal sample size calculations for these comparisons.

There was a high prevalence of abnormal echocardiographic features at baseline suggestive of cardiac remodelling and dysfunction, consistent with other studies(8,9,55), highlighting the importance of testing interventions in this high-risk group. Mean E/E' was abnormal at baseline and 88% of women had diastolic dysfunction, as defined by the British Society of Echocardiography(44).

This study included a heterogenous group of women with a relatively severe preeclampsia phenotype (46% of newborns were < 3rd centile and 26% required delivery < 34 weeks' gestation). Despite the heterogeneity and size of the cohort, this study was able to demonstrate an improvement in echocardiographic measurements in women treated for 6 months with enalapril, compared with placebo. Given the association between diastolic dysfunction and mortality(56), this treatment could have significant implications for long-term cardiovascular health. Modin et al.(52) quantified the prognostic value of different echocardiography parameters for the prediction of 10-year risk of ischaemic heart disease or heat failure. A 1 unit increase in E/E' (the between-group difference seen in this study at 6 months) had a hazard ratio of 1.11, (95% CI 1.09-1.13) and 5g/m^2 increase in LVMi (compared with 7g/m^2 between-group difference seen in this study at 6 months) had a hazard ratio of 1.16 (1.13 – 1.19)(52). From the current study, however, it is not possible to determine whether these improvements in cardiac function would persist beyond cessation of the intervention, or whether longer treatment duration would be required for improvement in long-term health. A sub-study of the SOLVD trial(57) compared LV volumes between enalapril and placebo groups, 15 days after treatment cessation. Importantly they demonstrated partial, but not complete, reversibility of enalapril effects, indicating the potential for enalapril to slow progression of LV remodelling. All study participants have consented to future contact, though the impact of 6 months' intervention on long-term CVD risk is beyond the scope of the current study.

The difference of E/E' between groups was not reciprocated with E/A; this is likely explained by inferior reproducibility and pseudonormalisation of E/A in women with stage II diastolic dysfunction and the non-linear relationship with disease severity. This study was underpowered to determine the impact of enalapril on the prevalence of cardiac pathology (diastolic or systolic dysfunction or LV remodelling, as defined by discrete cut-offs(43,44)). Our results suggest that treatment with enalapril for 6 months could reduce the prevalence of

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concentric remodelling / hypertrophy; however confirmation with larger numbers is required. Given the progressive nature of cardiovascular dysfunction and risk with increasing age, it is likely that in this relatively young cohort, subclinical differences in cardiac function and morphology will increase over time(58). This difference could therefore reduce long-term risk, as supported by the Framingham study(53), which found that a 50g increase in LVM was associated with a 1.57-fold increase in CVD risk. Although plausible, a larger study is needed to investigate whether long-term CVD and obstetric risk is reduced by postnatal enalapril treatment.

This study is the first of its kind to assess whether cardiovascular dysfunction following preterm preeclampsia is amenable to treatment in the early postnatal period. Other strengths include the prospective randomised controlled study design and that all measurements were performed blinded to treatment allocation. Recruitment was inclusive to all women with preterm preeclampsia in a multi-ethnic population. The process outcomes included realistic assessments of recruitment, compliance and retention. On the other hand, this was a single centre feasibility study and therefore a larger multicentre study is required to confirm generalisability. The positive findings of this study were in the secondary outcomes, and subject to potential type I error; results should therefore be interpreted with caution.

Perspectives

Women with preterm preeclampsia have substantial postnatal cardiovascular impairment. Postnatal treatment with enalapril for 6 months, in this high-risk group, was acceptable to women although in our study there was a significant non-completion rate. Treatment with enalapril was not associated with a change in TVR, but was associated with improved LV diastolic function and remodelling. These findings highlight the potential to use obstetric history to target intervention to improve maternal cardiovascular health in the postnatal period. A definitive, multi-centre randomised controlled trial is now required to confirm these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and significance

What is new?

- High prevalence of cardiovascular impairment in women with preterm preeclampsia immediately after birth and at 6 months post-delivery
- Treatment with enalapril for 6 months post-delivery is acceptable to women and a trial of enalapril to prevent future cardiac dysfunction in women with preterm preeclampsia is feasible
- Treatment with enalapril compared to placebo was associated with improvements in echocardiographic measurements associated with left ventricular diastolic function and remodelling at 6 months

What is relevant?

- These findings highlight the potential to target a postnatal intervention at high risk women to improve long-term maternal cardiovascular health; a definitive randomised controlled trial is achievable and justified

Summary

Six months' postnatal treatment with enalapril was associated with improved LV diastolic function and remodelling. These early improvements have the potential to reduce long-term CVD risk.

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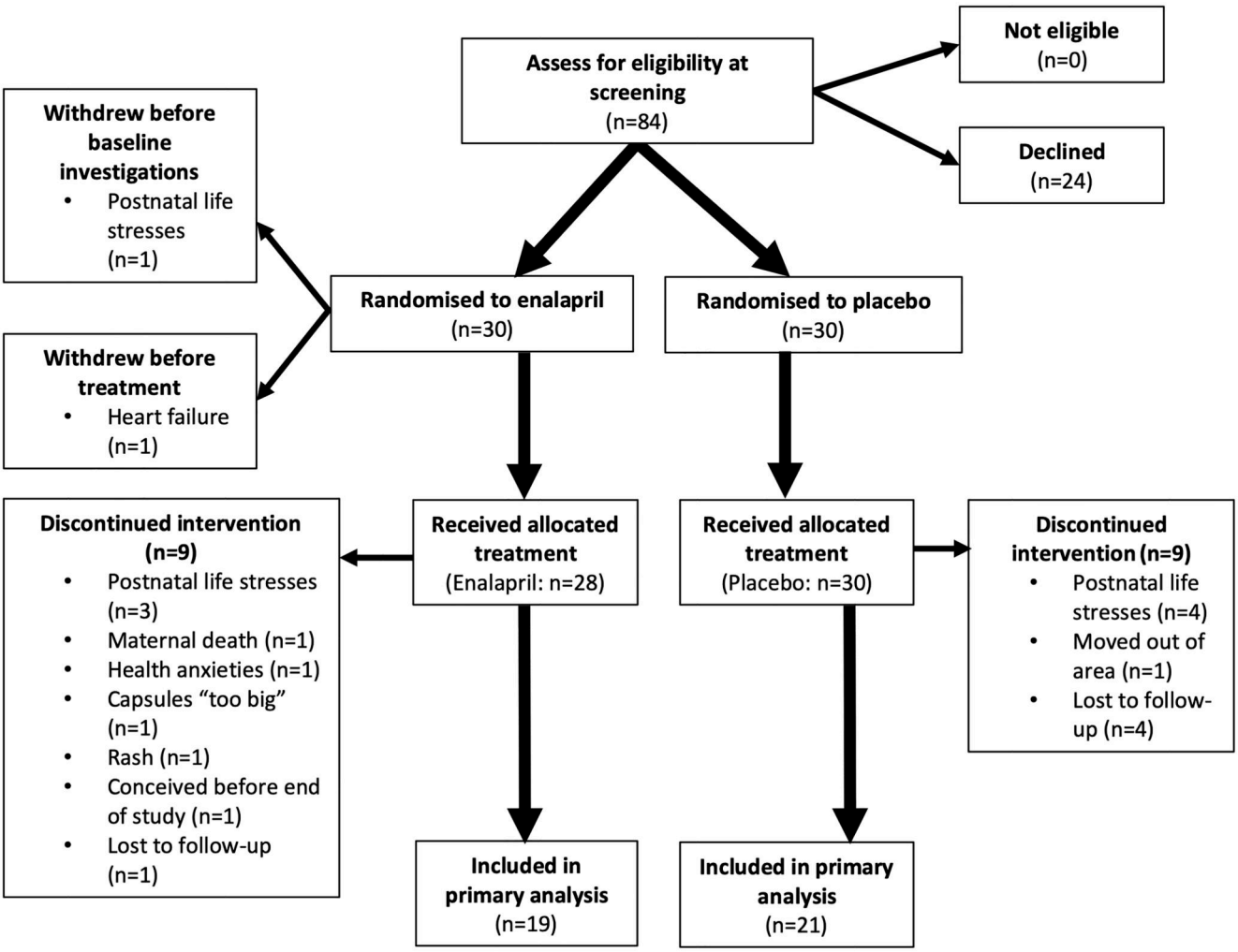

Figure 1. Consort diagram

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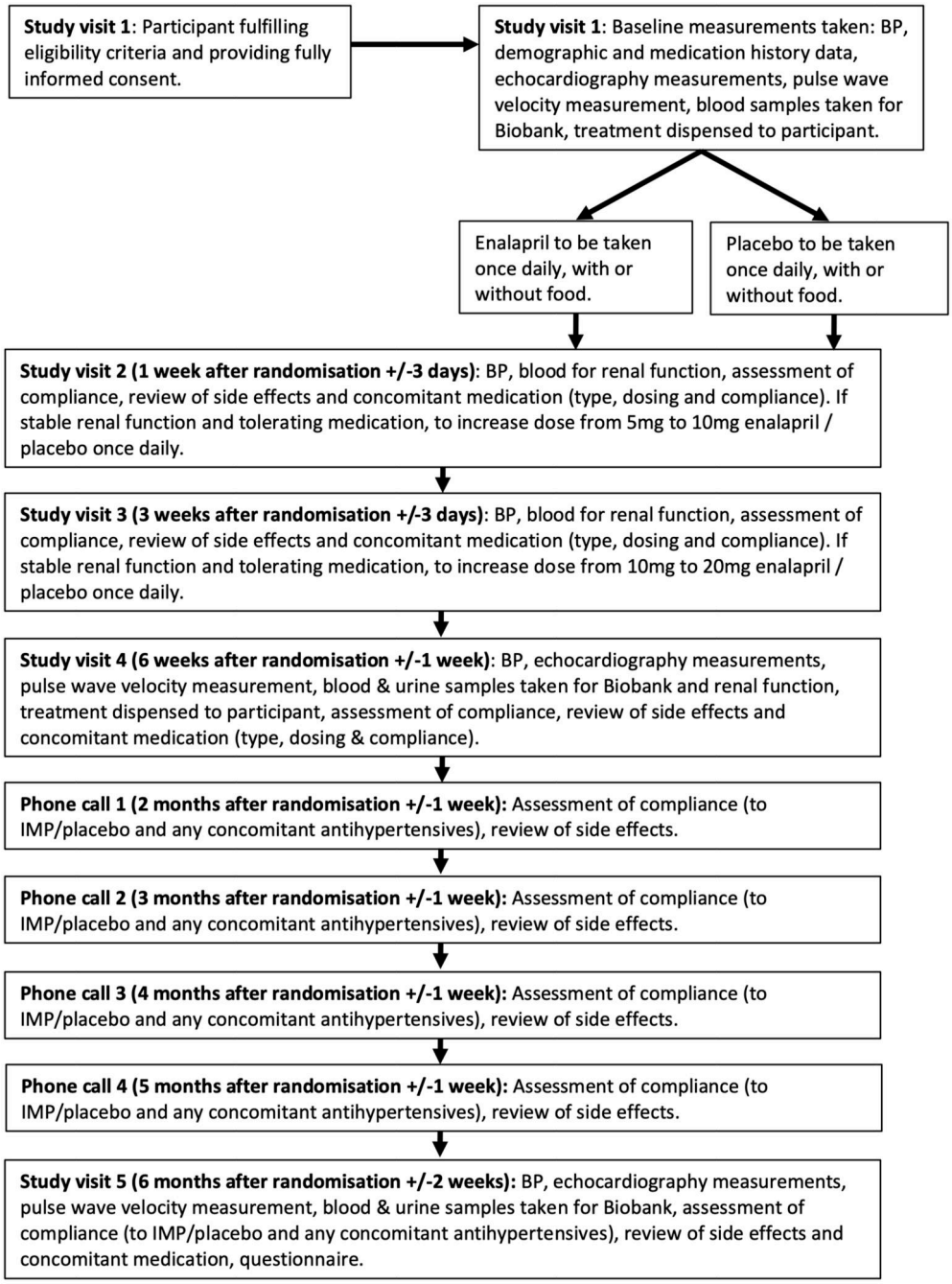

Figure 2. Schematic of study design

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Table 1

Baseline characteristics

Baseline characteristics		Enalapril (n=30)	Placebo (n=30)	All (n=60)
Demographics				
Age at enrolment (years)		34.5 (6.0)	30.9 (6.6)	32.7 (6.6)
Ethnicity	**White**	21 (70%)	17 (57%)	38 (63%)
	Black	4 (13%)	4 (13%)	8 (13%)
	Asian	4 (13%)	9 (30%)	13 (22%)
	Other	1 (3%)	0 (0%)	1 (2%)
Booking BMI*(kg/m^2)		28.0 (19.4 - 37.3)	27.6 (19.3 - 51.0)	27.7 (19.3-51.0)
BMI > 30kg/m^2 at randomisation		12 (40%)	11 (37%)	23 (38%)
Current smoker		5 (17%)	4 (13%)	9 (15%)
Medical history				
Essential hypertension		6 (20%)	6 (20%)	12 (20%)
Renal hypertension		3 (10%)	0 (0%)	3 (5%)
Pre-existing renal disease		3 (10%)	0 (0.00%)	3 (5.00%)
Antihypertensive medication at study entry		24 (80%)	20 (66%)	44 (73%)
Booking systolic BP*		118 (100-163)	117 (90-152)	118 (90-163)
Booking diastolic BP*		70 (60-101)	70 (58-100)	70 (58-101)
Diabetes		3 (10%)	2 (7%)	5 (8%)
Previous VTE		2 (7%)	1 (3%)	3 (5%)
Antiphospholipid syndrome		0 (0%)	1 (3%)	1 (3%)
Systemic lupus erythematosus		0 (0%)	0 (0%)	0 (0%)
Obstetric history				
Primiparous women		16 (53%)	15 (50%)	31 (52%)
No known PE risk factors †		12 (40%)	14 (47%)	26 (43%)
Multiparous with no known PE risk factors †		0/14 (0%)	4/15 (27%)	4 (14%)
Previous preeclampsia (if multiparous)		10/14 (71%)	5/15 (33%)	15 (52%)
Previous SGA <10th centile		10/14 (71%)	6/15 (40%)	16 (55%)

Frequencies: N(%)
Parametric: mean (SD)

*Non-parametric: median (range)

†Risk factors including hypertension, renal disease, diabetes, antiphospholipid syndrome, systemic lupus erythematous, age >40, BMI >30kg/m^2 or previous preeclampsia BMI, body mass index; BP, blood pressure; VTE, venous thromboembolism; SGA, small for gestational age.

Table 2

Echocardiography measures of cardiac structure and function at baseline, 6 weeks and 6 months, depending on treatment allocation

Cardiac indices	Enalapril			Placebo			Adjusted regression coefficients‡		
	Baseline (n=29)	6 weeks (n=22)	6 months (n=19)	Baseline (n=30)	6 weeks (n=22)	6 months (n=21)	Difference / odds ratio	C.I.	P
Function									
TVR (dyne.s^{-1}cm^{-5})	1451 (393)	1619 (433)	1516 (278)	1510 (430)	1774 (441)	1579 (438)	-63.2	-300.8 - 174.4	0.59
HR (bpm)	81.7 (15.5)	73.5 (12.1)	78.5 (12.0)	87.4 (12.8)	76.4 (11.6)	82.1 (14.0)	-1.8	-10.2 - 6.6	0.66
SV (mL)	74.1 (13.4)	64.0 (13.5)	64.6 (10.7)	69.2 (15.7)	60.6 (12.3)	65.2 (14.1)	-2.9	-10.1 - 4.4	0.43
CO (L/minute)*	6.0 (3.7 - 12.5)	4.5 (2.5 - 7.7)	4.90 (3.4 - 8.3)	5.58 (3.9 - 10.3)	4.7 (2.9 - 6.8)	5.2 (3.8 - 8.6)	-248.5	-1024.7 - 527.8	0.52
LVEF (%)	64.0 (7.8)	60.4 (4.5)	61.4 (4.3)	63.2 (5.7)	62.5 (4.7)	61.5 (3.9)	-1.1	-3.6 - 1.4	0.36
Myocardial strain and strain rate									
LV basal strain (%) †	-15.5 (3.0)	-16.7 (2.8)	-17.4 (2.5)	-14.9 (2.6)	-16.2 (2.1)	-16.6 (2.8)	0.6	1-.1 - -2.2	0.47
LV mid strain (%) †	-18.9 (2.86)	-19.0 (2.5)	-19.5 (2.2)	-18.1 (2.1)	-18.7 (1.7)	-19.1 (2.1)	0.9	-0.5 - 2.2	0.2
LV apical strain (%) †	-25.7 (4.8)	-23.0 (3.6)	-24.4 (3.3)	-24.6 (3.9)	-23.9 (3.2)	-24.5 (3.0)	1.0	-1.1 - 3.0	0.34
GLS (%) †	-20.0 (3.0)	-19.4 (2.8)	-20.3 (1.9)	-19.2 (2.2)	-19.5 (2.1)	-20.1 (2.1)	1.0	-0.3 - 2.3	0.14
E/A strain rate	1.83 (0.69)	2.16 (0.78)	2.19 (0.54)	2.11 (0.70)	2.59 (0.79)	2.17 (0.75)	-0.16	-0.57 - 0.25	0.44
Mitral inflow									
E deceleration time (ms)	207 (39)	211 (26)	193.50 (34)	199 (35)	194 (26)	194 (38)	-10.2	-34.4 - 13.9	0.40
E/A ratio	1.13 (0.30)	1.31 (0.32)	1.24 (0.33)	1.20 (0.28)	1.29 (0.23)	1.28 (0.34)	-0.03	-0.24- 0.17	0.74
Mitral annular motion									
Septal peak S' velocity (m/s)*	0.09 (0.06 - 0.14)	0.07 (0.06 - 0.11)	0.09 (0.06 - 0.12)	0.09 (0.06 - 0.14)	0.07 (0.05 - 0.10)	0.08 (0.05 - 0.12)	0.00	-0.01 - 0.01	0.52
Lateral peak S' velocity (m/s)*	0.10 (0.08 - 0.14)	0.11 (0.05 - 0.16)	0.12 (0.06 - 0.16)	0.10 (0.07 - 0.18)	0.10 (0.06 - 0.12)	0.10 (0.05 - 0.16)	0.01	-0.01 - 0.03	0.16
E/E' ratio	8.57 (2.07)	6.90 (2.10)	6.41 (2.03)	8.27 (2.22)	7.30 (1.50)	7.48 (1.40)	-1.07	-2.08 - 0.06	0.04
Tricuspid valve									
TR Vmax (cm/s)	0.69 (1.06)	0.65 (0.98)	0.31 (0.74)	1.15 (1.15)	0.61 (0.93)	0.52 (0.96)	-0.11	-0.69 - 0.47	0.69
Cardiac morphology									
LVIDd (cm)	4.58 (0.49)	4.35 (0.46)	4.34 (0.42)	4.44 (0.47)	4.29 (0.51)	4.25 (0.49)	0.00	-0.20 - 0.19	0.96

Cardiac indices	Enalapril			Placebo			Adjusted regression coefficients‡		
	Baseline (n=29)	6 weeks (n=22)	6 months (n=19)	Baseline (n=30)	6 weeks (n=22)	6 months (n=21)	Difference / odds ratio	C.I.	P
Function									
PWd (cm)	1.12 (0.18)	0.93 (0.19)	0.81 (0.12)	1.14 (0.22)	1.02 (0.15)	0.96 (0.19)	-0.14	-0.25 -0.04	<0.01
SWd (cm)	1.04 (0.16)	1.00 (0.17)	0.87 (0.19)	1.01 (0.18)	0.97 (0.14)	0.95 (0.17)	-0.07	-0.18 -0.03	0.16
LVM (g)*	179.86 (112.20 - 267.95)	139.58 (87.44 - 215.32)	103.33 (72.34 - 189.31)	165.54 (95.13 - 340.24)	134.72 (80.26 - 277.71)	125.84 (73.16 - 265.83)	-19.46	-37.34 - -1.57	0.03
LVMi (g/m^2)	94.47 (17.39)	77.35 (17.18)	64.90 (14.93)	90.72 (22.58)	78.95 (18.47)	71.91 (17.96)	-9.23	-17.75 - -0.71	0.03
RWT	0.50 (0.11)	0.43 (0.10)	0.38 (0.07)	0.52 (0.10)	0.48 (0.09)	0.45 (0.10)	-0.08	-0.13 - -0.02	<0.01
LAV (mL)	49.5 (12.3)	40.7 (11.1)	40.4 (9.8)	42.2 (12.8)	38.4 (11.3)	36.3 (7.2)	2.3	-3.3 - 7.9	0.40
LAVi (mL/m^2)	25.9 (5.7)	21.8 (4.6)	21.8 (4.1)	22.0 (5.3)	20.6 (4.6)	19.5 (3.6)	2.0	-0.7 - 4.7	0.14
No remodelling	7/29 (24%)	9 (41%)	14/19 (74%)	3/30 (10%)	7/22 (32%)	8/21 (38%)	-	-	-
Concentric remodelling	9/29 (31%)	9 (41%)	5/19 (26%)	17/30 (57%)	12/22 (55%)	11/21 (53%)	0.26§	0.1 - 1.0	0.05
Concentric hypertrophy	12/29 (41%)	3/22 (14%)	0/19 (0%)	9/30 (30%)	3/22 (14%)	1/21 (5%)			
Eccentric hypertrophy	1/29 (3%)	1/22 (5%)	0/19 (0%)	1/30 (3%)	0/22 (0%)	1/21 (5%)	-	-	-

Frequencies: N(%)
Parametric: mean (SD)

*Non-parametric: median (range)

†Adjusted for mean arterial pressure (MAP)

‡All regressions were performed on measurements at 6-months with the baseline measurement included in the model

§Odds ratio comparing the risk of concentric remodelling / hypertrophy (RWT>0.42) at 6 months, adjusting for the presence of concentric remodelling / hypertrophy at baseline

C.I., 95% confidence interval; HR, heart rate; SV, stroke volume; CO, cardiac output; LVEF, left ventricular ejection fraction; LV, left ventricular; GLS; global longitudinal strain; TVR, total vascular resistance; LVIDd, LV internal diameter in diastole; PWd, posterior wall diameter in diastole; SWd, septal wall diameter in diastole; LVM, left ventricular mass; LVMi, LVM indexed to body surface area; RWT, relative wall thickness; LAV left atrial volume; LAVi, LAV indexed to body surface area; TR Vmax, tricuspid regurgitation maximum velocity.

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Table 3

Placental and cardiovascular biomarkers at baseline, 6 weeks and 6 months, depending on treatment allocation

Biomarkers	Enalapril			Placebo			Adjusted regression coefficients		
	Baseline (n=26)	6 weeks (n=22)	6 months (n=19)	Baseline (n=29)	6 weeks (n=22)	6 months (n=21)	Coefficient	C.I.	P
sFlt (pg/mL)	1790 (542 - 22904)	84 (66 - 96)	84 (64 - 97)	1290 (262 - 9500)	87 (73 - 133)	84 (73 - 110)	0.0	-0.1 - 0.1	0.76
PlGF (pg/mL)	29 (13 - 152)	11 (4 - 19)	10 (5 - 15)	21 (8 - 133)	10 (6 - 20)	9 (6 - 15)	0.0	-0.2 - 0.2	0.75
sFlt:PlGF	54 (20 - 421)	7 (4 - 23)	8 (4 - 17)	56 (13 - 566)	10 (5 - 14)	8. (5 - 13)	0.0	-0.2 - 0.2	0.86
hs-cTnT (ng/L)	6 (2 - 62)	2 (2 - 13)	2 (2 - 9)	5 (2 - 28)	2 (2 - 14)	2 (2 - 7)	0.0	-0.2 - 0.2	0.94
NTproBNP (pg/mL)	102 (25 - 722)	22 (4 - 97)	30 (4 - 215)	51 (4 - 1259)	212 (12 - 129)	24 (4 - 162)	0.0	-0.7 - 0.8	0.91

Median (range)

Baseline measurements were up to 72 hours post-birth

Measurements were log-transformed for all regression analyses

All regressions are for 6-month data, adjusted for baseline measurements

C.I., 95% confidence interval; sFlt, soluble fms-like tyrosine kinase-1; PlGF, placental growth factor; hs-cTnT, high-sensitivity troponin C; NTproBNP, N-terminal pro b-type natriuretic peptide.

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Table 4
Adverse events reported during the study period

Adverse events	Enalapril n=30	Placebo n=30	Comment
Dry cough / breathlessness	3/30 (10%)	0/30 (0%)	All resolved despite continuing drug
Rash	1/30 (3%)	0/30 (0%)	Withdrew following GP advice
Seizure	1/30 (3%)	0/30 (0%)	Unrelated - investigated for epilepsy
LV failure	1/30 (3%)	0/30 (0%)	Unrelated - did not take allocated drug
Maternal death	1/30 (3%)	0/30 (0%)	Unrelated - Acute coronary syndrome secondary to coronary thrombus

GP, general practitioner; LV, left ventricular