Abstract—Hypertensive disease in pregnancy is associated with future cardiovascular disease 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 cardiovascular disease. We performed a single-center feasibility randomized controlled trial of 6 months’ treatment with enalapril to improve postnatal cardiovascular function. Echocardiography and hemodynamic measurements were performed at baseline (<3 days), 6 weeks, and 6 months postdelivery on 60 women. At randomization, 88% of women had diastolic dysfunction, and 68% had concentric remodeling/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′[the ratio of early mitral inflow velocity and early mitral annular diastolic velocity]: $P=0.04$) and left ventricular remodeling (relative wall thickness: $P=0.01$; left ventricular 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; these early improvements have the potential to reduce long-term cardiovascular disease risk. A definitive, multicenter randomized controlled trial is now required to confirm these findings.

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Key Words: angiotensin-converting enzyme • cardiovascular disease • echocardiography • enalapril • left ventricular remodeling • postpartum • pregnancy

Cardiovascular disease (CVD) is the leading cause of mortality worldwide, accounting for >80000 deaths in women in the United Kingdom per annum.1 It is increasingly recognized that primary prevention is more effective than treating established CVD; however, this requires identification of at-risk individuals before 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% to 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 multiorgan and placental dysfunction).5 Preeclampsia is thought to derive from placent al malperfusion, oxidative stress, release of inflammatory factors into the maternal circulation, 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 dysfunction4,9 and long-term CVD risk,10-14 including a 2-fold risk of ischemic heart disease and stroke...
and 4-fold risk of hypertension in later life.\textsuperscript{11} The association between preeclampsia and future CVD persists, despite accounting for mutual risk factors, including age, obesity, and prepregnancy hypertension.\textsuperscript{11} Women with preterm preeclampsia (delivery before 37 weeks) are at particular risk; they are 8× more likely to die from CVD.\textsuperscript{13}

Not only is CVD more common in women with preeclampsia, but it tends to occur earlier and with a higher fatality rate.\textsuperscript{12} Most recent studies demonstrating increased CVD risk following preeclampsia had a median follow-up <20 years, with some presenting as early as 1 year postpartum.\textsuperscript{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.\textsuperscript{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, ACE (angiotensin-converting enzyme) inhibitors are contraindicated in pregnancy, due to associated fetopathy,\textsuperscript{23} yet they are considered safe first-line antihypertensives postpartum, irrespective of breastfeeding status.\textsuperscript{24–26}

Women identified as having cardiovascular dysfunction in the interval between pregnancies are at an increased risk of preeclampsia recurrence.\textsuperscript{27} A postnatal case-control study of 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.\textsuperscript{27} Total vascular resistance (TVR) was the best independent predictive factor of recurrent preeclampsia.\textsuperscript{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,\textsuperscript{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.\textsuperscript{29,30} The HOPE (Heart Outcomes Prevention Evaluation) study,\textsuperscript{29} during which participants at high risk of CVD were randomized 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.\textsuperscript{29} ACE inhibitors provide cardioprotection through a variety of mechanisms, including anti-inflammatory effects,\textsuperscript{31} increased nitric oxide bioavailability,\textsuperscript{32} and diminished fibrosis.\textsuperscript{33} These are all relevant to preeclampsia which has an inflammatory component\textsuperscript{29} and is associated with reduced nitric oxide bioavailability\textsuperscript{34} and vascular fibrosis.\textsuperscript{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 remodeling.

Methods

**Trial Design**

The PICk-UP study (Postnatal Enalapril to Improve Cardiovascular Function Following Preterm Preeclampsia) was a single-center feasibility randomized 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.\textsuperscript{24,25} 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. The protocol and all participant-facing information were approved by the local research ethics committee (18/NW/0253), Health Research Authority and Medicines, and Healthcare products Regulatory Agency. All study procedures were carried out at St Mary’s Hospital, Manchester, United Kingdom, in accordance with institutional guidelines. All participants gave written informed consent before randomization. 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 <100 µmol/L, who had preterm preeclampsia (requiring delivery before 37 weeks’ gestation) were eligible for enrollment (see Data Supplement 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; or had known renal artery stenosis.

**Randomization and Study Procedures**

Participants were allocated to enalapril or placebo using block randomization in a 1:1 ratio. Following consent and randomization, postnatal baseline investigations were performed within 3 days of delivery. These included echocardiography (to measure left ventricular [LV] remodeling, systolic, and diastolic function), arteriography (to measure arterial stiffness using pulse wave velocity and augmentation index), blood pressure (BP)\textsuperscript{28} and cardiovascular, and placental biomarkers (hs-cTnT [high-sensitivity cardiac troponin T], NT-proBNP [N-terminal pro-B-type natriuretic peptide], PiGF [placental growth factor], and sFlt [soluble fms-like tyrosine kinase-1]; see Data Supplement). Enalapril dose was titrated as follows: 5 mg once daily for 1 week, then 10 mg for 2 weeks then 20 mg maintenance dose.\textsuperscript{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 the National Institute for Health and Care Excellence (NICE) guidance (with calcium channel blockers, beta-blockers, or alpha-blockers),\textsuperscript{38} 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 3 different methodologies: verbal recall during each visit and phone call, pill counts by pharmacy, and high-performance liquid chromatography-tandem mass spectrometry\textsuperscript{39} of urine samples from visits 4 and 5.

Details of the investigational medicinal product and clinical measurements are included in the Data Supplement.

**Reproducibility**

A subset of 20 participants had echocardiography exams performed by 2 observers to assess interobserver agreement. Both observers analyzed their own scans, blinded to the other’s results. Mean arterial pressure was not repeated for assessment of TVR reproducibility; therefore, this was assessed using repeat measurements of cardiac output (CO) alone. Intraclass correlation coefficients (ICC) were calculated using a 2-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).\textsuperscript{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 postrandomization 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. Prespecified secondary clinical outcomes included a change in measures of cardiac structure and function and biomarkers from baseline to 6 months postrandomization 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 regurgitation, left atrial volume index, left ventricular ejection fraction, CO, stroke volume, relative wall thickness, left ventricular mass indexed to body surface area (LVMi), concentric/eccentric remodeling, global longitudinal...
strain, LV basal, mid and apical strain, and E/A strain rate (SR E/A).
The measured biomarkers were hs-cTnT, PlGF, sFlt, and NT-proBNP. Prespecified normal cutoffs were defined for each of the echocardiography measures, as described in the Data Supplement.42–48

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

Continuous variables were compared between the 2 groups at 6 weeks and 6 months, using standard ANCOVA 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 χ² 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 nonrecurrence.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 noncompletion 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 recruited to PICK-UP was 60 out of 84 (71%). The proportion of eligible women who completed the study was 40 out of 84 (48%; Figure 2). Five women were lost to follow-up (8%), and 1 conceived before the end of study (2%). The most common reason for noncompletion 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 2 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 out of 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 out of 20 (85%) women in the enalapril arm at 6 weeks and 12 out of 19 (63%) at 6 months. Verbal recall of missed doses was higher in those without detectable urinary enalapril compared with those with (median missed doses at 6 months: 24 [4–55] versus 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 out of 40 (15%) women recalled that they neither easy nor difficult and 1 out of 40 (3%) found it difficult (Table S1 in the Data Supplement). In the last month, 20 out of 40 (50%) women recalled missing 1 to 5 doses, and 2 out of 40 (5%) recalled missing >20 doses. Of those that missed ≥10 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 and Pregnancy Outcome

Baseline characteristics and pregnancy outcome data are summarized in Table 1 and Table S2. At randomization, 52 out of 59 (88%) had diastolic dysfunction, 14 out of 59 (24%) had systolic dysfunction, and 47 out of 59 (68%) had concentric remodeling or hypertrophy (relative wall thickness >0.42).

### 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 left ventricular ejection fraction/global longitudinal strain/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 to −0.06]; P=0.04). Allocation to enalapril was also associated with improved LV remodeling at 6 months, compared with placebo (LVMi adjusted difference, −9.23 g/m² [95% CI, −7.73 to −0.71]; P=0.03). Twelve women in the placebo arm had persistent concentric remodeling/hypertrophy (relative wall thickness >0.42) at 6 months (57%), compared with 5 out of 19 (26%) in the enalapril arm (adjusted odds ratio, 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).

### Table 1. Baseline Characteristics

| Baseline Characteristics | Enalapril (n=30) | Placebo (n=30) | All (N=60) |
|--------------------------|------------------|---------------|-----------|
| Demographics             |                  |               |           |
| Age at enrollment, y     | 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/m²      | 28.0 (19.4–37.3) | 27.6 (19.3–51.0)| 27.7 (19.3–51.0)|
| BMI >30 kg/m² at randomization | 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%)    |
| Preexisting 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 mellitus        | 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 preeclampsia risk factors† | 12 (40%) | 14 (47%) | 26 (43%) |
| Multiparous with no known PE risk factors† | 0/14 (0%) | 4/15 (27%) | 4/29 (14%) |
| Previous preeclampsia (if multiparous) | 10/14 (71%) | 5/15 (33%) | 15/29 (52%) |
| Previous SGA <10th centile | 10/14 (71%) | 6/15 (40%) | 16/29 (55%) |

Frequencies: N(%). Parametric: mean (SD). BMI indicates body mass index; BP, blood pressure; PE, preeclampsia; SGA, small for gestational age; and VTE, venous thromboembolism.

*Nonparametric: median (range).
†Risk factors including hypertension, renal disease, diabetes mellitus, antiphospholipid syndrome, systemic lupus erythematosus, age >40, BMI >30 kg/m², or previous preeclampsia.
| Cardiac Indices | Enalapril (n=29) | Placebo (n=30) | Difference/ Odds Ratio | 95% CI | P Value |
|----------------|------------------|----------------|------------------------|-------|--------|
| **Function**   |                  |                |                        |       |        |
| TVR, dyne.s⁻¹.cm⁻⁵ | 1451 (393)       | 1619 (433)     | −63.2                  | −300.8 to 174.4 | 0.59   |
| HR, bpm        | 81.7 (15.5)      | 73.5 (12.1)    | −1.8                   | −10.2 to 6.6   | 0.66   |
| SV, mL         | 74.1 (13.4)      | 64.0 (13.5)    | −2.9                   | −10.1 to 4.4   | 0.43   |
| CO, L/min†     | 6.0 (3.7 to 12.5)| 4.5 (2.5 to 7.7)| −248.5                | −1024.7 to 527.8| 0.52   |
| LVEF, %        | 64.0 (7.8)       | 60.4 (4.5)     | −1.1                   | −3.6 to 1.4    | 0.36   |
| **Myocardial strain and strain rate** |                  |                |                        |       |        |
| LV basal strain, %‡ | −15.5 (3.0)     | −16.7 (2.8)    | 0.6                    | 1−.1 to −2.2   | 0.47   |
| LV mid strain, %‡ | −18.9 (2.86)    | −19.0 (2.5)    | 0.9                    | −0.5 to 2.2    | 0.20   |
| LV apical strain, %‡ | −25.7 (4.8)    | −23.0 (3.6)    | 1.0                    | −1.1 to 3.0    | 0.34   |
| GLS, %‡        | −20.0 (3.0)      | −19.4 (2.8)    | 1.0                    | −0.3 to 2.3    | 0.14   |
| E/A strain rate | 1.83 (0.69)      | 2.16 (0.78)    | −0.16                  | −0.57 to 0.25  | 0.44   |
| **Mitral inflow** |                |                |                        |       |        |
| E deceleration time, ms | 207 (39)        | 211 (26)       | −10.2                  | −34.4 to 13.9  | 0.40   |
| E/A ratio      | 1.13 (0.30)      | 1.31 (0.32)    | −0.03                  | −0.24 to 0.17  | 0.74   |
| **Mitral annular motion** |                |                |                        |       |        |
| Septal peak S’ velocity, m/s‡ | 0.09 (0.06 to 0.14) | 0.07 (0.06 to 0.11) | 0.00 | −0.01 to 0.01 | 0.52 |
| Lateral peak S’ velocity, m/s‡ | 0.10 (0.08 to 0.14) | 0.11 (0.05 to 0.16) | 0.01 | −0.01 to 0.03 | 0.16 |
| E/E’ ratio     | 8.57 (2.07)      | 6.90 (2.10)    | −1.07                  | −2.08 to 0.06  | 0.04   |
| **Tricuspid valve** |                |                |                        |       |        |
| TR Vmax, cm/s  | 0.69 (1.06)      | 0.65 (0.98)    | −0.11                  | −0.69 to 0.47  | 0.69   |
| **Cardiac morphology** |                |                |                        |       |        |
| LVIDd, cm      | 4.58 (0.49)      | 4.35 (0.46)    | 0.00                   | −0.20 to 0.19  | 0.96   |
| PWd, cm        | 1.12 (0.18)      | 0.93 (0.19)    | −0.14                  | −0.25 to −0.04 | <0.01 |
| Swd, cm        | 1.04 (0.16)      | 1.00 (0.17)    | −0.07                   | −0.18 to −0.03 | 0.16   |
| LVM, g†        | 179.86 (112.20 to 267.95) | 139.58 (87.44 to 215.32) | −19.46 | −37.34 to −1.57 | 0.03 |
| LVMi, g/m²      | 94.47 (17.39)    | 77.35 (17.18)  | −9.23                  | −17.75 to −0.71 | 0.03 |
| RWT             | 0.50 (0.11)      | 0.43 (0.10)    | −0.08                  | −0.13 to −0.02 | <0.01 |
| LAV, mL        | 49.5 (12.3)      | 40.7 (11.1)    | 2.3                    | −3.3 to 7.9    | 0.40   |
| LAVi, mL/m²    | 25.9 (5.7)       | 21.8 (4.6)     | 2.0                    | −0.7 to 4.7    | 0.14   |
| No remodeling   | 7/29 (24%)       | 9 (41%)        | 0.26§                  | 0.1 to 1.0     | 0.05   |
| Concentric remodeling | 9/29 (31%) | 9 (41%) | 12/22 (55%) | 11/21 (53%) | ... |
| Concentric hypertrophy | 12/29 (41%) | 3/22 (14%) | 9/30 (30%) | 3/22 (14%) | 1/21 (5%) |
| Eccentric hypertrophy | 1/29 (3%) | 1/22 (5%) | 1/30 (3%) | 0/22 (0%) | 1/21 (5%) |

Frequencies: N(%). Parametric: mean (SD). CO indicates cardiac output; E/A, ratio of early to late mitral inflow velocity; E/E', ratio of early mitral inflow velocity and early mitral annular diastolic velocity; GLS, global longitudinal strain; HR, heart rate; LAV, left atrial volume; LAVi, indexed to body surface area; LVIDd, LV internal diameter in diastole; LVM, left ventricular mass; LVMi, indexed to body surface area; MAP, mean arterial pressure; PWD, posterior wall diameter in diastole; RWT, relative wall thickness; SV, stroke volume; Swd, septal wall diameter in diastole; TR Vmax, tricuspid regurgitation maximum velocity; and TVR, total vascular resistance.

*All regressions were performed on measurements at 6 months with the baseline measurement included in the model.
†Nonparametric: median (range).
‡Adjusted for MAP.
§Odds ratio comparing the risk of concentric remodeling/hypertrophy (RWT>0.42) at 6 mo, adjusting for the presence of concentric remodeling/hypertrophy at baseline.
There was no difference in clinic systolic BP between groups at 6 months; however, allocation to enalapril was associated with a significant reduction in diastolic BP at 6 weeks and 6 months (Table S4). Conversely, arteriography demonstrated a significant difference between groups in peripheral and central systolic BP at 6 months, but not diastolic BP (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 NT-proBNP levels within the normal range at 6 months. Four women (7%) had raised hs-cTnT, and 4 different women had raised NT-proBNP at baseline. There was no difference in hs-cTnT, NT-proBNP, sFlt, or PI GF between the 2 groups at 6 weeks or 6 months (Table 3).

**Safety and 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 (20 mg enalapril/placebo), with stable renal function. Renal function was comparable between the 2 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′ was 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 S6.95,50

**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 noncompletion rate (33% of those recruited), largely attributable to unmodifiable postnatal factors. This led to a completion rate of 48% of eligible women. Although 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 remodeling and diastolic dysfunction.

TVR has previously been identified as predictive of preeclampsia recurrence20,27; for this reason, it was selected as the primary clinical outcome for this study, given the absence of other studies that have compared baseline (at the time of birth) to 6-month echocardiography changes. TVR is derived from CO and mean arterial pressure. No difference was seen between the groups, despite there being a trend towards a difference in mean arterial pressure. This could be due to (1) a lack of effect of enalapril on CO, (2) confounding factors affecting TVR (eg, intrapartum events at baseline, timing of intervention/other antihypertensives), or (3) high-level biological variability of the mean arterial pressure/CO measurement and, therefore, insufficient power in this small feasibility study. Both diastolic function and LV remodeling have been identified as predictors of long-term CVD risk,51–54 and, therefore, these echocardiography parameters were prespecified as secondary end points, 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 remodeling and dysfunction, consistent with other studies,8,95 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 heterogeneous group of women with a relatively severe preeclampsia phenotype (46% of newborns were <third 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

| Table 3. Placental and Cardiovascular Biomarkers at Baseline, 6 wk, and 6 mo, Depending on Treatment Allocation |
|----------------------------------------------------------|
| **Biomarkers** | **Enalapril** | **Placebo** | **Adjusted Regression Coefficients** |
|---------------|--------------|-------------|-----------------------------------|
|               | Baseline (n=26) | 6 wk (n=22) | 6 mo (n=19) | Baseline (n=29) | 6 wk (n=22) | 6 mo (n=21) | Coefficient | 95% CI | P Value |
| sFlt, pg/mL   | 1790 (542 to 22904) | 84 (66 to 96) | 84 (64 to 97) | 1290 (262 to 9500) | 87 (73 to 133) | 84 (73 to 110) | 0.0 | −0.1 to 0.1 | 0.76 |
| PlGF, pg/mL   | 29 (13 to 152) | 11 (4 to 19) | 10 (5 to 15) | 21 (8 to 133) | 10 (6 to 20) | 9 (6 to 15) | 0.0 | −0.2 to 0.2 | 0.75 |
| sFlt/PlGF     | 54 (20 to 421) | 7 (4 to 23) | 8 (4 to 17) | 56 (13 to 566) | 10 (5 to 14) | 8 (5 to 13) | 0.0 | −0.2 to 0.2 | 0.86 |
| hs-cTnT, ng/mL| 6 (2 to 62) | 2 (2 to 13) | 2 (2 to 9) | 5 (2 to 28) | 2 (2 to 14) | 2 (2 to 7) | 0.0 | −0.2 to 0.2 | 0.94 |
| NT-proBNP, pg/mL | 102 (25 to 722) | 22 (4 to 97) | 30 (4 to 215) | 51 (4 to 1259) | 212 (12 to 129) | 24 (4 to 162) | 0.0 | −0.7 to 0.8 | 0.91 |

Median (range). Baseline measurements were up to 72 h postbirth. Measurements were log-transformed for all regression analyses. All regressions are for 6-month data, adjusted for baseline measurements. hs-cTnT indicates high-sensitivity cardiac troponin C; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PlGF, placental growth factor; and sFlt, soluble fms-like tyrosine kinase-1.
cardiovascular health. Modin et al52 quantified the prognostic value of different echocardiography parameters for the prediction of 10-year risk of ischemic heart disease or heart 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 5 g/m² increase in LVMi (compared with 7 g/m² 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 substudy of the Studies of Left Ventricular Dysfunction (SOLVD) trial57 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 remodeling. All study participants have been underpowered to determine the impact of enalapril on the progression of LV remodeling, as defined by discrete cutoffs43,44). Our results suggest that treatment with enalapril for 6 months could reduce the prevalence of concentric remodeling/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,59 which found that a 50 g 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 are 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 randomized controlled study design and that all measurements were performed blinded to treatment allocation. Recruitment was inclusive to all women with preterm preeclampsia in a multiethnic population. The process outcomes included realistic assessments of recruitment, compliance, and retention. However, this was a single-center feasibility study, and, therefore, a larger multicenter 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 noncompletion rate. Treatment with enalapril was not associated with a change in TVR but was associated with improved LV diastolic function and remodeling. These findings highlight the potential to use obstetric history to target intervention to improve maternal cardiovascular health in the postnatal period. A definitive, multicenter randomized controlled trial is now required to confirm these findings.

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### Disclosures

None.

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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%)    | Withdrawed 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 indicates general practitioner; and LV, left ventricular.
References

1. British Heart Foundation, Institute of Applied Health Research. Heart & Circulatory Disease Statistics 2020. BHF. https://www.bhf.org.uk/what-we-do/our-research/heart-statistics/heart-statistics-publications/cardiovascular-disease-statistics-2020. Accessed July 1, 2020.

2. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corra U, Cosyns B, Deaton C, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice. Rev Esp Cardiol (Eng Ed). 2016;69:939. doi: 10.1016/j.escardio.2016.09.009

3. Hernández-Díaz S, Toh S, Cnattingius S. Risk of pre-eclampsia in first and subsequent pregnancies: prospective cohort study. BMJ. 2009;338:b2255. doi: 10.1136/bmj.b2255

4. Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, Zeeman GG, Brown MA. The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISHHP. Pregnancy Hypertens. 2014;4:97–104. doi: 10.1016/j.preghy.2014.02.001

5. Burton GT, Woods AW, Jauniaux E, Kingdon JCM. Rheological and physiological consequences of conversion of the maternal spiral arteries for uteroplacental blood flow during human pregnancy. Placenta. 2009;30:473–482. doi: 10.1016/j.placenta.2009.02.009

6. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of type 2 diabetes mellitus in the mother. Lancet. 2001;357:2002–2006. doi: 10.1016/S0140-6736(00)05112-6

7. Roberts JM, Lain KY. Recent insights into the pathogenesis of pre-eclampsia. Placenta. 2002;23:359–372. doi: 10.1053/plac.2002.0819

8. Evans CS, Gooch L, Flotta D, Lykinds D, Powers RW, Lindsdell LT, Roberts JM, Shroff SG. Cardiovascular system during the postpartum state in women with a history of preeclampsia. Hypertension. 2011;58:57–62. doi: 10.1161/HYPERTENSIONAHA.111.173278

9. Melchiorre K, Sutherland GR, Liberati M, Thalaganganath B. Preeclampsia is associated with persistent postpartum cardiovascular impairment. Hypertension. 2011;58:709–715. doi: 10.1161/HYPERTENSIONAHA.111.176537

10. Leon LJ, McCarthy FP, Direk K, Gonzalez-Izquierdo A, Prieto-Merino D, Casas JP, Chappell LC, Chisholm D, Doyle CM, Hutcheon JA, et al. Maternal cardiovascular disease during the postpartum period among women with a history of preeclampsia. BMJ. 2020;370:1–8. doi: 10.1136/bmj.m1122

11. Davis HW, Liu WK, Pooledpre-Sherlock S, Chisholm D, Doyle CM, Hutcheon JA, et al. Cardiovascular disease-related morbidity and mortality in women with a history of pregnancy complications. Circulation. 2019;139:1069–1079. doi: 10.1161/CIRCULATIONAHA.118.037648

12. Arnot C, Nelson M, AlfaroRamirez M, Hyett J, Gale M, Henry A, Celermaier DS, Taylor L, Woodward M. Maternal cardiovascular risk and pregnancy complications. BMJ. 2001;323:1213–1217. doi: 10.1136/bmj.323.7323.1213

13. McDonald SD, Maliniowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. Am Heart J. 2008;156:918–930. doi: 10.1016/j.ahj.2008.06.042

14. Persson GH, Reisaieter L, Engs LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. BMJ. 2001;323:1213–1217. doi: 10.1136/bmj.323.7323.1213

15. Gryglewski RJ, Uracz W, Chłopicki S, Marcinkiewicz E, Brydkinim as a major endogenous regulator of endothelial function. Pediatr Pathol Mol Med. 2002;21:279–290. doi: 10.1080/02770930290056514

16. Hornig B, Landmesser U, Kohler C, Ahlersmann D, Spiekermann S, Christoph A, Tarus H, Drexl H. Comparative effect of ace inhibition and angiotensin II type 1 receptor antagonism on bioavailability of nitric oxide in patients with coronary artery disease: role of superoxide dismutase. Circulation. 2001;103:799–805. doi: 10.1161/01.cir.103.6.799

17. Brilla CG, Rupp H, Maitsch B. Effects of ACE inhibition versus non-ACE inhibitor antihypertensive treatment on myocardial fibrosis in patients with arterial hypertension. Retrospective analysis of 120 patients with left ventricular endomyocardial biopsies. Herz. 2003;28:744–753. doi: 10.1007/s00393-002-2589-9

18. Pettersson A, Hedner T, Milson I. Increased circulating concentrations of asymmetric dimethyl arginine (ADMA), an endogenous inhibitor of nitric oxide synthesis, in preeclampsia. Acta Obstet Gynecol Scand. 1998;77:808–813.

19. Nikitina ER, Mikhailov AV, Nikandрова ES, Frolova EV, Fadeev AV, Shman VV, Shilova VY, Tapliskaya NL, Shapiro JJ, Fedorova OV, et al. In preeclampsia endogenous cardiogenic steroids induce vascular fibrosis and impair relaxation of umbilical arteries. J Hypertension. 2012;29:769–776. doi: 10.1097/HJH.0b013e328343a6a7

20. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, Ramirez A, Schlaich M, Stergios GS, Tomaszewski M, et al. 2020 International society of hypertension global hypertension practice guidelines. Hypertension. 2020;75:1334–1357. doi: 10.1161/HYPERTENSIONAHA.120.15026

21. Mazza LA, von Dadelszen P, Singer J, Lee T, Rey E, Ross S, Asztalos EB, Murphy KE, Menzies J, Sanchez J, et al; CHIPS Study Group. The CHIPS randomized controlled trial (Control of Hypertension in Pregnancy Study) is severe hypertension or just an elevated blood pressure? Hypertension. 2016;68:1153–1159. doi: 10.1161/HYPERTENSIONAHA.116.07862

22. Meher S, Duley L. Nitric oxide for preventing pre-eclampsia and its complications. Cochrane Database Syst Rev. 2007;CD004690. doi: 10.1002/14651858.CD004690

23. Bullo M, Tschumi S, Bucher BS, Bianchetti MG, Simonetti GD. Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists: a systematic review. Hypertension. 2012;60:444–450. doi: 10.1161/HYPERTENSIONAHA.112.196352

24. Redman CW, Kelly JO, Cooper WD. The excretion of enalapril and enalaprilat in human breast milk. Eur J Clin Pharmacol. 1990;38:99–99. doi: 10.1007/BF00314815

25. National Institute for Health and Care Excellence (NICE). Recommendations - Hypertension In Pregnancy: Diagnosis and Management. NICE Guideline [NG133]. 2019. https://www.nice.org.uk/guidance/ng133. Accessed June 20, 2020.

26. Bramham K, Nelson-Piercy C, Brown MJ, Chappell LC. Postpartum management of hypertension. BMJ. 2013;346:f894. doi: 10.1136/bmj.f894

27. Redman CW, Kelly JO, Cooper WD. The excretion of enalapril and enalaprilat in human breast milk. Eur J Clin Pharmacol. 1990;38:99–99. doi: 10.1007/BF00314815

28. Vasapollo B, Horne R, Buchanan H, Williams B, Tomaszewski M. How to screen for non-adherence to antihypertensive therapy. J Hypertens. 2016;34:1889. doi: 10.1097/HJH.0000000000001669
Postpregnancy Enalapril to Reduce CVD Risk

39. Frihku Z, Giered N, Huttin O, Courand PY, Bozec E, Olivier A, Lamiral Z, Zannad F, Rossignol P. Reproducibility in echocardiographic assessment of diastolic function in a population based study (the STANISLAS Cohort study). PLoS One. 2015;10:e0122336. doi: 10.1371/journal.pone.0122336

40. Ormsheser L, Myers JE, Chmiel C, Wareing M, Greenwood SL, Tropes T, Lundberg JO, Weizberg E, Nihlen C, Sibley CP, et al. Effects of dietary nitrate supplementation, from beetroot juice, on blood pressure in hypertensive pregnant women: a randomised, double-blind, placebo-controlled feasibility trial. Nitric Oxide. 2018;80:37–44. doi: 10.1016/j.niox.2018.08.004

41. Reynolds NR, Sun J, Nagaraja HN, Gifford AL, Wu AW, Chese MA. Optimizing measurement of self-reported adherence with the ACTG adherence questionnaire: a cross-protocol analysis. J Acquir Immune Defic Syndr. 2007;46:402–409. doi: 10.1097/QAI.0b013e318158a4ff

42. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28:1–59.e14. doi: 10.1016/j.echo.2014.10.003

43. Yang H, Wright L, Negishi T, Negishi K, Liu J, Marwick TH. Research to practice: assessment of left ventricular global longitudinal strain for surveillance of cancer chemotherapeutic-related cardiac dysfunction. JACC Cardiovasc Imaging. 2018;11:1196–1201. doi: 10.1016/j.jcmg.2018.07.005

44. Matthew T, Steeds R, Jones R, Kanagala P, Lloyd G, Knight D, et al. A guideline protocol for the echocardiographic assessment of diastolic function - a protocol of the British society of echocardiography. https://www.bscho.org.uk/common/UploadedFiles/Education/Protocols%20guidelines/Diastolic%20Dysfunction.pdf. Accessed June 1, 2020.

45. Harkness A, Ring L, Augustine DX, Oxborough D, Robinson S, Sharma V; Education Committee of the British Society of Echocardiography. Normal reference intervals for cardiac dimensions and function for use in echocardiographic practice: a guideline from the British Society of Echocardiography. Echo Res Pract. 2020;7:G1–G18. doi: 10.1530/ERP-19-0050

46. Timokhina E, Kuzmina T, Strizhakov A, Pitshelauri E, Igoutko I, Belousova V. Maternal cardiac function after normal delivery, preeclampsia, and eclampsia: a prospective study. J Pregnancy. 2019;2019:9795765. doi: 10.1155/2019/9795765

47. Chahal NS, Lim TK, Jain P, Chambers JC, Kooner JS, Senior R. What Is New?

48. Dalen H, Thorstensen A, Vatten LJ, Aase SA, Stoylen A. Reference values and distribution of conventional echocardiographic Doppler measures and longitudinal tissue Doppler velocities in a population free from cardiovascular disease. Circ Cardiovasc Imaging. 2010;3:614–622. doi: 10.1161/CIRCIMAGING.109.926022

49. Palmieri V, Dahlöf B, DeQuattro V, Harpe N, Bella JN, de Simone G, Parancas M, Fishman D, Devereux RB. Reliability of echocardiographic assessment of left ventricular structure and function: the PRESERVE study. Prospective randomized study evaluating regression of ventricular enlargement. J Am Coll Cardiol. 1999;34:1625–1632. doi: 10.1016/s0735-1097(99)00396-4

50. De Geer L, Orcasan A, Engvall J. Variability in echocardiographic measurements of left ventricular function in septic shock patients. Cardiovasc Ultrasound. 2015;13:19. doi: 10.1186/s12947-015-0015-6

51. Landorf B, Sengelov M, Godsk Jørgensen P, Pedersen S, Modin D, Eske Bruun N, Fritz-Hansen T, Skov Jensen J, Biering-Sørensen T. Echocardiographic predictors of mortality in women with heart failure with reduced ejection fraction. Circ Cardiovasc Imaging. 2018;11:e008031. doi: 10.1161/CIRCIMAGING.118.008031

52. Modin D, Biering-Sørensen SR, Mogelvang R, Landler N, Jensen JS, Biering-Sørensen T. Prognostic value of echocardiography in hypertensive versus nonhypertensive participants from the general population. Hypertension. 2018;71:742–751. doi: 10.1161/HYPERTENSIONAHA.117.10674

53. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med. 1990;322:1561–1566. doi: 10.1056/NEJM199005313222203

54. Krumbholz HM, Larson M, Levy D. Prognosis of left ventricular geometric patterns in the Framingham Heart Study. J Am Coll Cardiol. 1995;25:879–884. doi: 10.1016/0735-1097(94)00473-4

55. De Haas S, Ghossein-Doha C, Geerts L, van Kuijk SMJ, van Drongelen D, Spaanderman MEA. Cardiac remodeling in normotensive pregnancy and in pregnancy complicated by hypertension: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2017;50:683–696. doi: 10.1002/uog.17410

56. Halley CM, Houghtaling PL, Khalil MK, Thomas JD, Jabar WA. Mortality rate in patients with diastolic dysfunction and normal systolic function. Arch Intern Med. 2011;171:1082–1087. doi: 10.1001/archinte.2011.244

57. Konstam MA, Rousseau MF, Kronenberg MW, Udelson JE, Melin J, Stewart D, Dolan N, Edens TR, Ahn S, Kinan D. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. SOLVD Investigators. Circulation. 1992;86:431–438. doi: 10.1161/01.cir.86.2.431

58. Benschop L, Schalekamp-Timmermans S, Broere-Brown ZA, Roeters lanenp JE, Jaddoe VW, Roos-Hesselink JW, Ixak MK, Steegers EA, Robertson JS, Gandy LE. Placental growth factor as an indicator of maternal cardiovascular risk after pregnancy. JACC Cardiovasc Imaging. 2015;8:139–146. doi: 10.1016/j.jcmg.2014.11.052

59. Benschop L, Schalekamp-Timmermans S, Broere-Brown ZA, Roeters

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 randomized controlled trial is achievable and justified.

Summary

Six months’ postnatal treatment with enalapril was associated with improved left ventricular diastolic function and remodeling. These early improvements have the potential to reduce long-term cardiovascular disease risk.

Novelty and Significance

What Is New?

• High prevalence of cardiovascular impairment in women with preterm preeclampsia immediately after birth and 6 months postdelivery.

• Treatment with enalapril for 6 months postdelivery 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 with placebo was associated with improvements in echocardiographic measurements associated with left ventricular diastolic function and remodeling 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 randomized controlled trial is achievable and justified.

Summary

Six months’ postnatal treatment with enalapril was associated with improved left ventricular diastolic function and remodeling. These early improvements have the potential to reduce long-term cardiovascular disease risk.