Labetalol Versus Nifedipine as Antihypertensive Treatment for Chronic Hypertension in Pregnancy

A Randomized Controlled Trial

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Abstract—Data from randomized controlled trials to guide antihypertensive agent choice for chronic hypertension in pregnancy are limited; this study aimed to compare labetalol and nifedipine, additionally assessing the impact of ethnicity on treatment efficacy. Pregnant women with chronic hypertension (12^{+0}–27^{+6} weeks' gestation) were enrolled at 4 UK centers (August 2014 to October 2015). Open-label first-line antihypertensive treatment was randomly assigned: labetalol- (200–1800 mg/d) or nifedipine-modified release (20–80 mg/d). Analysis included 112 women (98%) who completed the study (labetalol n=55, nifedipine n=57). Maximum blood pressure after randomization was 161/101 mm Hg with labetalol versus 163/105 mm Hg with nifedipine (mean difference systolic: 1.2 mm Hg [−4.9 to 7.2 mm Hg], diastolic: 3.3 mm Hg [−0.6 to 7.3 mm Hg]). Mean blood pressure was 134/84 mm Hg with labetalol and 134/85 mm Hg with nifedipine (mean difference systolic: 0.3 mm Hg [−2.8 to 3.4 mm Hg], and diastolic: −1.9 mm Hg [−4.1 to 0.3 mm Hg]). Nifedipine use was associated with a 7.4-mm Hg reduction (−14.4 to −0.4 mm Hg) in central aortic pressure, measured by pulse wave analysis. No difference in treatment effect was observed in black women (n=63), but a mean 4 mm Hg reduction (−6.6 to −0.8 mm Hg; *P*=0.015) in brachial diastolic blood pressure was observed with labetalol compared with nifedipine in non-black women (n=49). Labetalol and nifedipine control mean blood pressure to target in pregnant women with chronic hypertension. This study provides support for a larger definitive trial scrutinizing the benefits and side effects of first-line antihypertensive treatment.

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Data to inform prescribing of antihypertensive treatments for chronic hypertension in pregnancy are sparse and subsequently no consensus on the optimal agent(s) exists.[1,2] The prevalence of chronic hypertension in pregnancy is estimated at 3%,[3] but this figure is set to increase with rising maternal age and the global obesity epidemic.[4,5] Given that chronic hypertension is associated with significantly increased adverse maternal and perinatal outcomes compared with the general pregnant population,[6] defining optimal antihypertensive treatment(s) is warranted.

A Cochrane review examining trials (including >4000 women) in mild to moderate hypertension in pregnancy (combining chronic and gestational hypertension) concluded that although the incidence of severe hypertension is reduced with antihypertensive treatment, no reduction in the incidence of adverse maternal and perinatal outcomes has been demonstrated.[7] There have been additional concerns that antihypertensive treatment might increase the risk of fetal growth restriction.[8] However, more recent evidence from the Control of Hypertension in Pregnancy Study concluded that tight control to a diastolic target of 85 mm Hg (compared with less-tight control to a diastolic target of 105 mm Hg) did not increase the risk of pregnancy loss or high-level neonatal care in women with nonsevere chronic and gestational hypertension, no proteinuria, and a singleton pregnancy.[9] This study also demonstrated that the incidence of severe maternal hypertension was significantly increased with less-tight control, which was associated with an increased risk of serious

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maternal morbidity in these women (post hoc analysis).[10] The study highlights the need to determine which antihypertensive agent(s) provides optimal control of chronic hypertension in pregnancy to ameliorate these risks.

Choice of antihypertensive outside pregnancy depends on ethnicity with those of African/Caribbean family origin receiving calcium channel blockers as first-line agent[11] and is thought to relate to differences in the pathophysiology causing hypertension in those of differing ethnic backgrounds.[12] Ethnic disparity in maternal and perinatal outcome in the general pregnant population is well described and likely to be multifactorial.[13] To our knowledge, no randomized controlled trials have investigated the impact of ethnicity on efficacy of antihypertensive treatment in pregnancy. The aims of the PANDA study (Pregnancy and Chronic Hypertension: Nifedipine Versus Labetalol as Antihypertensive Treatment) were 3-fold: to assess feasibility of such a randomized controlled trial, to evaluate mechanistic treatment effects, and to examine the impact of ethnicity on efficacy of nifedipine (a calcium channel blocker with a well-established safety profile in pregnancy) with labetalol (currently recommended as first-line by national UK guidance).

Methods

The study was an open-label, phase 4, randomized controlled clinical trial (EudraCT Number 2013-003144-23), registered with International Standard Randomized Controlled Trials Number (DOI 10.1186/ISRCTN40973936, www.isrctn.com); the protocol and other study literature were approved by the UK Research Ethics Committee (REC number 13/EE/0390). Women of varied ethnicities were enrolled by study investigators using written informed consent at 4 consultant-led National Health Service (NHS) obstetric units in the United Kingdom (Guy's and St Thomas' NHS Foundation Trust, Central Manchester University NHS Foundation Trust, University of Leicester Hospitals NHS Trust, and St George's University Hospitals NHS Foundation Trust). The eligibility criteria included women with a prenatal diagnosis of chronic hypertension (treated or untreated) or blood pressure (BP) readings ≥140 mm Hg systolic or ≥/90 mm Hg diastolic before 20 weeks' gestation requiring antihypertensive treatment before 27+6, as defined by the International Society for the Study of Hypertension in Pregnancy,[14] gestation between 12^{+0} and 27^{+6} weeks (to allow for second trimester BP nadir), singleton pregnancies, aged >18 years, and the ability to provide written informed consent. Women were excluded if they had a contraindication (relative or absolute) to either antihypertensive agent, such as labetalol in women with asthma. Details of the randomization process, intervention, and outcome measures are contained in the online-only Data Supplement.

Statistical Analysis

For the primary analysis, the intention to treat principle was applied; women were analyzed in the groups into which they were randomly allocated regardless of allocation received. The statistical software Stata/SE version 14 for Windows was used for all analyses. The number and percentage were calculated for binary and categorical variables. The mean and SD or the median and interquartile range were calculated for continuous variables. Linear regression with robust SE was used for the primary and other continuous outcomes. Adjustment was made for baseline covariates, including ethnicity (black [determined by self-report of whether the woman had a parent or grandparent who was African or Caribbean] versus non-black [all other ethnicities]), gestational age at randomization, and center. For continuous measures, an adjustment was also made for corresponding baseline measurement (systolic BP at randomization for the primary clinical outcome). For binary outcomes, binary regression with a log link was used to calculate risk ratios (RR). Analysis of the primary clinical outcomes was repeated excluding women delivering their baby before 24 completed weeks of pregnancy because women who deliver before viability did not complete the intended course of treatment.

Subgroup analyses assessing the impact of ethnicity on treatment efficacy were performed using linear regression adjusting for baseline covariates. Results are reported for both groups, and an interaction test performed for any moderation of the treatment effect by the subgroup. A sensitivity analysis was also performed to evaluate the impact of date recruited on the primary outcome, using linear regression with a treatment×time interaction. Explanatory analysis of longitudinal urinary protein: creatinine ratio (PCR; excluding women with chronic kidney disease) and pulse wave measures was conducted using interval regression models on log-transformed data allowing for gestation effects and the baseline measures. Group means and treatment effects were calculated as geometric means and ratios of geometric means given that log transformations were used. Serious adverse events and adverse events were collated and listed by allocation and grouped by symptom. Treatment effects were calculated as estimated differences in the mean or RR with 95% confidence intervals.

Results

Between August 2014 and October 2015, 265 women were screened to enter the trial (Figure), of whom 65% met all eligibility criteria. Nine women (3%) were ineligible because they had a concurrent diagnosis of asthma, and labetalol was therefore contraindicated. There were no women with a contraindication to nifedipine-modified release. Of eligible women, 66% agreed to participate. The most common reason given for declining participation was reluctance to change from current antihypertensive therapy. Recruitment stopped when the enrollment target was reached as per the prespecified primary process outcome. A total of 114 women with singleton pregnancies and a diagnosis of chronic hypertension were randomized to first-line antihypertensive therapy with either labetalol (n=56) or nifedipine (n=58). The participants not included in the analysis included 1 woman lost to follow-up (she emigrated during her pregnancy) and 1 who withdrew because of time constraints waiting for dispensing from the clinical trials pharmacy (no further information was available).

Most baseline maternal characteristics at enrollment were similar between treatment groups (Table 1), except that time from diagnosis of chronic hypertension to study entry was longer in the labetalol group (54 versus 20 months), and the number of women with renal disease (labetalol n=5 versus nifedipine n=9) and diabetes mellitus (labetalol n=5 versus nifedipine n=8) at study entry was higher in the nifedipine group. The results were adjusted allowing for these differences, but this had no significant impact on the outcomes observed (P=0.29).

Feasibility Outcomes

The feasibility of conducting this trial in women with chronic hypertension in pregnancy was confirmed (Table 2), with the enrollment target reached at 14 months. Overall recruitment rate was 2.6 women per month (range of 1.2–3.7). Disparity in recruitment rate by center was associated with variation in the incidence of chronic hypertension in pregnancy at each center. Women self-identifying as of black ethnicity accounted for 56% of those enrolled, confirming feasibility of recruiting women of differing ethnic backgrounds. Geographical

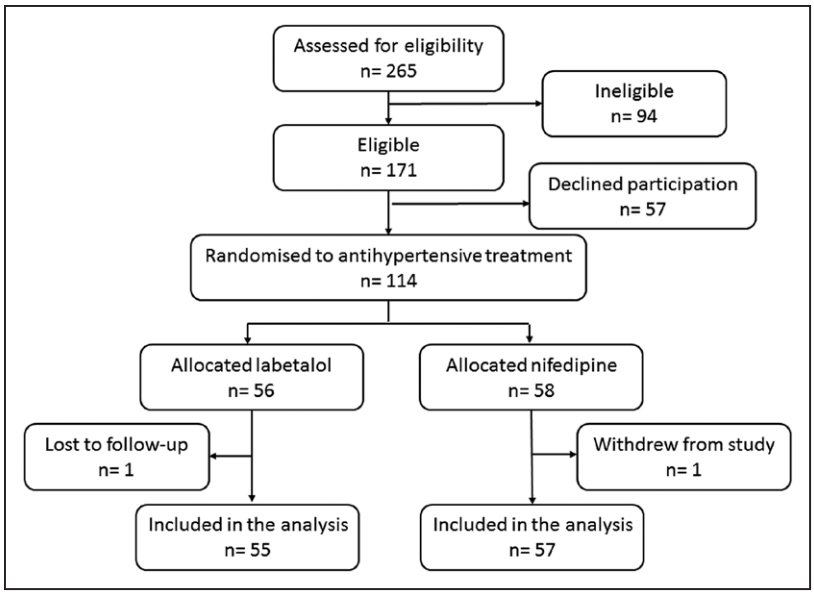

Figure. Flow diagram of trial participants.

variation in the proportion of black women enrolled was seen reflecting the demographics of the local population of each hospital. The assigned intervention was discontinued by 12 women because of side effects of the medication; 7 (13%) in the labetalol arm and 5 (9%) in the nifedipine arm.

Clinical Outcomes

Labetalol and nifedipine demonstrated effectiveness at controlling BP to therapeutic target in women with chronic hypertension in pregnancy (mean BP after randomization: labetalol 134/84 mm Hg versus nifedipine 134/85 mm Hg). No difference was observed in highest brachial BP after randomization to either treatment arm (Table 3). Sensitivity analyses included a per-protocol analysis excluding those who withdrew from their assigned intervention, analysis excluding those who delivered before 24 weeks' gestation, and evaluating the impact of date recruited; there was no impact on the results for any of these analyses. Further analysis of the number of days with brachial BP readings out of target ≥160 mm Hg systolic, ≥150 mm Hg systolic, and <80 mm Hg diastolic demonstrated no difference between treatment groups.

Secondary maternal and perinatal outcomes (Table 4) showed more women receiving nifedipine developed superimposed preeclampsia than those allocated labetalol, but these differences were not significant (RR, 1.78; 0.84–3.77). The same number of women in each group were diagnosed with early onset superimposed preeclampsia before 34 weeks' gestation (n=6 [11%] in each treatment group). The number of women requiring additional oral antihypertensive agents was comparable between groups. There was a greater proportion of women treated with intravenous antihypertensive agents in the nifedipine group (14% versus 4%). The proportions of women requiring induction of labor and caesarean section were comparable. The median gestation at delivery was similar between groups. Adverse maternal outcomes were reported for 6 (11%) women in the labetalol arm compared with 8 (14%) in the nifedipine arm (Table S1 in the online-only Data Supplement).

Six women delivered their baby before 24 weeks, and 3 women had a stillbirth after 24 weeks' gestation. Four had late miscarriages (1 in the labetalol group and 3 in the nifedipine group). Two women (1 in each treatment group) underwent second trimester termination of pregnancy after enrolling in the study (1 for abnormal amniocentesis result after randomization and 1 for severe early onset growth restriction). There were 2 stillbirths in the labetalol group (both with severe early onset growth restriction) and 1 in the nifedipine group (trisomy 13 diagnosed on amniocentesis after study enrollment). There was no significant difference in mean birthweight: 2960 g in the labetalol arm versus 2730 g in the nifedipine arm (adjusted mean difference −240 g; −590, 110 g). There was a high proportion of babies born below the 10th and third birthweight centile in each treatment group. Neonatal unit admission was slightly lower in the labetalol group compared with the nifedipine group (22% versus 29%). Adverse neonatal outcomes were reported for 11 (22%) infants in the labetalol arm and 17 (33%) infants in the nifedipine arm (Table S2). Maternal and neonatal health resource use was similar between treatment groups (Table S3).

A prespecified exploratory subgroup analysis of the impact of ethnicity on efficacy of each treatment did not show any significant difference in mean systolic or diastolic brachial BP in black women (systolic 0.5 mm Hg; −4 to 5 mm Hg; diastolic 0.1 mm Hg; −3 to 3 mm Hg). No difference in mean systolic BP was seen between treatment groups in the non-black women (−0.4 mm Hg; −4 to 3 mm Hg), but a 4-mm Hg (−6.6 to −0.8 mm Hg; P=0.015) reduction in mean diastolic BP was seen in the labetalol arm in non-black women.

Mechanistic Outcomes

Pulse wave analysis was performed in a subgroup of 83 women at 3 centers (nifedipine n=43, labetalol n=40). There was a mean 7.4 mm Hg decrease (−0.4 to −14.4 mm Hg) in central aortic pressure between randomization and delivery in those assigned nifedipine compared with labetalol; this difference in reduction of central pressure was not observed in the peripheral BPs, which were the same between treatment groups. Augmentation index was 8.2% lower (−3.0% to −13.3%) in

Table 1. Baseline Maternal Characteristics at Enrollment

Characteristic	Randomized to Labetalol n=56	Randomized to Nifedipine n=58
Age at enrollment,* y	36.0 (32.0–39.1)	35.0 (30.3–38.5)
Gestational age at randomization,* wk	16.6 (13.7–21.3)	16.9 (14.6–21.1)
Ethnicity†		
Black	30 (54%)	32 (55%)
White	17 (30%)	18 (31%)
Asian	6 (11%)	3 (5%)
Other	3 (5%)	5 (9%)
Current smoker†	1 (2%)	1 (2%)
Body mass index,‡ kg/m^2	31.2 (7.1)	30.5 (4.9)
Nulliparous women†	14 (25%)	13 (22%)
Time since diagnosis of chronic hypertension,* mo	53.5 (8.3–109.5)	20.4 (1.1–75.1)
Type of chronic hypertension†		
Primary	51 (91%)	48 (83%)
Secondary§	5 (9%)	10 (17%)
Diabetes mellitus (type I or type II)†	5 (9%)	8 (14%)
Renal disease†	5 (9%)	9 (16%)
BP at study entry,* mm Hg		
Systolic	143 (133–150)	141 (132–151)
Diastolic	92 (85–98)	91 (86–96)
Antihypertensive medication taken at study entry†	41 (73%)	38 (66%)

BP indicates blood pressure.
*Median and interquartile range.
†Number and percentage.
‡Mean and SD.
§Predominantly because of renal disease.

Table 2. Summary of Feasibility Outcomes

Feasibility Outcome	Total Number Enrolled n=114
Women enrolled per center n (%)	
Guy's and St Thomas' NHS Foundation Trust	56 (49%)
Central Manchester University Hospitals NHS Foundation Trust	33 (29%)
University Hospitals of Leicester NHS Trust	12 (11%)
St George's University Hospitals NHS Foundation Trust	13 (11%)
Enrollment rate per center (women enrolled per month site recruiting)	
Guy's and St Thomas' NHS Foundation Trust	3.7
Central Manchester University Hospitals NHS Foundation Trust	2.8
University Hospitals of Leicester NHS Trust	1.2
St George's University Hospitals NHS Foundation Trust	1.9
Mean of all centers	2.6
Proportion of those enrolled of Black ethnicity	
Guy's and St Thomas' NHS Foundation Trust	70%
Central Manchester University Hospitals NHS Foundation Trust	46%
University Hospitals of Leicester NHS Trust	17%
St George's University Hospitals NHS Foundation Trust	77%

NHS indicates National Health Service.

those assigned nifedipine compared with labetalol although a sensitivity analysis examining the impact of center on this finding demonstrated significant variation in this parameter by center. There was no significant difference in pulse wave velocity between treatment groups (Table 3).

Analysis of gestational change in urinary PCR by treatment group included samples from 73 women (collected at 3 centers) without chronic kidney disease (nifedipine n=35, labetalol n=38). The PCR increased by 44% (21%–71%) across gestation after randomization in women assigned nifedipine compared with women prescribed labetalol (Figure S1). The mean PCR after randomization was 11.5 mg/mmol (SD, 1.9) in the nifedipine group compared with 7.5 mg/mmol (SD, 1.8) in the labetalol group. The analysis was repeated excluding the women who developed superimposed preeclampsia (labetalol n=35 versus nifedipine n=27) with minimal effect on the results; PCR increased by 43% (18%–74%), and the mean PCR after randomization was 11.5 mg/mmol (SD, 1.9) in the nifedipine group compared with 7.4 mg/mmol (SD, 1.9) in the labetalol group.

Adverse Events and Acceptability

There were 4 serious adverse events reported, all for unplanned hospital admissions not related to the pregnancy; 1 was in the labetalol arm (admission for epistaxis) and 3 in the nifedipine arm (1 case of gastroenteritis, 1 case of deep vein thrombosis, and 1 case of influenza). None were deemed to be related to the assigned intervention. The adverse events reported are presented in Table S4 and are consistent with the summary of product characteristics as expected side effect profile for each drug. In the labetalol group, 21 (38%) women reported an adverse event compared with 15 (26%) in the nifedipine group. The postnatal questionnaire was answered by 34% of the women who completed the study. When asked if they would take the same treatment again in another pregnancy, 72% of the women taking labetalol said they definitely would compared with 90% of those assigned nifedipine, and 11% of those assigned labetalol said they probably would not take the treatment again compared with 5% of those assigned nifedipine.

Discussion

To our knowledge, this is the first randomized controlled trial comparing labetalol and nifedipine for control of chronic hypertension in pregnancy. The maximum and mean BP after randomization were comparable between treatment groups; given the contraindications and potential side effects of these drugs, evidence that they have similar ability to control hypertension to treatment target is beneficial. Evidence from the Control of Hypertension in Pregnancy Study demonstrates

Table 3. Effect of Treatment on Brachial Blood Pressure and Pulse Wave Analyses

Parameter	Randomized to Labetalol n=55	Randomized to Nifedipine n=57	Adjusted Mean Difference (95% CI)
Maximum brachial BP, mm Hg			
Systolic	161 (14.7)	163 (19.2)	1.2 (–4.9 to 7.2)
Diastolic	101 (10.2)	105 (11.7)	3.3 (–0.6 to 7.3)
Mean brachial BP, mm Hg			
Systolic	134 (8.5)	134 (9.2)	0.3 (–2.8 to 3.4)
Diastolic	84 (6.6)	85 (5.5)	–1.9 (–4.1 to 0.3)
	n=42	n=45	
Central aortic pressure, mm Hg	132 (20.2)	126 (12.9)	–7 (–0.4 to –14.4)
Augmentation index, %	21 (14.9)	13 (11.7)	–8.2 (–3.0 to –13.3)
Pulse wave velocity, m/s	8.8 (1.7)	8.7 (1.5)	–0.1 (–0.4 to 0.7)

Results adjusted for systolic BP at randomization ethnicity, gestational age at randomization, and center. Pulse wave analyses were only assessed at 3 sites, which accounts for the reduction in the number of participants presented. BP indicates blood pressure; and CI, confidence interval.

maternal benefit of tight control of BP using antihypertensive agents in reducing the incidence of severe hypertension without an increase in adverse perinatal outcomes.[9] This is the largest head-to-head trial in pregnant women with chronic hypertension assessing effectiveness of antihypertensive agents in controlling BP. Randomized controlled trials comparing antihypertensive treatment of chronic hypertension in pregnancy are limited and most were conducted at least 20 years ago; only 3 previous head-to-head studies (total 101 women) have compared the incidence of severe hypertension between randomized treatment groups (RR, 1.1; 0.71–1.81).[1] This study was not powered to assess variation in the secondary maternal and perinatal outcomes, so further larger trials should evaluate differences in the incidence of superimposed preeclampsia, preterm delivery, and small for gestational age infants. Variation in treatment effect by ethnicity was also noted, with labetalol having a greater effect on reducing diastolic BP in non-black women, as previously demonstrated with β-blocker use outside pregnancy.[15] The clinical significance of this potential difference needs to be established.

Recruitment to randomized controlled trials of medication in pregnancy is challenging in view of the real and perceived risk of fetal harm. We confirmed the feasibility of conducting a randomized controlled trial investigating effectiveness of first-line antihypertensive agents for the treatment of chronic hypertension in pregnancy. Of the women meeting all eligibility criteria to enter the study, two thirds consented to participation and 98% completed the study. Ethnic diversity in recruitment was also achieved, enabling investigation of variation in treatment efficacy. Demonstrating feasibility is important given the costly nature of large multicenter studies and need for suitable pragmatic designs to ensure definitive studies will fully answer the research questions posed.[16]

Nifedipine was associated with reduced central aortic pressure and augmentation index (markers of arterial stiffness). Calcium channel blockers (versus β-blockers) have been demonstrated to lower central aortic pressure in the Conduit Artery Functional Endpoint Study (nonpregnant hypertensive population).[17] The exact mechanism behind these hemodynamic differences is not clear, but this finding in combination with the Anglo Scandinavian Cardiac Outcomes Trial results (of which the Conduit Artery Functional Endpoint Study was a subgroup analysis) suggested a greater decrease in long-term cardiovascular risk with calcium channel blockers as first-line antihypertensive agent compared with β-blockers, perhaps mediated through reduction in central aortic pressure.[18] National guidance no longer recommends β-blockers as first-line antihypertensive treatment outside pregnancy; calcium channel blockers are recommended as first-line antihypertensive treatment in black women and angiotensin-converting enzyme inhibitors (avoided in pregnancy because of fetal risks) are recommended for women <55 years of age of other ethnic backgrounds.[11] African and Caribbean women are at increased risk of chronic hypertension and its associated cardiovascular morbidity, from a younger age than women of other ethnic origins.[19] There is evidence that maternal and perinatal outcomes vary by ethnic background.[13] The implications of first-line treatment recommendations outside pregnancy on the selection of antihypertensive agents in pregnancy needs to be established.

Increased proteinuria across gestation with nifedipine (compared with labetalol) was demonstrated even when those who developed superimposed preeclampsia and with preexisting renal disease were excluded from the analysis. Proteinuria is known to increase across gestation in normotensive pregnancy because of increased glomerular filtration.[20] In this cohort, the mean PCR increased after study enrollment by 2.4 mg/mmol. It is not clear whether the difference in proteinuria between treatment groups is a beneficial effect of labetalol or a side effect of nifedipine on renal function, and the clinical significance is unclear given the concentrations fall within the normal range. It seems probable that this is a side effect of nifedipine given similar findings in a Cochrane systematic review of an increase in proteinuria/preeclampsia in women with mild to moderate hypertension in pregnancy randomized to calcium channel blockers versus none (4 studies, 725 women; RR, 1.40 [1.06–1.86])[7]; however, the difference in the incidence of preeclampsia between treatment groups

Table 4. Secondary Maternal and Perinatal Outcomes

Outcome	Randomized to Labetalol n=55	Randomized to Nifedipine n=57	Adjusted Difference in Mean/Median or Risk Ratio (95% CI)
Time between randomization and delivery,* d	134 (39)	127 (44)	
Superimposed preeclampsia†	8 (15%)	15 (26%)	1.78 (0.84 to 3.77)
Superimposed preeclampsia <34 wk†	6 (11%)	6 (11%)	
Additional oral antihypertensive agents†‡			
0	37 (67%)	36 (63%)	
1	15 (27%)	20 (35%)	
≥2	2 (4%)	1 (2%)	
Additional intravenous antihypertensive agents†	2 (4%)	8 (14%)	
Adverse maternal outcome†§	6 (11%)	8 (14%)	
Mode of delivery†			
Spontaneous vaginal delivery	22 (40%)	21 (37%)	
Assisted vaginal delivery	2 (4%)	4 (7%)	
Elective prelabor LSCS	9 (16%)	13 (23%)	
Emergency prelabor LSCS	14 (26%)	11 (19%)	
Emergency LSCS in labor	8 (15%)	8 (14%)	
Estimated blood loss at delivery,* mL	600 (500)	610 (550)	
Gestation at delivery,‖ wk	38.6 (37.7 to 39.4)	38.0 (36.4 to 39.1)	–0.6 (–1.3 to 0.1)
Preterm birth <37 wk†	12 (22%)	20 (35%)	
Preterm birth <34 wk†	10 (18%)	11 (19%)	
Condition of fetus at delivery†			
Livebirth	51 (93%)	52 (91%)	
Miscarriage	1 (2%)	3 (5%)	
Termination of pregnancy	1 (2%)	1 (2%)	
Stillbirth	2 (4%)	1 (2%)	
Neonatal outcomes	n=51	n=52	
Birthweight,* g	2957 (790)	2732 (883)	–240 (–589 to 109)
Birthweight <10th centile†	16 (31%)	17 (33%)	
Birthweight <3rd centile†	6 (12%)	10 (19%)	
Admitted to neonatal unit†	11 (22%)	15 (29%)	1.3 (0.7 to 2.5)
Adverse perinatal outcome†§	11 (22%)	17 (33%)	

CI indicates confidence interval; and LSCS, lower segment Cesarean section.

*Mean and SD.

†Number and percentage.

‡Of those receiving additional oral antihypertensive agents, 94% (n=16) of the labetalol group were prescribed a calcium channel blocker and 86% (n=18) of the nifedipine group were prescribed an α-/β-blocker. Results adjusted for ethnicity, gestational age at randomization, and center. Risk ratios only calculated for prespecified secondary outcomes.

§Details of adverse maternal and perinatal outcomes provided in Tables S1 and S2.

‖Median and interquartile range.

within our study was not significant. Studies in nonpregnant individuals with hypertension and chronic kidney disease suggest that dihydropyridine calcium channel blockers (including nifedipine) are less effective at reducing proteinuria and therefore offer less renal protection than other antihypertensive agents.[21] Investigation into the mechanism behind these differences has suggested that glomerular hypertension may be caused by dihydropyridine calcium channel blockers that dilate the afferent but not the efferent renal arterioles.[22] The variation in mechanism of action of antihypertensive agents in pregnancy needs to be explored further given that crossing a threshold of proteinuria is used in the diagnosis of preeclampsia; however, the benefits of hypertensive control may outweigh a small increase in proteinuria.

The strengths of this study include enrollment at 4 UK centers, reducing the risk of clinical practice bias. The study was designed and conducted as a randomized controlled trial in-line with CONSORT guidance (Consolidated Standards of Reporting Trials).[23] A computer-generated minimization protocol was used to ensure balance within groups of maternal baseline characteristics. This reduced the risk of imbalance of baseline characteristics within treatment arms affecting the outcomes of the study. The study enrolled women with primary and secondary hypertension (predominantly because of renal disease), which increases generalizability of the results; however, this introduced potential bias as reflected in the imbalance of women with renal disease and diabetes mellitus between treatment groups.

Although this study has confirmed feasibility, a larger definitive study is required to assess further the effectiveness of labetalol and nifedipine as antihypertensive treatment in pregnancy complicated by chronic hypertension. The study was not powered to answer the additional question of ethnic variation in effectiveness of first-line antihypertensive agents in pregnancy but demonstrated the feasibility of recruiting women of many ethnic groups. The study was open-label subjecting the results to potential performance bias.[24] It was considered clinically not feasible to mask allocation to clinicians and women in view of the differing recommended dosing frequency and need to escalate treatment and add a second agent where needed. Criteria for addition of second or third antihypertensive agent were not stipulated in the protocol because this study aimed to investigate pragmatic clinical effectiveness rather than efficacy. Although methyldopa was considered for inclusion in the comparison, the sites chosen for this feasibility study indicated that methyldopa was not used as a first-line antihypertensive agent in their practice, and thus a head-to-head labetalol versus nifedipine comparison was undertaken. Recent evidence (although not from a randomized head-to-head comparison) suggested that this agent may be associated with benefit in maternal and perinatal outcome compared with labetalol, and it should be considered for inclusion in a definitive trial.[25] In the nonpregnant population, there is evidence that some antihypertensive agents have additional therapeutic benefits beyond reduction in arterial BP, including anti-inflammatory and oxidative stress–lowering properties.[26] Given the role of inflammation and oxidative stress in the pathophysiology of preeclampsia,[27] future research should further explore the mechanistic actions of each drug to establish if other therapeutic benefits exist in pregnancy. In addition, given the variation in dosing regimens and side effect profiles of the first-line antihypertensive agents prescribed in pregnancy, future studies should further assess adherence and acceptability of individual agents.

Perspectives

Labetalol and nifedipine control mean systolic and diastolic BP to target in pregnant women with chronic hypertension. Good recruitment was demonstrated, and mechanistic treatment effects observed. This study provides support for a larger definitive trial scrutinizing the benefits and side effects of first-line antihypertensive treatment in pregnancy complicated by chronic hypertension.

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Disclosures

C. Nelson-Piercy reports personal fees from Alliance Pharmaceuticals, UCB Pharmaceuticals, LEO Pharmaceuticals, Sanofi Aventis, and Warner Chilcott outside the submitted work. J.K. Cruickshank is current President of the Artery Society which has had donations from Servier Pharmaceuticals. The other authors report no conflicts

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Novelty and Significance

What Is New?

- Labetalol and nifedipine are both effective at lowering brachial blood pressure in pregnancy complicated by chronic hypertension.
- Labetalol reduces brachial diastolic blood pressure more than nifedipine in non-black women.
- Nifedipine reduces central aortic blood pressure significantly more than labetalol in women of varying ethnicities.

What Is Relevant?

- Chronic hypertension in pregnancy is associated with adverse maternal and perinatal outcome.
- The optimal antihypertensive agent(s) is yet to be identified.
- Ethnic variation in antihypertensive treatment effect in women with chronic hypertension in pregnancy is evident and warrants further exploration.
- Labetalol and nifedipine demonstrate differing mechanistic treatment effects, and the clinical importance of these requires investigation.

Summary

This study provides support for a larger definitive trial scrutinizing the benefits and side effects of first-line antihypertensive treatment in pregnant women with chronic hypertension.

Hypertension
Journal of the American Heart Association

Labetalol Versus Nifedipine as Antihypertensive Treatment for Chronic Hypertension in Pregnancy: A Randomized Controlled Trial

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SUPPLEMENTAL MATERIAL:

LABETALOL VERSUS NIFEDIPINE AS ANTIHYPERTENSIVE TREATMENT FOR CHRONIC HYPERTENSION IN PREGNANCY: A RANDOMISED TRIAL

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Supplemental methods:

Randomisation, Intervention and Outcome Measures

Women were randomly assigned antihypertensive treatment via a MedSciNet online minimisation protocol with stratification for: gestation at randomisation (divided into four week groups: 12^{+0}-15^{+6}, 16^{+0}-19^{+6}, 20^{+0}-23^{+6} and 24^{+0}-27^{+6}), maternity centre, systolic BP at randomisation (<140 mm Hg (on treatment at study enrolment), 140-149 mm Hg and ≥150 mm Hg), and ethnicity (Black (determined by self-report of whether the woman had a parent or grandparent who was African or Caribbean) versus non-Black (all other ethnicities)). Minimum divided daily doses of labetalol (combined alpha and beta-blocker) were 200 mg (100 mg twice per day) and maximum 1800 mg (600 mg three times per day) and for nifedipine modified release (a calcium channel) 20 mg (10 mg twice per day) and maximum 80 mg (40 mg twice per day). Starting doses were decided by the attending clinician. Treatment was open-label as it was considered clinically not feasible to mask allocation to clinicians and women in view of the differing recommended dosing frequency, need to escalate treatment and add a second agent where required at clinicians' discretion. Allocated treatment was taken as first-line antihypertensive agent until delivery (or discontinuation at clinician or woman's request) and women were followed-up until six weeks' post-partum wherever feasible. If additional antihypertensive agents were required or women opted to discontinue their assigned intervention, treatment was prescribed at their clinician's preference. Diastolic BP treatment target was 85 mm Hg in accordance with recommendations from the outcomes of the Control of Hypertension In Pregnancy Study (Magee LA, Dadelszen P, Rey E, et al. Less-tight versus tight control of hypertension in pregnancy. The New England journal of medicine. 2015;372(5):407-417.). All other antenatal care was as standard UK practice in accordance with NICE guidelines for the management of chronic hypertension in pregnancy (National Institute for Health and Clinical Excellence. Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. 2010;(Clinical Guideline 107), including standard administration of aspirin (75 mg/day) for prevention of pre-eclampsia.

Baseline demographic and antenatal booking data were collected at enrolment. BP readings taken at all subsequent antenatal visits in the routine clinical environment (using manual and automated devices validated for use in pregnancy) and daily during hospital admissions (highest of that day) were recorded in addition to maternal and neonatal outcome data. The primary process outcome was recruitment per maternity centre per month and the primary clinical outcome was maximum systolic BP post-randomisation until delivery (mean highest systolic and corresponding diastolic in each treatment group). Secondary clinical outcomes with effect size calculated included: mean systolic and mean diastolic BP post-randomisation until delivery (measured using the trapezium method analysing the area under the curve), proportion of days with BP recordings of systolic BP >=160 mm Hg, >=150 mm Hg, or diastolic BP <80 mm Hg between randomisation and delivery, proportion of women diagnosed with superimposed pre-eclampsia (defined as new-onset proteinuria (protein: creatinine ratio >30 mg/mmol), a sudden increase in proteinuria if already present in early gestation, and an increase in hypertension (ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002;77(1):67)), median gestation at delivery, mean birthweight, and proportion of infants admitted to the neonatal

care unit in each group. Other secondary clinical outcomes recorded included: additional antihypertensive agent use (oral and parenteral), mode of delivery, estimated blood loss, other adverse maternal outcome, condition of the fetus at birth (including Apgar score and umbilical cord gas analysis), customised birthweight centiles, and other adverse neonatal outcomes. Customised birthweight centiles were calculated using the GROW formula with adjustment for maternal height, maternal weight, maternal ethnicity, parity, infant sex, infant birthweight and gestation at birth (Gardosi J. New definition of small for gestational age based on fetal growth potential. Hormone Research in Paediatrics. 2006;65(Suppl. 3):15-18. version 6.7.5.1 (2014)). Secondary process outcomes included: proportion of women withdrawing from the study, proportion of women able to adhere to the assigned intervention, and proportion and range of adverse events reported in each treatment arm. Health resource use was captured as antenatal outpatient visits (including scans, antenatal clinic and maternity assessment unit visits), antenatal and postnatal maternal ward nights, maternal intensive care and high dependency unit nights, neonatal intensive care and high dependency care unit nights, neonatal special care and transitional care nights, and neonatal postnatal ward nights. Women were asked to complete a questionnaire regarding their views on trial participation at the six-week follow-up. Planned collection of data from home BP readings was not feasible as few women monitored their BP at home in this cohort. Assessment of adherence through pill count was planned, but not implemented to reduce the time commitment involved in study participation.

Pre-specified mechanistic analyses included: collection of urine samples for protein: creatinine ratio (PCR) quantification, and pulse wave analyses that were obtained using the Arteriograph® (Tensiomed, Budapest, Hungary) at randomisation, 20 weeks, 28 weeks, 34 weeks' gestation. PCR was defined as the ratio of urinary protein excretion to urinary creatinine excretion and hence renal function. PCR values were considered normal below 30 mg/mmol. Pulse wave analyses were performed to assess if parameters of arterial stiffness (central aortic pressure, augmentation index and pulse wave velocity) could offer additional insight into treatment effects beyond the scope of brachial blood pressure alone. All pulse wave measurements were performed with participants in the sitting position. The Arteriograph® cuff was then applied to the left arm over the brachial artery for estimation of central aortic pressure (the estimated peak systolic pressure in the aorta, measured in mm Hg), pulse wave velocity (speed of travel of the pulse along an arterial segment, measured in m/s) and augmentation index (increase in aortic pressure after the peak of blood flow in the vessel, measured as a percentage) as previously described by Khalil and colleagues (Khalil A, Akolekar R, Syngelaki A, Elkhouli M, Nicolaides KH. Maternal hemodynamics in normal pregnancies at 11–13 weeks' gestation. Fetal diagnosis and therapy. 2012;32(3):179-185). All recordings were made by researchers who had received appropriate training on the use of the Arteriograph®. The results of the pulse wave analyses were not given to the women or their doctors and did not influence the subsequent management of the pregnancies.

Supplemental Results:

Supplemental Table S1: Details of adverse maternal outcomes

Outcome	Randomised to labetalol n=55	Randomised to nifedipine n=57
Any maternal complication	6 (11%)	8 (14%)
Maternal death	0	0
Central Nervous System		
Eclampsia	0	0
Glasgow coma score <13	0	0
Intracranial haemorrhage or infarct	0	0
Transient ischaemic attack	0	0
Cortical blindness or retinal detachment	0	0
Posterior reversible encephalopathy	0	0
Cardiorespiratory		
Positive inotropic support required	0	0
Myocardial ischaemia or infarction	0	0
Oxygen saturations <90% >2 hours	0	0
≥50% Oxygen therapy required for >1 h	0	0
Intubation	0	0
Pulmonary oedema	0	0
Haematological		
Transfusion of any blood product	2 (4%)	5 (9%)
Platelet count $<50\times10^9$/L (no transfusion)	1 (2%)	0
Hepatic		
Dysfunction	0	0
Haematoma or rupture	0	0
Renal		
Acute renal insufficiency (creat >150 µmol/L; no pre-existing renal disease)	1 (2%)	0
Acute renal failure (creatinine >200 µmol/L; pre-existing renal disease)	1 (2%)	2 (4%)
Dialysis	0	0
Obstetric		
Placental abruption	0	1 (2%)
HELLP syndrome	1 (2%)	0
Postpartum haemorrhage, >1.5L	4 (7%)	4 (7%)

Supplemental Table S2: Details of adverse neonatal outcomes

Outcome	Randomised to labetalol n=51	Randomised to nifedipine n=52
Any neonatal complication	11 (22%)	17 (33%)
Neonatal Death	0	0
Infant death >28 days post delivery	0	1 (2%)
Central nervous system		
Interventricular Haemorrhage	0	0
Seizures	0	0
Encephalopathy	0	0
Retinopathy of prematurity	0	0
Respiratory		
Respiratory Distress Syndrome	7 (14%)	11 (21%)
Need for additional respiratory support	6 (12%)	12 (23%)
Gastrointestinal		
Necrotising enterocolitis	3 (6%)	2 (4%)
Hypoglycaemia	6 (12%)	8 (15%)
Sepsis	1 (2%)	5 (10%)
Congenital anomalies*	1 (2%)	4 (8%)
Chromosomal abnormalities*	0	1 (2%)

Neonatal outcome data is only presented for the livebirths.

***Congenital anomalies by treatment group included; labetalol: one infant with hypospadias; nifedipine: one infant with jejunal atresia and a deletion on the short arm of chromosome 16, one infant with trachea-oesophageal fistula, and one infant with tetralogy of fallot. All of these women were randomised after 16 weeks' gestation.*

Supplemental Table S3: Health resource use category by randomised treatment group (mean and standard deviation)

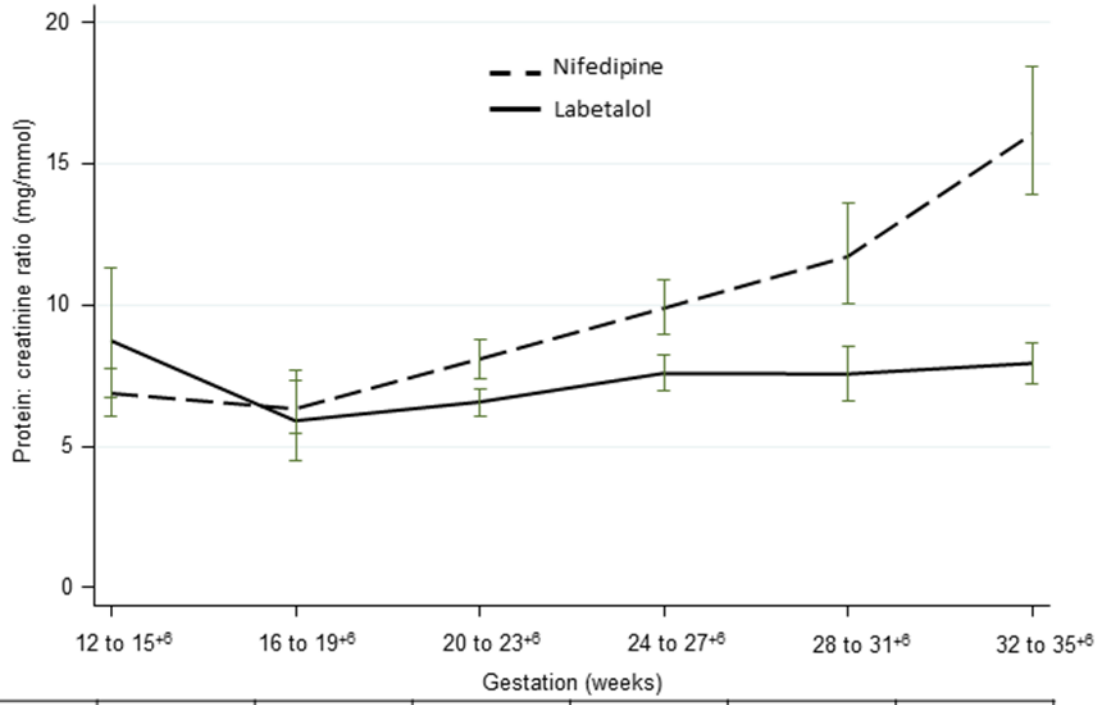
Health resource	Randomised to labetalol n=55	Randomised to nifedipine n=57
Number of antenatal clinics, antenatal day unit visits and ultrasound visits in pregnancy	19 (8)	20 (8)
Number of maternal antenatal and postnatal ward nights	4 (3)	7 (7)
Number of maternal intensive care unit and/or high dependency unit nights	0.4 (1.1)	0.9 (1.9)
Number of neonatal intensive care unit and/or high dependency care nights	2 (10)	6 (23)
Number of neonatal special care and/or transitional care nights	2 (6)	3 (12)
Number of neonatal postnatal ward nights	2 (2)	2 (2)

Supplemental Table S4: Summary of adverse events reported in each treatment arm

Adverse event	Randomised to labetalol n=55	Randomised to nifedipine n=57
Total	21 (38%)	15 (26%)
Headache	10 (18%)	11 (19%)
Dizziness	5 (9%)	2 (4%)
Lethargy	2 (4%)	0
Epistaxis	1 (2%)	1 (2%)
Scalp tingling	2 (4%)	0
Shortness of breath	5 (9%)	1 (2%)
Abdominal pain/nausea	2 (4%)	2 (4%)
Peripheral oedema	2 (4%)	1 (2%)
Hot flashes	1 (2%)	1 (2%)

In addition, nipple pain, nasal congestion, eye spasm and chest pain were experienced by one woman each in the labetalol group

Supplemental Figure S1



Number of samples						
Nifedipine	12	14	23	18	17	28
Labetalol	9	10	23	22	22	25

Treatment effects on urinary protein: creatinine ratio across gestation post-randomisation
Number of participants sampled at each time point is detailed in the table below the graph and the standard error bars are included at each time point.