Are Calcium-Channel Blockers the Most Effective Anti-hypertensive Agent in Black Women With Hypertensive Disorders of Pregnancy? A Systematic Review

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Research Article

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Abstract

Background

Black women are four times more likely to die than White women due to complications during pregnancy or childbirth in the U.K. This cohort are also more prone to Hypertensive Disorders in Pregnancy (HDP). Outside of pregnancy, there are race based differences in the management of hypertension as Calcium-Channel Blockers (CCB) are more effective in reducing blood pressure in Black patients. It is unclear whether these differences in anti-hypertensive management extend to the management of hypertension in pregnancy. The primary objective was to address this gap in evidence by undertaking a systematic review of randomised control trials, where one treatment arm comprised of CCBs, investigating pharmacological management of HDP to assess whether CCBs are the most effective anti-hypertensive agent in Black pregnant women.

Methods

The following electronic databases were searched: MEDLINE and Embase. We used MeSH and free text terms in conjunction to increase sensitivity to potentially relevant studies. Inclusion criteria included: (1) study involved drug treatment of HDP; (2) study was of randomised control trial design; (3) one of the treatment arms involved CCBs (4) English full-text and (5) outcome data was stratified by race, and included Black women. Information regarding baseline participant data, type of anti-hypertensive, and clinical outcomes was extracted from each study.

Results

This review highlighted four randomised control trials, which published race or ethnicity demographics, with only one trial that stratified HDP outcomes by ethnicity.

Conclusions

There is a lack of evidence to draw definite conclusions as to whether CCBs are the most effective anti-hypertensive agent for Black patients with HDP, highlighting the need for further research in this area. However, this review demonstrates some evidence to support the hypothesis that CCBs could be more effective in the management of HDP in Black patients and that Labetalol, which is the current first-line management of HDP, may not represent the gold standard of treatment in this cohort.

Background

In the United Kingdom (U.K.), although the overall maternal mortality rate (MMR) has remained low\(^1\), significant racial disparities within maternal outcomes have persisted. The most recent Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries-U.K. (MBRRACE-U.K.) report revealed that Black women are four times more likely to die than their White counterparts due to pregnancy related complications.\(^1\) Black women are also more likely to suffer from severe maternal morbidity, or so called
“near-miss” events even when potential confounding factors such as socioeconomic and smoking status, and high Body Mass Index (BMI) are accounted for.\(^2\)

Amongst indirect causes of maternal mortality, cardiovascular disease remains the most significant contributor.\(^1\) Hypertensive disorders in pregnancy (HDP), which encompass gestational hypertension, pre-eclampsia and pre-existing hypertension, are classified as direct causes of maternal mortality, however it is irrefutable that HDP in addition to the physiological changes of pregnancy can considerably exacerbate pre-existing cardiovascular disease leading to increased morbidity and mortality.\(^3\) HDP complicate up to 10 percent of pregnancies\(^4\) and having a diagnosis of HDP also increases the risk of developing cardiovascular disease in later life.\(^5\) It is therefore imperative that HDP is managed in an appropriate and timely manner.

In a non-pregnant patient, first line management of hypertension differs based on ethnicity.\(^6\) In the U.K., NICE guidelines recommend commencing Calcium Channel Blockers (CCB) initially for treatment of raised blood pressure in patients of any age from Black African and African Caribbean origin.\(^7\) The variance in initial pharmacological management is because in Black patients with hypertension, there is evidence to suggest that CCB monotherapy is more effective at reducing blood pressure than Beta Blocker monotherapy.\(^8\) Presently, the first line pharmacological management of all pregnant women with hypertension and pre-eclampsia in the U.K. is the non-specific alpha- and beta- blocker, Labetalol.\(^9\) Although, there have been numerous clinical trials investigating the management of hypertensive disorders in pregnancy, there is a lack of knowledge regarding whether the race based differences in first line anti-hypertensive management out with pregnancy should extend to pregnant women.

Therefore, our primary objective was to address this gap in evidence by undertaking a systematic review of randomised control trials, where one treatment arm comprised of CCBs, investigating pharmacological management of HDP to assess whether CCBs are the most effective anti-hypertensive agent in Black pregnant women.

**Methods**

**Protocol and sources**

The study was developed and completed in compliance with the PRISMA guidelines.\(^10\) The following electronic databases were searched: MEDLINE (via Ovid) and Embase (via Ovid). The databases were searched from date of first publication until January 2021. We used MeSH and free text terms in conjunction to increase sensitivity to potentially relevant studies. For details of the search performed, see Supporting Information Appendix S1. Endnote software (X8; Clarivate Analytics, Philadelphia, PA, USA) was used to export and organise the abstracts, and subsequently remove duplicate publications.

**Study selection**
We included randomised control trials focussed on management of HDP where one treatment arm comprised of CCBs, and the study demographics explicitly stated involvement of Black pregnant women. Studies were included in our review if they met the following criteria: (1) study involved treatment of HDP; (2) study was of a randomised control trial design; (3) one of the treatment arms involved CCBs; (4) English full-text and (5) outcome data was stratified by race, and included Black women. Studies were excluded if relevant outcome data were not reported or there was no mention of ethnicity or race demographics within the study. We also excluded case-control studies, case reports, reviews, letters to editors, and animal/in vitro studies. Corresponding authors were contacted individually to obtain the full text article or where additional information was required if inclusion criteria were met based on the information provided in the abstract. All study abstracts were independently screened by two authors (J.J. and G.C.) with disagreements reviewed and settled by discussion. Following abstract screening, potentially eligible studies underwent full-text review by the same authors.

**Data extraction**

Data extraction and assessment of study quality were performed by two independent reviewers (J.J. and G.C.) using standardised data collection forms. Information regarding baseline participant data, type of anti-hypertensive, and clinical outcomes was extracted from each study. Any discrepancy between reviewers was resolved by discussion and consensus.

**Assessment of risk of bias**

Included randomised control trials were assessed in all domains of bias as defined by the Cochrane Collaboration. In addition, the prevalence of conflict of interest was investigated.

**Results**

**Study selection and description**

An initial search yielded 1380 abstracts, subsequently narrowed to 4 articles following full text review, as shown in Fig. 1. These 4 articles comprised of randomised control trials comparing CCB to other anti-hypertensives in women with HDP, and included Black women in their demographics. An overview of the included studies’ characteristics and primary outcomes is illustrated below.

However, 3 out of 4 articles did not publish treatment effect by race, and therefore could not be used to answer the review question. We established contact with authors from all 3 studies where race based outcomes were not published however they were unable to grant access to original trial data, and therefore a meta-analysis was not possible.

Scardo et al randomised pregnant patients admitted to the Medical University of South Carolina with hypertensive emergencies, defined as a sustained systolic blood pressure of ≥ 170 mm Hg or diastolic blood pressure of > 105 mm Hg, to receive either oral Nifedipine (CCB) and 50 millilitres of Sodium
Chloride or intravenous Labetalol and oral placebo consisting of corn starch powder in a double-blind trial. Black pregnant women comprised 62 percent of the sample size. The primary outcome was the time interval required to achieve the therapeutic blood pressure goal of < 160 mm Hg systolic and < 100 mm Hg diastolic. Patients receiving oral Nifedipine more rapidly achieved the therapeutic blood pressure goal in 25.0 ± 13.6 minutes (mean ± SD) as compared with 43.6 ± 25.4 minutes in those receiving Labetalol (p = 0.002). They also demonstrated that the Nifedipine group required significantly fewer doses (1.5 ± 0.5 vs 2.5 ± 1.5; p ≤ 0.001) to reach the target blood pressure.

Belfort et al conducted an unblinded, randomised, multicentre trial in which 1650 patients with severe pre-eclampsia, defined as elevated blood pressure (≥ 140/90 mm Hg) with > 1 + proteinuria and presence of one or more of the following: symptoms of pre-eclampsia, deranged liver function tests, intrauterine growth restriction or oligohydramnios; or persistent blood pressure ≥ 160/110 mm Hg with proteinuria in the absence of other features, were included. Patients were allocated to oral Nimodipine (CCB) or intravenous Magnesium Sulphate. Blood pressure control was one of this study’s secondary outcomes. Baseline blood pressures and overall blood pressure readings were similar in both groups, although the authors noted that the group that received Magnesium Sulphate required Hydralazine more frequently to achieve target blood pressure levels. In the first hour after drug administration, there was a higher reduction of mean arterial pressure in the Nimodipine group compared to the Magnesium Sulphate group (-8.2% vs -4.2%). Within three hours of drug administration, reduction in mean arterial pressure was maintained in the Nimodipine group at 8.3 percent whereas the Magnesium Sulphate group had a 7.2 percent decrease in this time frame. Black patients accounted for 42 percent of the study group.

Sharma et al conducted a prospective, unblinded, randomised control trial amongst postpartum women with persistent hypertension, defined as sustained systolic blood pressure ≥ 150 mm Hg and diastolic blood pressure ≥ 100 mm Hg. 25 participants each were allocated to Labetalol versus extended release Nifedipine. Time elapsed prior to achieving blood pressure control was similar between both groups (36.6 hours with Labetalol vs 38.2 hours with Nifedipine; p = 0.51). In this study, where 36 percent of the group were Black, both oral Labetalol and Oral extended release Nifedipine were effective for the treatment of post-partum hypertension. At 72 hours post-partum, mean systolic blood pressure recorded for the Labetalol group was 140 (± 15) mm Hg (mean ± SD) vs 141 (± 27) mm Hg in Nifedipine group (p = 0.94) and mean diastolic blood pressures were measured at 89 (± 4) mm Hg vs 87 (± 13) mm Hg (p = 0.70) in Labetalol and Nifedipine groups respectively. Although time to blood pressure control did not differ significantly between medication groups, Labetalol achieved control more often with the starting dose (76 percent with Labetalol vs 46 percent with Nifedipine; p = 0.04) and with fewer minor side effects compared to Nifedipine (20 percent with Labetalol vs 48 percent with Nifedipine; p = 0.04).

The remaining article by Webster et al was a multi-centre randomised control trial in the U.K., which compared the effectiveness of Labetalol and Nifedipine in the management of chronic hypertension in pregnancy. This study comprised of 62 Black pregnant patients who accounted for 54 percent of the study population of 112 women. A pre-specified 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 blood pressure 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 blood pressure was seen between treatment groups in study participants (−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 blood pressure was seen in the Labetalol arm in non-Black participants. The authors concluded that some variation in treatment effect by ethnicity was noted, with Labetalol having a greater effect on reducing diastolic blood pressure in non-Black women. Nifedipine was associated with reduced central aortic pressure however the study was not powered to calculate what the most effective anti-hypertensive treatment for Black women with HDP is.

**Risk of bias**

Included randomised control trials were assessed in the following domains of bias as defined by the Cochrane Collaboration: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. See Fig. 2 below for details of risk of bias. None of the authors reported any conflicts of interest.

**Discussion**

*Main findings*

This is the first systematic review to our knowledge that investigates the efficacy of CCBs as treatment for Black women with diagnoses of HDP. The striking finding from this review is that there is a paucity of randomised control trials focussed on HDP that publish race or ethnicity of their study participants, Fewer still report outcomes in relation to race or ethnicity, representing a significant gap in evidence in these trials. This is despite the extensive documentation of racial and ethnic differences in cardiovascular health outcomes out with, during and following pregnancy. It is therefore impossible to definitively conclude which anti-hypertensive is most effective for each pregnant ethnic group.

Outside of the context of pregnancy, national guidelines in the U.K. and U.S.A. (United States of America) recommend ethnicity based stratification of first-line anti-hypertensive agents, with Black patients receiving CCB rather than Angiotensin-Converting Enzyme inhibitors (ACE-i) as first line management of hypertension, regardless of age. These guidelines are based on data from large randomised control trials, which indicate that CCB are more effective in reducing the risk cardiovascular disease and stroke in Black patients.

Another study by Weir et al found that Black patients required between two and four times the dose of Trandolapril (ACE-i) to obtain a response similar to that observed in White patients. A systematic review of hypertension treatment for non-pregnant Black patients concluded that thiazide-like diuretic and CCB monotherapy were better at achieving target blood pressure levels compared with beta-adrenergic blocker, ACE-i or angiotensin receptor blocker (ARB) monotherapy. These studies demonstrate that it is possible that Black patients may have different responses to certain hypertensive drugs compared to other
ethnicities. Black patients are at increased risk of hypertension associated end-organ damage at lower blood pressure levels compared to other ethnicities, and it is therefore essential that anti-hypertensives achieve tight control of blood pressure in this group.\textsuperscript{26}

Previous population studies have demonstrated that chronic hypertension is more prevalent in younger Black women than Black men or women of White ethnicity until 75 years of age.\textsuperscript{27} In particular, Black women are at higher risk for developing refractory hypertension and often require multiple anti-hypertensive drugs for adequate blood pressure control.\textsuperscript{28-29}

Women with HDP are more likely to develop essential hypertension and have an elevated risk of future cardiovascular disease.\textsuperscript{30-31} In fact, it has been shown that the onset of cardiovascular dysfunction can be noted as early as shortly after the index pregnancy affected by HDP.\textsuperscript{32} Black women are known to be particularly at risk of developing HDP.\textsuperscript{33} In one study, women of Black ethnicity with HDP were significantly more likely to require post-partum care in a high dependency unit compared with White women, suggesting a correlation between Black ethnic background and increased disease severity.\textsuperscript{34} Disparities in socioeconomic status have been theorised as a plausible explanation for these differences\textsuperscript{35} but these do not account entirely for the variances, given that studies based in free at point-of-care healthcare systems have previously adjusted for deprivation score as a baseline characteristic, and still noted that Black women had significantly worse perinatal outcomes.\textsuperscript{36-37} In another study, Black women were more likely to have had pre-eclampsia in a previous pregnancy compared to other ethnicities regardless of BMI (p=0.014).\textsuperscript{38} They also reported that on any postpartum day, a Black woman with BMI < 35 was 50 percent less likely to achieve resolution of HDP than a non-Black woman in the same BMI category (HR 0.51, 95% CI 0.27–0.95).\textsuperscript{38} The probability of a Black woman with a BMI ≥ 35 achieving blood pressure resolution was 71 percent lower (HR 0.29, 95% CI 0.12–0.74).\textsuperscript{38} This data highlights the potential role of increased severity of maternal disease in Black women with HDP, independent of other risk factors, further strengthening the argument that optimisation of anti-hypertensive treatment in this cohort is crucial in order to ameliorate these clinical discrepancies.

HDP contribute to 2.8 percent, 7.4 percent, and 14 percent of pregnancy related deaths in the U.K., U.S.A. and worldwide respectively.\textsuperscript{39-41} Previous reviews have shown that deaths from HDP are largely preventable, and associated with substandard care.\textsuperscript{42} The lack of consensus around whether race based differences in first line management of hypertension outside of pregnancy should extend to HDP due to lack of good quality research represents a lack of evidence-based gold standard care, which may contribute to the persistent racial disparities in maternal mortality and morbidity.

This current review highlighted just one randomised control trial, which stratified HDP outcomes by ethnicity. Webster et al commented on some treatment effect by ethnicity in their trial comparing Labetalol with Nifedipine. They reported that Labetalol had a greater effect in reducing mean diastolic blood pressure in non-Black participants. Another article included in this review, which could not be used for meta-analysis due to unavailability of race based outcomes, by Scardo et al is also of interest as 62
percent of its study population was Black, the trial with the highest proportion of Black participants. They demonstrated that Nifedipine was associated with quicker resolution of raised blood pressure. Additionally, the cohort allocated to Nifedipine required fewer doses of anti-hypertensive medication to reach target blood pressure. These two articles in combination support the hypothesis that CCBs could be more effective in the management of HDP in Black patients and that Labetalol, which is the current first-line management of HDP, may not represent the gold standard of treatment in this cohort. It certainly highlights the need for further research in this area.

**Conclusion**

There is a lack of evidence to draw conclusions as to whether CCBs are the most effective anti-hypertensive agent for Black patients with HDP. Although we do not advocate for randomised control trials to investigate HDP in specific ethnic groups, this review emphasises the need for routine reporting of race and ethnicity demographics, as well as stratification of clinical outcomes by ethnicity in trials investigating HDP.

**Abbreviations**

U.K. United Kingdom

HDP Hypertensive Disorders in Pregnancy

CCB Calcium-Channel Blockers

MeSH Medical Subject Heading

MMR Maternal Mortality Rate

MBRRACE-U.K. Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries-U.K.

BMI Body Mass Index

SD Standard Deviation

U.S.A United States of America

ACE-I Angiotensin Converting Enzyme- inhibitor

ARB Angiotensin Receptor Blocker

**Declarations**

*Competing interests*
The authors declare that they have no competing interests

Contribution to authorship

OB was involved in study conceptualization, planning, data extraction and analysis, and interpretation of findings, and was the primary writer of the manuscript. MIY and TF contributed to data extraction and analysis. LS contributed to planning and data extraction. SS was involved in study conceptualization and interpretation of findings. All authors contributed to the final manuscript.

Details of ethics approval

Not applicable.

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Authors’ contributions

JJ was involved in study conceptualization, planning, data extraction and analysis, and interpretation of findings, and was the primary writer of the manuscript. GC contributed to data extraction and analysis. Both authors contributed to the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Consent for publication

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Availability of data and materials
All data generated or analysed during this study are included in the supplementary information associated with this manuscript.

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**Figures**
### Figure 1

#### Study characteristics and primary outcomes

| First Author | Year | Sample size | Black Participants (%) | Type of antihypertensive | Primary outcome |
|--------------|------|-------------|-------------------------|--------------------------|-----------------|
| Scardo       | 1999 | 50          | 62                      | Nifedipine vs Labetalol  | Time to achieve blood pressure goal of <160 mm Hg systolic and <100 mm Hg diastolic |
| Belfort      | 2003 | 1650        | 42                      | Nimodipine vs Magnesium Sulphate | Development of eclampsia |
| Sharma       | 2016 | 50          | 36                      | Nifedipine vs Labetalol  | Time to blood pressure control |
| Webster      | 2017 | 112         | 54                      | Nifedipine vs Labetalol  | Blood pressure |

#### Risk of bias

| Study          | D1 | D2 | D3 | D4 | D5 | D6 | D7 | Overall |
|----------------|----|----|----|----|----|----|----|---------|
| Scardo 1999    | +  | +  | +  | +  | +  | +  | -  | +       |
| Belfort 2003   | -  | -  | -  | +  | +  | +  | -  | X       |
| Sharma 2016    | +  | -  | -  | -  | +  | +  | -  | X       |
| Webster 2017   | -  | -  | -  | +  | +  | +  | -  | X       |

- **D1**: Random sequence generation
- **D2**: Allocation concealment
- **D3**: Blinding of participants and personnel
- **D4**: Blinding of outcome assessment
- **D5**: Incomplete outcome data
- **D6**: Selective reporting
- **D7**: Other sources of bias

#### Judgement
- Red: High
- Yellow: Unclear
- Green: Low

### Figure 2

#### Risk of bias assessment