Systematic review: antihypertensive drug therapy in black patients

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CRD summary
The review concluded that efficacy differed by drug type. Most of the commonly used hypertensives were more effective than placebo in lowering systemic blood pressure in black adults, but evidence was lacking for reduced morbidity and mortality once blood pressure goal was achieved. This was a reasonably well-conducted review and the authors’ conclusions are likely to be reliable.

Authors’ objectives
To determine the efficacy of different classes of antihypertensive drugs in hypertensive black adults for the reduction of blood pressure, morbidity and mortality.

Searching
MEDLINE, EMBASE, LILACS, African Index Medicus and The Cochrane Library were searched without language restriction from inception through November 2003. PUBMED was searched from September 2003 to March 2004. DARE, Best Evidence and Reviews in Progress were searched. Index Medicus was handsearched (backwards) from 1953. Internet sources and references from relevant textbooks and reviews were checked. Experts and pharmaceutical companies were contacted to identify any additional trials.

Study selection
Randomised controlled trials (RCTs) that compared antihypertensive monotherapy with placebo (blood pressure and morbidity and mortality outcomes), another antihypertensive agent or combinations of drugs (morbidity and mortality outcomes only) in black adult patients were eligible for inclusion in the review. Studies were required to provide quantitative data on systemic arterial blood pressure, morbidity or mortality. Adverse events and the effect of increasing drug dose or addition of other drugs were assessed. Trials that included oral treatment with diuretics, calcium-channel blockers, centrally acting agents, peripheral adrenergic neuron antagonists, β-blockers, α-blockers, single agents with combined α- and β-blocking activity, direct vasodilators, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers were eligible for inclusion.

Trials included eight classes of drugs; diuretics were the most common. Drug doses were reported and varied across studies. Blood pressure was the main outcome in most of the included trials. All studies reported blood pressure outcomes as change in mmHg or as the percentage of patients who reached the diastolic blood pressure goal. Studies with blood pressure outcomes used preset doses and did not report whether they assessed the minimum dose needed to reach maximum hypertensive effect. Most trials included patients with uncomplicated primary hypertension and no clinically significant end organ damage. Reported mean age ranged from 44 to 58 years. Pre-treatment diastolic blood pressure ranged from 90 to 155mmHg.

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
The methodological quality of the included studies was assessed using the Jadad scale (maximum score of 5 points based on criteria of randomisation, blinding and treatment of withdrawals and dropouts). Studies were also assessed in terms of whether the minimum drug dose needed to reach a maximum hypertensive effect was reported, whether outcome assessment was blinded and whether adverse effects were reported.

At least two reviewers assessed the validity of the included studies; any disagreements were resolved by consensus.

Data extraction
The differences in means and standard deviations (SDs) for blood pressure were extracted. Where standard deviations
were not provided, they were imputed for each drug type by using available standard deviations for each drug class.

Intention to treat data (primary analysis) and per protocol data (secondary analysis) were extracted. Attempts were made to contact the investigators if additional information was required.

At least two reviewers independently extracted data from the selected studies. Any disagreements were resolved through discussion.

Methods of synthesis

Studies were combined in a meta-analysis using a random-effects model. Summary effects were reported as mean difference (WMD) for continuous outcomes and relative risks (RR) for dichotomous outcomes, along with their associated 95% confidence intervals (CIs). Studies were assessed for both clinical and statistical heterogeneity. Statistical heterogeneity was assessed using $X^2$ test and the $I^2$ statistic; where high variation was found ($I^2 \geq 75\%$) results were not aggregated. Sensitivity analyses (data reanalysed with a fixed-effect model and exclusion of studies with imputed standard deviations, crossover studies and studies that used per protocol analysis) was performed. Subgroup analysis (specified in advance) were based on severity of hypertension, country of origin (African versus USA and Caribbean) and gender.

Results of the review

Thirty trials involving 53 interventions (eight classes of hypertensive drugs) were included in the review (n=20,006). Jadad scores ranged from 2 to 4 in studies with blood pressure outcomes and from 3 to 5 in studies with morbidity and mortality outcomes. Most of the studies were conducted in USA; other countries included South Africa, Nigeria, Jamaica, Bahamas and Zimbabwe.

Blood pressure:

For systolic blood pressure, mean difference ranged from -13.20 (95% CI -16.72 to -9.68) for centrally acting agents to -3.53 (95% CI -7.51 to 0.45) for β-blockers. For diastolic blood pressure, mean difference ranged from -8.06 (95% CI -10.01 to -6.11) for diuretics to -2.09 (95% CI -3.28 to -0.91) for angiotensin II receptor blockers.

There was no pooled effect for calcium channel blockers due to heterogeneity. Calcium channel blockers, diuretics, central sympatholytics, α-blockers and angiotensin II receptor blockers were significantly more effective than placebo in reducing blood pressure (systolic and diastolic).

No statistically significant difference from placebo was found either for β-blockers in reducing systolic blood pressure (WMD -3.53mmHg, 95% CI -7.51 to 0.45) or ACE inhibitors in achieving diastolic blood pressure goals (RR 1.35, 95% CI 0.81 to 2.26).

Evidence of moderate to substantial heterogeneity was found for calcium channel blockers and β-blockers for systolic blood pressure outcomes and calcium channel blockers, diuretics, ACE inhibitors and α-blockers for diastolic blood pressure outcomes. Only calcium channel blockers remained effective in all prespecified subgroups, including patients with a baseline diastolic blood pressure of 110mmHg or more.

Diastolic blood pressure goal was defined as diastolic blood pressure ≤90mmHg or reduction of diastolic blood pressure of ≥10mmHg (or 10% reduction). The percentage of patients who reached diastolic blood pressure goal was 23%; this ranged from 0% (postganglionic sympathetic neuron blockers) to 46% (calcium channel blockers).

Sensitivity analyses:

These revealed a significant difference in favour of β-blockers compared to placebo for systolic blood pressure and a significant difference in favour of ACE inhibitors for reaching blood pressure goal. Sensitivity analyses did not significantly alter the magnitude of effect for any other outcome reported.

Morbidity and mortality:

When drugs were combined to reach blood pressure goals, no statistically significant between-group differences were
found for morbidity and mortality outcomes (based on data from four trials).

**Adverse effects:**

Adverse events were reported in 12 trials and occurred more frequently with drugs than with placebo. In particular, a greater incidence of diabetes was found with diuretics and a higher risk of cardiovascular events was found with drug regimens that included angiotensin-converting enzyme inhibitors. Studies with higher drug doses did not appear to report greater frequency of adverse events.

**Authors' conclusions**

Efficacy differed by drug type. Most of the commonly used hypertensives were more effective than placebo in lowering systemic blood pressure. However, evidence was lacking for reduced morbidity and mortality outcomes once patients achieved the blood pressure goal.

**CRD commentary**

The review question and inclusion criteria were clear. Several relevant databases were searched without language restriction. Attempts to identify unpublished studies were reported, but publication bias was not assessed. Rigorous methodology was reported for data extraction and quality assessment, but it was unclear whether similar methodology was used for study selection and so the likelihood for reviewer error or bias at this stage could not be assessed. The validity assessment tool used appropriate criteria. The use of meta-analysis seemed appropriate and potential sources of statistical heterogeneity were investigated. This was a reasonably well-conducted review and the authors' conclusions are likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that drugs that ensure tight blood pressure control with low risk of side effect should be used. For many black adults with primary hypertension, calcium agonists might be appropriate for first-line treatment; if this was not an affordable option, diuretics may be the best alternative.

**Research:** The authors stated that future trials should recruit sufficient adult black participants to allow primary analysis based on ethnicity and should report adequate details on blood pressure reduction, adverse events and dropouts for this group. Further research was required on the effect of extended dose titration on the percentage of patients who achieved blood pressure goals. Trial designs should stratify patients on baseline severity of hypertension. Future studies should determine the efficacy of angiotensin-converting enzyme inhibitors, α-blockers and angiotensin receptor blockers compared with other drugs in reduction of cardiovascular events in black patients. Studies should also investigate whether use of diuretics and β-blockers in younger patients with uncomplicated hypertension led to greater morbidity and mortality as a consequence of newly developed or worsening diabetes mellitus.

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