INPLASY

How quickly do blood pressure lowering drugs reduce blood pressure? A systematic review and meta-analysis of randomized double-blind placebo-controlled trials

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ADMINISTRATIVE INFORMATION

Support - National Health and Medical Research Council, Australia.

Review Stage at time of this submission - Data analysis.

Conflicts of interest - The George Institute for Global Health (TGI) has submitted patent applications for low-dose combination products for hypertension and Professor Rodgers is listed as an inventor. George Medicines Pty Ltd (GM) is a subsidiary of TGI, holds a license for these patents and has received investment to develop these combination therapies. Professor Rodgers is seconded part-time to GM. Professor Rodgers and other employees of TGI have no financial interest in these patents or in GM.

INPLASY registration number: INPLASY202510094

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 January 2025 and was last updated on 23 January 2025.

INTRODUCTION

Review question / Objective How does blood pressure-lowering effect of antihypertensive drugs evolve over time?

Rationale Effective management of hypertension is essential for reducing the risk of cardiovascular events. Antihypertensive drugs are primary treatment for hypertension. It is unclear how blood pressure-lowering effect of antihypertensive drugs evolve overtime. Understanding this is critical for optimizing therapeutic strategies and improving patient outcomes. The findings from this systematic review will inform future clinical practice guideline recommendations regarding the optimal time to modify antihypertensive therapy if desired blood pressure control is not achieved.

Condition being studied Adult participants with hypertensive condition.

METHODS

Participant or population Participants (≥18 years of age) with hypertension (SBP ≥140 mmHg and/or DBP ≥90 mmHg; or taking antihypertensive drugs or had hypertension as defined by the study) who were antihypertensive drug therapy naive or had a washout of previous antihypertensive drugs for at least 1 weeks before randomisation.

Intervention Oral fixed dose of antihypertensive drug(s) as either monotherapy or combination therapy from five major classes: angiotensin-converting enzyme inhibitors (ACEs), angiotensin II receptor blockers (ARBs), beta-blockers (BBs),

Calcium channel blockers (CCBs), diuretics for at least four weeks.

Comparator Placebo.

Study designs to be included Randomized, double-blind, placebo-controlled trials.

Eligibility criteria
Inclusion criteria:
Participants: adults (≥18 years of age) with hypertension (SBP ≥140 mmHg and/or DBP ≥90 mmHg; or taking antihypertensive drugs or had hypertension as defined by the study) who were either antihypertensive drug therapy naive or had a washout of previous antihypertensive drug(s) for at least 1 weeks before randomisation to study intervention/comparator.
Intervention: oral fixed dose of antihypertensive drug(s) as either monotherapy or combination therapy from five major classes (ACEs, ARBs, CCBs, BBs, and diuretics) for at least four weeks.
Comparator: placebo.
Outcomes: studies reporting clinic SBP and/or DBP data at baseline and at least at week 2 and week 4 for a maximum of up to week 8 following randomisation.
Study type: randomized, double-blind, placebo-controlled trials.
Other: Non-differential concomitant therapy between the groups. Same BP measurement position, device type, and antihypertensive drug therapy dosing and BP measurement time at and between baseline and follow-up visits.
Exclusion criteria:
Trials with participants age <18 years or with any of the following conditions were excluded:
1. Acute/unstable cardiovascular conditions: hypertensive crisis/urgency, acute myocardial infarction (MI), recent MI (within <1 month), acute coronary syndrome, unstable angina, acute stroke, acute heart failure.
2. Renal diseases: nephrotic syndrome, dialysis dependent renal failure, IgA-Nephropathy, acute renal failure.
3. Severe liver disease.
4. Mental illnesses/neurological disorders: acute schizophrenia, acute mania etc., epilepsy, seizers, tremor, and Parkinson's disease.
5. Recent major surgeries/transplants.
6. Endocrine disorders except diabetes (e.g. hyperthyroidism and gigantism).
7. Pregnant women, pre-eclampsia.
8. Portal hypertension, pulmonary hypertension.
9. Benign prostatic hyperplasia.
10. Raynaud's disease.
Trials with following Intervention/comparator will be excluded:
1. Concomitant differential treatment between randomised trial groups with drugs other than those from the five major classes or with non-pharmacological therapy.
2. Optional titration of antihypertensive drugs such that different participants within a treatment group receive different drugs/doses.
Trials with following outcomes will be excluded:
1. Outcome measurement immediately after exercise, altitude induced and cold induced BP.
2. No outcome data for fixed dose treatment periods.
Trials with following study design were excluded
1. Cluster/step-wedge randomised controlled trials.
2. Subgroup analyses, post-hoc analyses.
Trials with non-English language will be also excluded.

Information sources A systematic literature search was performed in multiple electronic databases: MEDLINE, The Cochrane Central Register of Controlled Trials Library, and Epistemonikos, from inception to December 2022, to identify relevant RCTs. Additionally, the bibliographies of systematic reviews and the FDA website were searched to find relevant trials.

Main outcome(s) The primary outcome will be SBP and DBP reduction at week 2, 4, and 8.

Additional outcome(s) Secondary outcomes will be the percentage of any additional SBP and DBP reduction from week 2 to week 4, and from week 4 to week 8. Difference in change in mean BP from baseline between active and placebo group will used as the effect estimate.

Data management Two reviewers screened each record in duplicate, independently, by first reviewing the titles and abstracts and then full text against the eligibility criteria. Any disagreements between the reviewers on eligibility of studies were resolved by discussion or by consulting a third senior reviewer.
Distiller SR was used to collect data in standard, piloted data collection forms. Information was extracted from each trial on the characteristics of the trial (author, year, study site, design, sample size, etc.), participants (median/mean age, percentage females), interventions (drug names, dosage, and class), and outcomes (blood pressure, adverse events, and biochemical measures). For each group, the mean change from baseline and the standard deviation of change for systolic and diastolic blood pressure at an interval of at mostleas 2 weeks were extracted, up to a maximum of eight weeks. Two reviewers

independently collected data from each included trial. Disagreements in the collected data between the reviewers were resolved by discussion or by adjudication by a senior reviewer. If BP data were not reported numerically, and if possible, they were extracted from figures using Webplot Digitizer.

Quality assessment / Risk of bias analysis Risk of bias in the included trials will be assessed using Cochrane risk of bias tool.

Strategy of data synthesis Treatment effect (efficacy) will be defined as the difference in mean BP change from baseline between treatment and placebo. Fixed-effects meta-analyses will be conducted to obtain the summary estimates of treatment effect baseline to follow-up weeks 1 through 8. For modeling expected BP-lowering efficacy over time (time course efficacy), several parametric dose-response models, including quadratic, power, splines, exponential association, and saturation growth rate models, will be iteratively fitted to the meta-estimates for each follow-up week. . The optimal smoothing parameter will be selected based on the highest R-square value. Scatter plots of mean BP with 95% confidence intervals for each trial group across follow-up weeks will be provided in the appendix.
Separate fixed-effect meta-analyses will be performed to determine the summary treatment effect from baseline to weeks 2 and 4, and from baseline to weeks 4 and 8. Additional BP reductions from weeks 2 to 4 and from weeks 4 to 8 will be calculated. Percentage change of treatment effect from baseline will be presented using box-whisker plots and descriptive statistics by drug class. Subgroup analyses will assess effects by drug class, baseline mean systolic and diastolic BP strata, and type of therapy (mono or combination).
For trials contributing more than one active vs. placebo comparison, the placebo group sample size will be split equally among the comparators, following the Cochrane Handbook guidelines. Heterogeneity will be tested using Q statistics, and the extent of heterogeneity will be quantified using the I^2 statistic.

Subgroup analysis Subgroup analyses will be conducted to assess effect by class of drugs, baseline mean SBP (160 mmHg) and DBP strata and type of therapy (mono or combination).

Sensitivity analysis Sensitivity analyses may be conducted excluding studies with outlier BP data, and trials with high risk of bias.

Language restriction Only trials published in English language were included.

Country(ies) involved Australia and India.

Other relevant information None

Keywords Anti-hypertensive agents, diastolic blood pressure, systolic blood pressure, pharmacological therapy, systematic review.

Dissemination plans We will publish the findings leading journal in this field, present them a scientific conference. We will also share our findings with guideline writing committee.

Contributions of each author

Author 1 - Abdul Salam - conceived and designed the study.
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