INPLASY

Sex-specific differences in the effects of blood pressure lowering treatment. A systematic review and meta-analysis of randomized, double-blind 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 - George Health Enterprises, the social enterprise arm of The George Institute for Global Health, has received investment to develop fixed-dose combination products containing aspirin, statin and blood pressure (BP) lowering drugs. George Health Enterprises has submitted patents for low-dose blood pressure combinations, on which Professor Rodgers is listed as one of the inventors. Professor Rodgers is seconded part-time to George Medicines Pty Ltd (GM). All staff employed by TGI have an institutional interest to declare with respect to George Health Enterprises. None of the TGI staff have a direct financial interest in these investments.

INPLASY registration number: INPLASY2024110077

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 November 2024 and was last updated on 18 November 2024.

INTRODUCTION

Review question / Objective The aim of this systematic review and meta-analysis is to evaluate the blood pressure lowering effects of antihypertensive drugs among men compared to women.

Rationale Women have long been underrepresented in medical research, which has led to major uncertainties about the sex-specific effects of cardiovascular drugs. Clinical guidelines do not provide sex-specific treatment recommendations for both the primary and secondary prevention of cardiovascular disease (CVD). In clinical practice, however, women and men often receive different treatments. Whilst women are less likely than men to receive statin therapy, men are less likely to receive BP-lowering drugs. Of the BP-lowering drugs classes, women are more likely to receive diuretics whereas men are more likely to be receive beta-blockers. Randomised trials are the gold-standard for studying the efficacy and safety of medical interventions. Yet, they are underpowered to evaluate sex-specific effects. Meta-analyses of trials, however, can help evaluate sex-specific effects.

Condition being studied Hypertension.

METHODS

Search strategy Electronic databases includingMEDLINE , The Cochrane Central Register of Controlled Trials Library, and Epistemonikos. Additionally, bibliographies of systematic reviews, Regulatory agency (FDA) website.

Participant or population Participants, both male and female, who are on BP-lowering drug treatment and are aged 18 years or older.

Intervention BP-lowering drug (s) from the following five major classes: angiotensin-converting enzyme inhibitors (ACEs), angiotensin II receptor blockers (ARBs), beta-blockers (BBs), Calcium channel blockers (CCBs), diuretics, and their combinations administered orally at fixed doses for a minimum of 2 weeks.

Comparator Placebo or five major BP-lowering drug class(es) (ACEs, ARBs, CCBs, BBs, and diuretics).

Study designs to be included Randomized double-blind trials.

Eligibility criteria Inclusion criteria: Participants: both male and female, who are on BP-lowering drugs and are aged 18 years or older. Intervention: oral fixed dose of BP-lowering drug(s) as either monotherapy or combination therapy from five major classes (ACEs, ARBs, CCBs, BBs, and diuretics). Comparator: placebo or other BP-lowering drug classes (ACEs, ARBs, CCBs, BBs, and diuretics). Outcomes: change in blood pressure (BP) from the baseline or BP control should be reported separately for both sexes. Study Design type: randomized double-blind controlled trials. Other: Non-differential concomitant therapy between the groups. Same BP measurement position, device type, and BP-lowering 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 are 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 were excluded:
1. Optional titration of BP-lowering drugs such that different participants within a treatment group receive different drugs/doses.
Trials with following outcomes are excluded:
1. Trials not reported BP outcome data separately for each sex.
2. Outcome measurement immediately after exercise, altitude induced and cold induced BP.
3. No outcome data for fixed dose treatment periods.
Trials with following study design are excluded
1. Cluster/step-wedge randomised controlled trials.
2. Subgroup analyses, post-hoc analyses, interim reports of RCTs.
Trials published in non-English language were also excluded.

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

Main outcome(s) Main/primary outcome was difference in change in blood pressure from baseline to follow-up.

Additional outcome(s) Additional outcome was BP control rate.

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 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). For each group, mean change from baseline, and standard deviation of change, for systolic and diastolic blood pressure at an interval of at least 2 weeks was extracted up to a maximum of twenty-six weeks. Two reviewers independently collected data from the each included trial. Disagreements in the collected data between the reviewers were resolved by discussion between the reviewers or by adjudication by a senior reviewer. If BP data was not reported numerically, and if possible, they were extracted from figures using Webplot Digitizer.

Quality assessment / Risk of bias analysis Two reviewers independently evaluated the methodological quality of each study included in the meta-analysis using the Cochrane Collaboration tool for assessing risk of bias (Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0). The assessment covered the following domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other sources of bias. For each domain, the risk of bias was scored as a low, unclear, and high risk.

Strategy of data synthesis Separate meta-analyses will be conducted for men and women to assess the impact of BP-lowering drug therapy on blood pressure outcomes. Mean differences with 95% confidence intervals will be used to present data regarding the change in systolic and diastolic blood pressure, while summary relative risks with 95% confidence intervals will be used to present data on blood pressure control rate. The I2 test will be used to measure between-study heterogeneity, with a significance threshold set at $p<0.10$. Pooled analyses will be conducted using the random effects (DerSimonian–Laird) model, regardless of the underlying heterogeneity across studies.
Sources of heterogeneity will also be explored by sensitivity and subgroup analyses, stratifying studies by various factors, including follow-up duration, age (eg, younger vs older women, younger vs older men, younger women vs younger men, older women vs older men), ethnicity/race, class of BP-lowering drug therapy and treatment dosage.
All statistical analyses for meta-analysis will be performed using STATA MP 16.1 software (StataCorp LLC, College Station, TX, USA).

Subgroup analysis Subgroup analyses based on follow-up duration, sample size, age, and percentage of males did not affect the change in diastolic blood pressure between males and female.

Sensitivity analysis Not Performed.

Language restriction Only trials published in English language are included.

Country(ies) involved Australia, India and UK.

Keywords BP-lowering drug, diastolic blood pressure, systolic blood pressure, pharmacological therapy, Randomized controlled trials, systematic review, meta-analysis.

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