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Safety of antihypertensive drugs – a network meta-analysis of double blind randomized clinical 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 - Authors Anthony Rodgers, Abdul Salam, are employed at The George Institute for Global Health (TGI), which holds an interest in GMRx2 via its ownership of George Health Enterprises. None of the TGI staff have a personal financial interest in GMRx2. Anthony Rodgers is seconded part-time to George Medicines of George Health Enterprises. TGI holds patents for ultra-low-dose fixed-dose combination products for the treatment of hypertension and diabetes, and Anthony Rodgers is listed as one of the inventors (US 10,369,15; US 10,799,487; US 10,322,117; US 11,033,544). None of the Geroge Institute for Global Health employees have any financial interest in these patents.

INPLASY registration number: INPLASY202540102

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 April 2025 and was last updated on 28 April 2025.

INTRODUCTION

Review question / Objective To quantify the safety of antihypertensive drugs from the five major classes and their combinations.

Condition being studied High blood pressure, hypertension.

METHODS

Participant or population 1. Adults (age ≥18 years or as defined by the included trial)
Exclusion:
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 (e.g., hyperthyroidism and gigantism) except diabetes
7. Pregnancy, pre-eclampsia
8. Portal hypertension, pulmonary hypertension
9. Benign prostatic hyperplasia
10. Raynaud's disease.

Intervention BP-lowering drug(s) from five major classes (ACEIs, ARBs, BBs, CCBs, diuretics) that have WHO's daily defined dose or regulatory

approved strength, taken orally in fixed dose, for 2-26 weeks.

Comparator Placebo or BP lowering drug(s) from another major antihypertensive class (ACEIs, ARBs, BBs, CCBs, diuretics).

Study designs to be included Randomised double-blind trials.

Eligibility criteria Additional inclusion
1) double-blind randomized clinical trials; 2) adult participants (age ≥18 years), with or without hypertension; 3) randomization to antihypertensive drug(s) from one or more of the five major classes (ACEIs, ARBs, BBs, CCBs, and diuretics); 4) treatment and follow-up duration between 4-26 weeks; 5) reported adverse events and/or treatment discontinuation/withdrawals due to adverse events.
Additional exclusion
1. Trials with an active run-in period were excluded because these trials enrolled participants who have already demonstrated tolerance to the intervention.
2. Concomitant differential treatment between randomised trial groups with drugs other than those from the five major classes or with non-pharmacological therapy.
3. Outcome measurement immediately after exercise, altitude induced and cold induced BP.
4. No outcome data for fixed dose treatment periods.
5. Trials with no explicit mention of randomisation.
6. Cluster/step-wedge randomised trials.
7. Subgroup analyses, post-hoc analyses, interim reports of randomised trials.
8. Trials reported in non-English language.

Information sources Cochrane Central Register of Controlled Trials and regulatory submission packages on FDA website (until December 2022) for trials. MEDLINE and Epistimonikos for systematic reviews from which trials were identified. An updated systematic literature search will also be conducted.

Main outcome(s) The primary outcome is withdrawals due to adverse events (WDAEs), defined as an adverse event that led to the discontinuation of randomized treatment. Secondary outcomes included any adverse events, treatment-related adverse events (TRAEs), serious adverse events (SAEs), hypotension, dizziness, headache, cough and edema. TRAE was defined as an event that was definitely, probably, or possibly related to the randomized treatment. SAEs were as defined in the included trials.

Quality assessment / Risk of bias analysis Risk of bias will be assessed using Cochrane Risk of Bias Tool.

Strategy of data synthesis Odds ratios and their 95% CIs will be pooled using random effects models with inverse variance weighting. Heterogeneity between studies will be assessed using the I2 test with >50% considered as substantial heterogeneity. Analyses will be conducted according to drug class: angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers (BBs), calcium channel blockers (CCBs) and diuretics. Further analyses will be conducted according to subclasses of CCBs - dihydropyridine and non-dihydropyridine CCBs; and subclasses of diuretics - thiazide/thiazide-like, mineralocorticoid receptor antagonists or other diuretics.

Subgroup analysis Prespecified subgroup analyses will be performed according to the following dose categories: low dose, standard dose or high dose. For monotherapy, low, standard and high doses is defined as less than one standard, one standard or more than one standard dose. For dual combination therapy, low, standard and high doses is defined as both drugs being at less than one standard dose, one standard or more than one standard dose, respectively. We will also conduct drug-class specific meta-regressions with WDAE as the dependent variable, and drug dose and baseline BP as covariates (Supplemental Appendix). Separate meta-regressions will also be constructed for any AE as the dependent variable, and drug dose and baseline BP as covariates. We will exclude pairwise meta-analyses for drug classes with <5 total events.

Network meta-analysis (NMA) will be undertaken to inform drug class level rankings for odds of WDAE. We will undergo a multilevel NMA based on all available aggregate data using a multilevel Bayesian NMA using the multinma R package.17 Non-informative prior distributions will be used in all models. We will use both fixed and random effects models to data aggregated at the class level to initially assess heterogeneity by comparing deviance information criterion and then select most appropriate model in subsequent steps.
Separate NMA will be performed restricted to monotherapies to better compare to results from the placebo-controlled pairwise meta-analyses.
Relative effects will be presented showing an estimate and 95% credible intervals for the effect for each treatment and class compared with placebo. Class level ranks, rank probabilities, and Surface Under the Cumulative Ranking curve

(SUCRA) will be presented. All analyses will be performed with Stata version 18.1 and R version 4.1.2.

Sensitivity analysis Sensitivity analyses will be performed after exclusion of trials assessed to be at high risk of bias.

Language restriction English only.

Country(ies) involved India, Australia.

Keywords Blood pressure lowering drugs, antihypertensive drugs, efficacy, safety, meta-analysis.

Contributions of each author

Author 1 - Anthony Rodgers - Conception, design, conduct, analysis, interpretation, and reporting.
Author 2 - Abdul Salam - Conception, design, conduct, analysis, interpretation, and reporting.
Author 3 - Stephen Van Der Hoorn - Conception, design, conduct, analysis, interpretation, and reporting.
Author 4 - Nelson Wang - Conception, design, conduct, analysis, interpretation, and reporting.