INPLASY

INPLASY202410036

doi: 10.37766/inplasy2024.1.0036

Received: 09 January 2024

Published: 09 January 2024

Corresponding author:
Anthony Rodgers

arodgers@georgeinstitute.org

Author Affiliation:
The George Institute for Global Health, University of New South Wales.

Blood pressure-lowering efficacy of antihypertensive drugs and their combinations: systematic review and meta-analysis of double-blind placebo controlled randomised trials

Rodgers, A[1]; Salam, A[2]; Pant, R[3]; Wang, N[4]; Kota, V[5]; Dhurjati, R[6].

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). Anthony Rodgers does not have a financial interest in these patents.

INPLASY registration number: INPLASY202410036

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 09 January 2024 and was last updated on 09 January 2024.

INTRODUCTION

Review question / Objective To quantify and compare the dose-wise blood pressure (BP)-lowering efficacy of drugs from the five major classes of antihypertensive drugs.

Rationale When treating high blood pressure, each 1 mmHg additional reduction in systolic BP (SBP) confers a 2% reduction in cardiovascular disease. Antihypertensive regimens that differ in efficacy by a few mmHg difference are therefore clinically important. Reliable estimates of average BP lowering efficacy for any treatment regimen are therefore needed.

Condition being studied High blood pressure, hypertension.

METHODS

Search strategy A systematic literature search was performed in multiple electronic databases: MEDLINE (from 1946 to September Week 1 2017), The Cochrane Central Register of Controlled Trials Library (from inception to October 2018), and Epistemonikos (inception to September Week 3 2017) for identifying relevant RCTs. Full search strategy is reported below. Additionally, bibliographies of systematic reviews, Regulatory

agency (FDA) website, were searched to find relevant trials.
Search terms will include: meta-analysis, antihypertensive drugs, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, diuretics and beta-blockers. Specific search strategies will be attached in separate documents.
#
Searches
1
exp meta-analysis/
2
meta-analy$.tw.
3
metaanaly$.tw.
4
exp Meta-Analysis as Topic/
5
exp Network Meta-Analysis/
6
(systemat$ adj2 review).tw.
7
pooled analy$.tw.
8
individual pa$ data.tw.
9
(individual pa$ data adj3 level).tw.
10
IPD.tw.
11
or/1-10
12
exp Antihypertensive Drugs/
13
exp Angiotensin-Converting Enzyme Inhibitors/
14
((angiotensin$ or dipeptidyl$ or kininase) adj3 (convert$ or enzyme or inhibit$ or recept$ or block$)).tw.
15
exp Angiotensin Receptor Antagonists/
16
(angiotensin adj3 (receptor antagon$ or receptor block$)).tw.
17
exp Adrenergic beta-Antagonists/
18
(beta adj2 (adrenergic? or antagonist? or block$ or receptor?)).tw.
19
exp Calcium Channel Blockers/
20
(calcium adj2 (antagonist? or block$ or inhibit$)).tw.
21
exp Thiazides/
22
exp Sodium Chloride Symporter Inhibitors/
23
(sodium chloride adj (symporter? or cotransporter? or cotransporter?)).tw.
24
(potassium depleting adj2 diuretic?).tw.
25
((loop or ceiling) adj diuretic?).tw.
26
exp sodium potassium chloride symporter inhibitors/
27
(sodium potassium chloride adj2 (cotransporter? or cotransporter? or symporter?)).tw.
28
exp Mineralocorticoid Receptor Antagonists/
29
((K or potassium) adj sparing adj diuretic$).tw.
30
exp adrenergic alpha antagonists/
31
(adrenergic adj2 (alpha or antagonist?)).tw.
32
((adrenergic or alpha or receptor?) adj2 block$).tw.
33
(renin inhibi$ or renin blocker).tw.
34
(Centra$ adj2 antihypertensive$).tw.
35
or/12-34
36
11 and 35
37
limit 36 to humans.

Participant or population Inclusion: 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.

Study designs to be included Randomised double-blind trials.

Eligibility criteria Additional inclusion: 1. Trials reporting data for assessing change in SBP or DBP. Additional exclusion: 1. Concomitant differential treatment between randomised trial groups with drugs other than those from the five major classes or with non-pharmacological therapy. 2. Conditional or optional titration of antihypertensive drugs such that different participants within a treatment group receive different drug(s)/dose(s). 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 [until December 2022] for systematic reviews from which trials were identified.

Main outcome(s) The primary outcome is the difference in mean change from baseline in systolic (SBP) and/or diastolic BP (DBP) between active and placebo for the maximum available follow-up week (≥4 weeks). Treatment efficacy is calculated as: treatment efficacy = [(mean change in BP from baseline in active group) – (mean change in BP from baseline in placebo group]. If the BP data is not available at baseline or follow-up, we will use the trials reported change from baseline or difference between the groups or difference in follow up BP.

Quality assessment / Risk of bias analysis Given the large number of studies to be included (>600), inadequate reporting of information in many old trials, conducting a traditional risk of bias assessment would be impractical and unreliable. We will instead exclude, in sensitivity analyses, studies with potentially high risk of bias based on imbalance in baseline BP, significant loss to follow up, and those reporting only SBP or DBP data and not both.

Strategy of data synthesis Fixed-effects meta regression will be done, separately for each drug class and for SBP and DBP, to 1) determine drug and dose response relationship and 2) to determine the effect of baseline BP on treatment efficacy. Variables included in the model will be: treatment efficacy as outcome and, baseline BP, log proportional standard dose of drug, mean age, sex and comorbidities (Hypertension, diabetes mellitus, chronic kidney disease, respiratory disease). Final models will include those co-variates that significantly improve model performance.

Strategy for calculating the treatment effect adjusted for baseline BP: We will adjust the BP lowering treatment effect for each comparison to the sample size weighted baseline mean BP of the active and placebo group across all trials. These baseline adjusted treatment effects will then be used for all subsequent analyses in this study.

Meta-analysis: A fixed-effects meta-analysis using the inverse-variance weighting will be conducted to estimate the placebo-controlled treatment efficacy for SBP and DBP at an individual drug and drug class level. Treatment effects will be reported as mean difference in change from baseline and 95% CIs.

These standardised BP treatment effects are also used to calculate linear-log regression dose response estimates, estimating the increase in placebo-corrected BP reduction for each doubling of dose from quarter of the standard dose, for each drug and drug class, for SBP and DBP. Mixed methods models will be used to assess differences in dose-response parameters (intercept and slope of the regressions) across drugs belonging to same class i.e., how much of the variation in treatment effect can be attributed to class and how much to individual drug differences.

To test whether the efficacy of BP-lowering drugs are additive, we will compare the observed BP reduction from placebo-controlled trials of combination therapies to the expected BP reduction from derived meta-regression equations.

We will conduct further subgroup analyses by separating out the diuretics drug class into three further groups: 1) mineralocorticoid receptor antagonists, 2) thiazide or thiazide-like diuretics and 3) other diuretics. We also will separate the calcium channel blocker class into the dihydropyridine and non-dihydropyridine calcium channel blockers.

Subgroup analysis Separate subgroup analyses will be performed by drug class, and for monotherapies versus combination therapies.

For each drug class analysis, we will perform subgroup analyses by separating out the diuretics

drug class into three groups: 1) mineralocorticoid receptor antagonists, 2) thiazide and thiazide-like diuretics and 3) other diuretics; and separating calcium channel blockers into dihydropyridine and non-dihydropyridine calcium channel blockers. Sensitivity analyses will include exclusion of comparisons with, 1) baseline imbalance in BP (>5 mmHg for SBP); 2) antihypertensive drug(s) which did not have a washout period and 3) less than 8 weeks of fixed drug(s) and dose(s).

Sensitivity analysis Sensitivity analyses will be performed, where possible, after exclusion of comparisons with, 1) baseline imbalance in BP (>5 mmHg for SBP); 2) antihypertensive drug(s) for at least 2 weeks before randomization and did not have a washout period; 3) less than 8 weeks of a fixed drugs and dose in case there is any further treatment effect after 4 weeks;4) loss to follow up of >10% of the participants in one of the two groups of the comparison; 5) and comparisons with data only on either SBP or DBP and not both.

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. Conduct, analysis, interpretation, and reporting.
Email: arodgers@georgeinstitute.org
Author 2 - Abdul Salam - Conception, design, conduct, analysis, interpretation, and reporting. Conduct, analysis, interpretation, and reporting.
Email: asalam@georgeinstitute.org.in
Author 3 - Rashmi Pant - Conduct, analysis, interpretation, and reporting.
Email: rpant@georgeinstitute.org.in
Author 4 - Nelson Wang - Conduct, analysis, interpretation, and reporting.
Email: nwang@georgeinstitute.org.au
Author 5 - Vidyasagar Kota - Conduct, analysis, interpretation, and reporting.
Email: vkota@georgeinstitute.org.in
Author 6 - Rupasvi Dhurjati - Conduct, analysis, interpretation, and reporting.