INPLASY

Effects of blood pressure lowering drugs on major cardiovascular events in short-term randomised, doubled-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 - 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 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: INPLASY202410049

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 January 2024 and was last updated on 12 January 2024.

INTRODUCTION

Review question / Objective To assess, among adults with hypertension, the effects of Antihypertensive drugs compared to placebo on major adverse cardiovascular events (MACE) in short-term randomised trials.

Rationale High blood pressure (BP) is the leading reversible cause of mortality in the world, affecting more than 1 billion people globally. There is clear evidence that BP lowering is associated with long term cardiovascular impacts, with every 10 mmHg reduction in systolic BP associated with a reduction in major cardiovascular events by 20%, stroke by 27%, heart failure by 27%, and all-cause mortality by 13%. Short randomised controlled placebo control trials are required for regulatory approval to assess the efficacy and safety of new therapeutic regimens compared to placebo. Whether there are adverse effects on cardiovascular outcomes or safety endpoints in short to medium term placebo-controlled trials is poorly understood. A descriptive meta-analysis by DeFelice et al 2008 demonstrated no difference in cardiovascular events between the intervention and placebo groups at short term follow-up (4-8 weeks), but the analysis was limited by only a small number of cardiovascular events, analysis limited to very short-term follow-up and more trials have been performed in the fifteen years since

publication. This meta-analysis aims to assess, among adults with hypertension, the effects of blood pressure (BP) lowering drugs compared to placebo on major adverse cardiovascular events (MACE) in randomised trials at short- to medium term (4 to 26 week) follow up). There remains uncertainty about the short-term effects on blood pressure lowering drugs on cardiovascular events.

Condition being studied Hypertension is a leading risk factor for cardiovascular disease and death. Antihypertensive drugs reduce blood pressure (BP), prevent cardiovascular disease events and mortality.

METHODS

Search strategy 1 exp Angiotensin-Converting Enzyme Inhibitors/
2 (alacepril or altiopril or ancovenin or benazepril or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril or epicaptopril or fasidotril or fosinopril or foroxymithine or gemopatrilat or idapril or imidapril or lisinopril or moexipril or moveltipril or omapatrilat or pentopril$ or perindopril$ or pivopril or quinapril$ or ramipril$ or rentiapril or saralasin or s nitrosocaptopril or spirapril$ or temocapril$ or teprotide or trandolapril$ or utibapril$ or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril or Enalaprilat).tw.
3 exp Angiotensin Receptor Antagonists/
4 (abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or KT3-671 or losartan or milfasartan or olmesartan or saprisartan or tasosartan or telmisartan or valsartan or zolasartan).tw.
5 exp calcium channel blockers/
6 (amlodipine or aranidipine or barnidipine or bencyclane or benidipine or bepridil or cilnidipine or cinnarizine or clentiazem or darodipine or diltiazem or efonidipine or elgodipine or etafenone or fantofarone or felodipine or lercanidipine or lidoflazine or lomerizine or manidipine or mibefradil or nicardipine or nifedipine or niguldipine or nilvadipine or nimodipine or nisoldipine or nitrendipine or terodiline or tiapamil or verapamil or Cardizem CD or Dilacor XR or Tiazac or Cardizem Calan or Isoptin or Calan SR or Isoptin SR Coer or Covera HS or Verelan PM or azelnidipine or clevidipine).tw.
7 (aliskiren or ciprokiren or ditekiren or enalkiren or remikiren or rasilez or tekturna or terlakiren or zankiren or ketanserin).tw.
8 (methyldopa or alphamethyldopa or amodopa or dopamet or dopegyt or dopegit or dopegite or emdopa or hyperpax or hyperpaxa or methylpropionic acid or dopergit or meldopa or methyldopate or medopa or medomet or sembrina or aldomet or aldometil or aldomin or hydopa or methyldihydroxyphenylalanine or methyl dopa or mulfasin or presinol or presolisin or dihydroxyphenylalanine or methylphenylalanine or methylalanine or alpha methyl dopa or guanfacine or guanabenz or guanadrel or guanethidine or debrisoquine or betanidine or guanoxan or guanoclor or guanazodine or guanoxabenz).tw.
9 (reserpine or serpentina or rauwolfia or serpasil).tw.
10 (clonidine or adesipress or arkamin or caprysin or catapres$ or catasan or chlofazolin or chlophazolin or clinidine or clofelin$ or clofenil or clomidine or clondine or clonistada or clonnirit or clophelin$ or dichlorophenylaminoimidazoline or dixarit or duraclon or gemiton or haemiton or hemiton or imidazoline or isoglaucon or klofelin or klofenil or m-5041t or normopresan or paracefan or st-155 or st 155 or moxonidine or rilmenidine or rescinnamine or deserpidine or methoserpidine or bietaserpine or azamethonium or mecamylamine).tw.
11 exp hydralazine/
12 (dihydralazine or hydralazin$ or hydrallazin$ or hydralizine or hydrazinophtalazine or hydrazinophthalazine or hydrazinophtalizine or dralzine or hydralacin or hydrolazine or hypophthalin or hypoftalin or hydrazinophthalazine or idralazina or 1-hydrazinophthalazine or apressin or nepresol or apressoline or apresoline or apresolin or alphapress or alazine or idralazina or lopress or plethorit or praeparat hydralazine or diazoxide or minoxidil or nitroprusside sodium or todralazine or tolazoline or endralazine or cadralazine or pinacidil).tw.
13 exp adrenergic beta-antagonists/
14 (acebutolol or adimolol or afurolol or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or flestolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iprocrolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthiopropranolol or metipranolol or metoprolol or moprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol

or nebivolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or primidolol or prizidilol or procinolol or pronetalol or propranolol or proxodolol or ridazolol or salcardolol or soquinolol or sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol or esatenolol).tw.
15 exp adrenergic alpha antagonists/
16 (alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin or Indoramin or phenoxybenzamine or phentolamine or tolazoline or urapidil).tw.
17 exp thiazides/
18 exp sodium potassium chloride symporter inhibitors/
19 (amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or thiazide?).tw.
20 (chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamideor altizide or bemetizide or benzthiazide or benzylhydrochlorothiazide or butizide or clopamide or epitizide or hydrochlorothiazide or hydroflumethiazide or mefruside or meticrane or metipamide or teclothiazide or tripamide or xipamide or quinethazone).tw.
21 (azosemide or furosemide or frusemide or fursemide indacrinone or ozolinone or phenoxybenzoic acid or muzolimine or bumetanide or burinex or cicletanine or etozolonie or torsemide or ethacrynic acid or veratide or piretanide or ticrynafen or tienilic acid or tizolemid).tw.
22 exp Mineralocorticoid Receptor Antagonists/
23 (amiloride or triamterene or canrenoate potassium or canrenone$ or spironolactone$ or aldosterone antagonist$ or aldactone$ or practon$ or sc-9420$ or spiractin$ or sc-14266$ or soldactone$ or soludactone$ or aldadiene$ or phanurane$ or sc-9376 or eplerenone$).tw.
24 exp BP-lowering agents/
25 or/1-24
26 randomized controlled trial.pt.
27 random$.tw.
28 (placebo or ?blind or parallel or cross?over or trial).tw.
29 or/26-28
30 (abstract or conference or meeting or proceedings or protocol or cluster or letter or comment or editorial or opinion or commentary or process evaluation or non-comparative or single-group or cochrane).ti.
31 (abstract or conference or letter or comment or editorial or or commentary).pt.
32 (conference or abstract or meeting or scientific).vo.
33 (mice or rabbit$ or rats or dogs).ti.
34 or/30-33
35 25 and 29
36 35 not 34
37 limit 36 to english language.

Participant or population Inclusion: 1. Adults (age ≥18 years or as defined by the included trials). 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 (FDA, MHRA or EU country) approved strength, taken orally for 2-26 weeks.

Comparator Placebo, taken orally for 2-26 weeks.

Study designs to be included Randomised double-blind trials.

Eligibility criteria Additional inclusion: 1. Trials reporting data for one of more MACE (as defined in the outcomes section). 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 (until October 2018) for trials. MEDLINE and Epistimonikos [until September 2017] for systematic reviews from which trials were identified.

Main outcome(s) The primary outcome is major adverse cardiovascular events (MACE), defined as a composite of mortality, myocardial infarction; angina; revascularisation (percutaneous coronary intervention; coronary stenting or coronary artery bypass grafting); congestive cardiac failure hospitalisation; stroke (ischaemic or haemorrhagic) at the maximum available follow-up (minimum of 4 weeks).

Additional outcome(s) Secondary outcomes are all-cause mortality, cardiovascular mortality, individual events of MACE, association between magnitude of systolic blood pressure (BP) reduction and MACE, and association between duration of follow-up and MACE.

Data management DistillerSR (Version 2.35. DistillerSR Inc. 2022) was used to collect data in duplicate, independently, in standard piloted data collection forms. Data was collected on characteristics of the trial participants, interventions and outcomes. For cardiovascular events and mortality, data was collected for incidence (number of participants with ≥1 event). Incidence was recorded as zero if it was reported as such or if it was reported that there were no serious adverse events or adverse events reported during the trial. Comparisons with zero in both the groups were not included in the meta-analyses. For comparisons with zero in one of the groups zero cell correction approach was used.

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 Intent-to-treat approach will be adopted where the number of participants randomised was used, if this data is not available, number completed the trial or included in the analysis will be used. Pair-wise meta-analyses were performed using Mantel-Haenszel fixed effect model for estimating summary relative risk (RR) and its 95% confidence intervals. For studying association between BP reduction and MACE, we will assess effect sizes for per mmHg difference between active and placebo. We will standardise the analysis to a 5 (or 10) mmHg reduction in SBP to enable comparisons of the proportional effects of reducing SBP. The log of the RR of each trial will be multiplied by 1/d, where d was the mean SBP reduction in mmHg in that trial. Meta-regression analyses will be done with the following covariates: follow-up duration of the trial and baseline SBP. A two-tailed p-value of 5% will be used for hypothesis testing, with a p-value of ≤0.05 used to determine statistical significance). Heterogeneity across the included trials that is true heterogeneity and not due to sampling error (chance) will be quantified by I2 statistic. I2 values will be interpreted as unimportant (0% to 40%), moderate (30% to 60%), substantial (50% to 90%), and considerable (75% to 100%) heterogeneity.

Subgroup analysis Subgroup analyses will be performed according to class of antihypertensive medications, magnitude of blood pressure effect and trial duration.

Sensitivity analysis Sub-group interactions will be tested using Cochran's Q statistic, and $\chi 2$ test will be used to test tend in analyses. Sensitivity analyses will be performed, excluding studies with inferred zero events and using random-effects model.

Language restriction English only.

Country(ies) involved India, Australia.

Keywords Meta-analysis; blood pressure lowering drugs; antihypertensive drugs; cardiovascular events; mortality; heart attack; heart failure hospitalisation; stroke; revascularisation.

Contributions of each author

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