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Original Research Paper

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TREATMENT EFFICACY OF ANTI-HYPERTENSIVE DRUGS IN MONOTHERAPY OR COMBINATION ON LONG TERM BLOOD PRESSURE: META-ANALYSIS OF RANDOMISED CLINICAL TRIALS

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ABSTRACT

Aim: Evidence from randomized trials of anti-hypertensive drugs in monotherapy or combination on long-term blood pressure (BP) reduction is limited. We investigated the antihypertensive drug effects on BP over time and across different participant characteristics. **Methodology:** We conducted an individual patient-level data meta-analysis of a few large-scale randomized clinical trials in the Blood Pressure Lowering Treatment Trials using mixed models to examine treatment effects on long-term blood pressure. Information sources and searches were conducted in Embase, Medline, CENTRAL, and the Science Citation Index databases. **Results:** Among all participants, with a baseline mean age of 54.5 years and mean systolic/ diastolic BP of 155/99 mm Hg, who were current smokers, had cardiovascular disease and diabetes and were taking antihypertensive treatment at baseline. Drugs were effective in lowering BP, showing maximal effect after 12 months and gradually attenuating towards later years. Based on measures taken ≥12 months post-randomization, mean systolic/diastolic BP difference (95% CI) between more and less intense long-term BP-lowering. BP reductions were observed across different baseline BP values and ages, and by sex, history of cardiovascular disease and diabetes and prior antihypertensive treatment used. **Conclusion:** These findings suggest that long-term BP-lowering anti-hypertensive drugs in monotherapy or combination is effective in lowering BP in people with different characteristics. Appropriate treatment strategies are needed to sustain substantive long-term BP reductions.

KEYWORDS : Antihypertensive Drugs, Hypertension, Meta-analysis

INTRODUCTION

Clinical guidelines for the management of hypertension have invariably lowered the recommended blood pressure (BP) targets for patients at high risk of cardiovascular disease, well-versed by evidence from large-scale randomized clinical trials (RCTs) and their meta-analyses showing substantial reductions in cardiovascular risk with more intensive BP-lowering treatment and independently of baseline BP values.[1-3] Selection of antihypertensive drugs should be based on the knowledge of the drug's ability to reduce blood pressure (BP) levels, which is the main target factor to avoid cardiovascular complications in these patients.[4] Thus, the different treatments have been validated by means of studies showing their antihypertensive efficacy.

For the majority of hypertensive patients, the lower BP targets predictably lead to a larger gap between their usual BP and the recommended target value, requiring more aggressive pharmacological treatment. Attributing changes to treatment based on repeated measures of the BP of an individual patient can be unreliable since measurements are subject to random fluctuations, regression to the mean, non-pharmacological effects and other sources of variability that can exceed true variability in treatment response.[5-7]

To date, randomized evidence on the effect of antihy pertensive drugs on BP has come from efficacy trials with small numbers of highly selected participants and short follow-up durations.[8]

However, most of these trials have been performed comparing just 2 agents, 2 combinations, or 2 treatment strategies, and they are considerably heterogeneous, with noncomparable study populations with respect to age, sex, and ethnic group, baseline BP or dose.

Pooled evidence from RCTs using information from individual participants' repeated BP measurements currently does not exist, which might explain why there is no guidance on the expected magnitudes of BP reduction with the various proposed treatment strategies and whether these reductions are expected to vary among people with different characteristics.

We addressed this evidence gap by using information from randomized trials involving many participants with individual-level data on repeated BP measurements over several years to conduct a meta-analysis to quantify the unconfounded effects of BP-lowering drugs on BP over time and examine these effects across different subgroups. Therefore, the comparison of the relative antihypertensive effect of several drugs, or that of the most common combinations, is not well known. Moreover, the results obtained with their use, as well as the variables associated with treatment response, differ. Although some meta-analyses have been published,[8,9] their ability to determine significant clinical differences among drugs was questioned since they were restricted to certain pharmacological drugs, and no analyses of combinations were performed, or they were performed as simple meta-analyses (i.e., adjusting for specific variables); all of which, made it difficult to generalize the results. Hypertension (HTN) guidelines recommend antihypertensive drug classes without detailing specific drugs. As not all drugs from the same class have the same antihypertensive potency, their selection could potentially affect the probability of achieving BP control. Considering the explanations, it would be of most importance to know the antihypertensive effect of the most frequently used drugs, adjusted according to the most relevant clinical variables, as well as the characteristics related to better or worse treatment response. This knowledge would potentially help the clinician to choose the most adequate treatment, since the response to a specific drug could be better predicted.

METHODS

A systematic search for clinical trials assessing the efficacy of

antihypertensive drugs was conducted. The initial selection of the studies obtained by the syntax search in the literature databases was assessed by reading the title or the abstract, when doubting the subject of the paper. In this first part, we selected those trials, which could be included, and then we obtained the original papers to be reviewed. We conducted an individual patient-level data meta-analysis of few large-scale randomized clinical trials in the blood pressure lowering treatment trials using mixed models to examine treatment effects on long-term blood pressure.

Information sources and searches were conducted in Embase, Medline, CENTRAL, and the Science Citation Index databases according to the following syntax: "drug's generic name" AND "hypertension" OR "blood pressure" AND "efficacy" with "randomized clinical trials." Randomized clinical trials were eligible for inclusion if there was randomization of patients between a BP-lowering agent and a placebo arm or inactive control, between various BP-lowering intensities or between various BP-¬lowering drugs. This meta-analysis was performed in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE). We used R (V.3.4.4) 24 to analyze the data.

RESULTS

Several randomized clinical trials were searched from PubMed, Embase, Medline, CENTRAL, and the Science Citation Index databases. For each study, the following data were gathered: reference, study, age, baseline SBP and DBP (mean), an antihypertensive drug, and dose. The patients characteristics are shown in Table 1.

Table – 1 Baseline Characteristics Of Total Patients Included

Characteristics	Average value
Age, y	54.5
Sex: women	45
CVD	82
Coronary heart disease	55
Stroke	37
Diabetes	60
CKD	42
SBP, mm Hg	155
DBP, mm Hg	99

Amongst all participants, with baseline mean age=54.5 years and mean systolic/ diastolic BP=155/99mm Hg, who were current smokers, had cardiovascular disease, and diabetes and were taking antihypertensive treatment at baseline.

The decreases in BP were overall similar among the different cardiac risk factors. There is an average reduction of 11.4 mm Hg in SBP and 5.5 mm Hg for DBP in treatment arms for different co-morbid conditions shown in Table 2.

Table – 2 Cardiac Risk Factors And Reduction In SBP/DBP

Baseline Characteristics	SBP Difference, mmHg	DBP Difference, mmHg
Age	-10.5	-4.3
Men/Women	-11.5	-4.9
CVD	-10.9	-5.5
Diabetes	-11.6	-5.6
Antihypertensive drug used	-11.4	-5.5

In different randomized clinical trials, beta-blockers were the most commonly used anti-hypertensive medication (n=4500) to achieve the target BP (Table 3). Followed by beta-blockers, calcium channel blockers (n=3450) and ACE inhibitors (n=3100) were most commonly used treatment arms.

Table – 3 Antihypertensive Medications Used In Different Randomized Clinical Trials

Antihypertensive	Reports from Pubmed/medline/Embase
Thiazide diuretics	1781
Beta -Blockers	4500
ACEI	3100
CCBs	3450
ARBs	435

Across all included trials, adverse events were poorly defined and probably varied across studies. For instance, many studies referred to syncope as an outcome, but did not say what type of syncope event they might have included.

DISCUSSION

It is important to note that the selection of antihypertensive drugs should be based on their ability to reduce blood pressure levels, as lowering BP is the main goal in preventing cardiovascular complications in patients with hypertension. This is why numerous studies have been conducted to validate the antihypertensive efficacy of various treatments.

Meta-analyses of RCTs have been conducted to compare the effectiveness of different classes of antihypertensive drugs, including diuretics, ACE inhibitors, ARBs, calcium channel blockers, and beta-blockers. The present meta-analysis could aid in determining the most effective drugs for lowering blood pressure levels, as well as identifying those drugs that carry the least risk of adverse effects.

The selection of antihypertensive drugs should be based on a thorough understanding of their efficacy and safety profiles, as well as the individual patient's medical history and risk factors for cardiovascular disease. By taking these factors into consideration, clinicians can choose the most appropriate treatment to achieve optimal blood pressure control and reduce the risk of cardiovascular events.

The net achieved BP reduction varied by trial design, with BP-lowering intensity trials achieving the largest mean reduction of over 11.4 mm Hg systolic BP and 5.5 mm Hg diastolic BP. The effects were evident across patient subgroups, as defined by their baseline age, sex, history of cardiovascular disease or diabetes and prior use of antihypertensive treatment.

There are limited numbers of studies that have compared the efficacy of the most commonly used antihypertensive drugs. The current meta-analysis shows similar results to those of Larochelle P, et al.[10] regarding use of beta-blockers as most common anti-hypertensive agent.[10] The class of beta-blockers comprises a range of agents with diverse pharmacokinetics and pharmacodynamics properties including lipo- and hydrophilicity, intrinsic sympathomimetic activity, duration of action, vasodilation, and metabolism, which is influenced by genetic polymorphisms. Due to these properties, certain - blockers are indicated for cardiovascular conditions as well as non-cardiovascular indications.

Across all included trials, adverse events were poorly defined and probably varied across studies. For instance, many studies referred to syncope as an outcome, but did not say what type of syncopal event they might have included. A conservative approach to inclusion of outcomes was taken when possible, and only those explicitly stating the outcome of interest were included. For example, trials reporting hypotension or acute kidney injury were included, but those reporting hypotension or dizziness or renal impairment were excluded. Despite this approach, some studies were included that did not specify the thresholds used to define hypotension or acute kidney injury. This could have resulted in some relevant data for certain outcomes being missed, but this meant those that were included were likely to be sufficiently similar to enable pooling in a meta-analysis. Although the quality of adverse event ascertainment is likely to have varied between trials, it would not be expected to vary between

treatment arms within trials. Thus, it is unlikely that differences in the quality of adverse event ascertainment would have affected the relative treatment effects presented in this review.

CONCLUSIONS

Even with the assumption that all drug classes promote similar BP reductions, clinically relevant differences exist among specific drugs. This should be reflected in hypertension guidelines since a general drug class recomme ndation could eventually promote the use of a specific drug with not enough potency to achieve therapeutic goals. Findings suggest that long term BP-lowering anti-hypertensive drugs in monotherapy or combination is effective in lowering BP, in people with different characteristics. Appropriate treatment strategies are needed to sustain substantive long-term BP reductions.

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