A Review: Anti-Hypertensive Drugs

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***Abstract*—This review presents publication trends, characteristics, and quality of systematic reviews (SRs) of randomized controlled trials (RCTs) of antihypertensive drugs (AHTDs). Between 1985 and 2017, 1,173 SRs were published, and in the last 20 years, 10, 35, and 116 were published in the year 1996, 2006, and 2016, respectively. Angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers were the most common class of drugs studied. Fourteen percent of the SRs were prospectively registered/published protocol. Three-fourth of the SRs did not report a full search strategy, and 45% did not report a PRISMA or similar diagram. Of the 34 SRs published in the five high impact factor journals in the last 10 years, 15%, 21%, and 65% have unclear, low, and high risk of bias, respectively. There has been a steady increase in the publication of SRs of RCTs of AHTDs. However, adherence to standard methods of conduct and reporting continues to be low.**

I. INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of death globally, and hypertension is the leading risk factor for CVD. Antihypertensive drugs (AHTDs) are among the most commonly used prescription drugs worldwide. Drug regulatory agencies have approved many AHTDs primarily based on evidence of efficacy and safety from randomized controlled trials (RCTs). Although RCTs are considered the gold standard for generating evidence of effects of interventions, health care decisions based on only some of all the available RCTs are not considered credible. Systematic reviews (SRs) aim to identify all relevant literature on a topic, critically appraise, and summarize evidence to answer well-defined questions. Decision-makers, guideline developers, and health care providers use SRs to inform decisions to improve health care. Mapping of SRs can be a useful one-stop resource for the consumers of evidence synthesis to enable evidence-informed research and health care decisions. Mapping reviews can provide information about the current state, research trends, and future research needs in a particular area of interest. Numerous SRs of effects of AHTDs have been published so far. Mapping reviews have been produced in several disciplines of medicine, but not of SRs of AHTDs. We, therefore, undertook this study with the objective of

identifying SRs of RCTs of AHTDs and sought to assess their publication trends, characteristics, and quality.

Successful treatment of hypertension is possible with limited side effects given the availability of multiple antihypertensive drug classes. The translation of pharmacological research to the treatment of hypertension has been a continuous process, starting with drugs discovered 60 years ago, such as thiazide diuretics (1958) and currently finishing with the newest antihypertensive agent available on the market, the orally active direct renininhibitor aliskiren, discovered more than 10 years ago (2000). In between, there has been a continuous rate of discovery, including spironolactone (1957), beta-blockers (propranolol, 1973), centrally acting alpha-2 adrenergic receptor agonists (clonidine, 1970s), alpha1-adrenergic receptor blocker (prazosin, 1975), angiotensin converting enzyme inhibitors (captopril, 1977), calcium channel blockers (verapamil, 1977), and angiotensin II receptor blockers (losartan, 1993).

The aim of this review is to describe the various pharmacological classes of antihypertensive drugs, under two major aspects: their mechanisms of action and side effects. The mechanism of action is analysed through a

pharmacological approach, i.e. the molecular receptor targets, the various sites along the arterial system, and the extra-arterial sites of action, in order to better understand in which type of hypertension a given pharmacological class of antihypertensive drug is most indicated (see other articles of this issue). In addition, side effects are described and explained through their pharmacological mechanisms, in order to better understand their mechanism of occurrence and in which patients drugs are contra-indicated. This review does not address the effectiveness of monotherapies in large randomized clinical trials and combination therapies, since these are the matters of other articles of the present issue.

II. OBJECTIVES

- Describe the guidelines for using antihypertensive medications and guide the treatment choices for first-line treatment.
- Review the different anti-hypertensive medication classes, summarizing the guidelines for the indication to use combination treatment when mono-therapy fails.
- Outline the significant side effects of each class of antihypertensive medications.
- Identify the approach of the interprofessional team to identify an appropriate care plan for a hypertension patient.

III. CLASSIFICATION

Five major pharmacological classes of antihypertensive drugs are detailed here: beta-blockers, diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, and calcium channel blockers. Four additional pharmacological classes are described in a shorter

manner: renin inhibitors, alpha-adrenergic receptor blockers, centrally acting agents, and direct acting vasodilators.

Beta-blockers

Beta-blockers are a heterogeneous pharmacological class, and their pharmacodynamic properties depend on their cardiac-selectivity, partial agonist activity and associated vasodilating properties. They all lower BP to the same extent, although using various amounts of reduction in cardiac output and vasodilatation, according to their pharmacological properties.

Diuretics

Thiazide diuretics and loop diuretics increase natriuresis and diuresis. Both can be considered as one major therapeutic class of antihypertensive drugs, although they represent two distinct pharmacological classes. Their major mechanisms of action and side effects are described separately. Potassium sparing diuretics represent another therapeutic class.

Angiotensin converting enzyme inhibitors

The first ACEI available for hypertension treatment was captopril in the early 1980s, rapidly followed by enalapril, perindopril, lisinopril, ramipril, quinapril, benazepril, cilazapril, trandolapril, fosinopril, moexipril, imidapril and zofenopril.

Angiotensin ii receptor blockers

The first angiotensin II receptor blocker (ARB) available for hypertension treatment was losartan in the late 1990s, rapidly followed by candesartan, eprosartan, irbesartan, valsartan, telmisartan, and olmesartan.

Calcium-channel blockers

Calcium-channel blockers (CCBs) are a heterogeneous class of drugs, which include verapamil (a benzothiazepine), diltiazem (a phenylalkylamine), and dihydropyridines (DHPs) such as nifedipine and amlodipine. Renin inhibitors

The only direct renin inhibitor currently available for treating hypertensive patients is aliskiren, a non-peptide and orally active drug. Aliskiren is a highly potent and selective inhibitor of human renin [52]. The increase in plasma renin concentration, which is observed after aliskiren administration, is higher than in response to ACEIs and ARBs. However, the increase in plasma renin concentration does not translate into a paradoxical rise in BP since the reactive

IV. MECHANISM OF ACTION

Thiazide and Thiazide like diuretics: mechanism of action for thiazide-type diuretics is not fully understood. Thiazides inhibit sodium transport in the distal tubule by blocking the Na/Cl channels. Thiazides can have a small effect on the proximal tube by impairing sodium transport, but the main action is on the distal tubule. Thiazides cause initial volume depletion associated with decreased cardiac output, which recovers within 6 to 8 weeks of starting the treatment in a reverse autoregulation mechanism while the blood pressure remains controlled; thiazide diuretics can

acutely activate the renin-angiotensin system and cause systemic vascular resistance, which prevents a good response to the diuretic treatment, this increase in renin-angiotensin activity may resolve with chronic thiazide treatment, the addition of an ACE inhibitor or ARB can enhance the blood pressure control. Also, the thiazide-type diuretics have a modest vasodilation effect, although the mechanism is still unclear.

Calcium channel blockers: The mechanism of action of CCBs is related to the inhibition of Ca2+ entry to the cells; this occurs by binding to the L-type voltage-gated calcium channels located in the heart muscle. This effect can cause peripheral vasodilation, which is seen mainly in dihydropyridines, or a negative inotropic effect on the heart muscle in non-dihydropyridines, inhibiting the sinoatrial and atrioventricular nodes, leading to slow cardiac contractility and conduction.

ACE inhibitors decrease blood pressure by inhibiting the angiotensinconverting enzyme; this causes a decline in the production of angiotensin II and increases the bradykinin level by inhibiting its degeneration, which leads to vasodilation.

ARBs work by blocking the binding of angiotensin II to the angiotensin 1 AT1 receptors, which inhibit the angiotensin II effect. In contrast to ACE inhibitors, ARBs do not affect the kinin levels.

Beta-blockers work by inhibiting the catecholamines from binding to the Beta 1, 2, and 3 receptors. Beta-1 receptors are found primarily in the heart muscle, beta-2 receptors are located in the bronchial and peripheral vascular smooth muscles, and beta-3 receptors appear in the adipose tissue of the heart. Cardio-selective beta-blockers (e.g., metoprolol succinate, metoprolol tartrate, atenolol, betaxolol, and acebutolol) inhibit only beta-1 receptors, causing fewer bronchospasms. By inhibiting the catecholamines binding to the beta

receptors, the beta-blockers have a negative inotropic effect, which results in a decrease in the heart rate, which helps to reduce oxygen consumption.

Loop diuretics work by increasing the sodium exertion at the level of the medullary and cortical aspects of the thick ascending limb. This action causes a decrease in volume, which leads to decreased blood pressure.

Potassium Sparing Diuretics: Act on the principal cells in the late distal tubule and the collecting duct; they inhibit sodium reabsorption at this level in association with decreased excretion of potassium and hydrogen ions. Spironolactone and eplerenone are considered mineralocorticoid receptor antagonists, inhibiting the mineralocorticoid receptor.

Hydralazine is an arteriolar vasodilator; it inhibits Ca2+ release in the smooth muscles of the vessels by decreasing its cytoplasmic concentration.

Clonidine stimulates alpha-2 receptors located in the rostral ventrolateral medulla, which reduces the sympathetic outflow from the central nervous system and decreases plasma norepinephrine levels, leading to decreased cardiac output.

Alpha-blockers act by inhibiting alpha-1 receptors, which decrease vascular smooth muscle contractions, leading to vasodilation.

V. CONCLUSION

In conclusion, the various mechanisms of action of the pharmacological classes of antihypertensive drugs described in this review show their complementarity for treating hypertension, well known as a mosaic of pathophysiological disturbances. Successful treatment of hypertension is possible with limited side effects. A better knowledge of the molecular receptor targets, the various sites of action along the arterial system, and the extra-arterial sites of action, allows the physician to better.

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