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A REVIEW ON CURRENT TRENDS AND NOVEL DRUG APPROACH IN THE TREATMENT OF HYPERTENSION

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ABSTRACT

Hypertension is one of the most significant public health challenges and is regarded as the primary cause of the global burden of disease. It is a major contributor to the risk of coronary heart disease, stroke, and chronic kidney disease. Effective hypertension management will undoubtedly have one of the biggest contributions to saving lives in the upcoming years. Regular blood pressure measurements are necessary due to the asymptomatic nature of hypertension and the medical impact it carries. Due to intolerance to the existing antihypertensive medications, a large number of hypertensive patients remain uncontrolled. Hence, new therapeutic targets and treatments are required to control hypertension and may provide additional BP-lowering with broader cardiovascular disease protection. In comparison to current medications, several novel drugs have demonstrated greater safety and efficacy in clinical studies and may end up being a preferable alternative due to minimal adverse effects and the prevention of end-organ damage. The process of development of a drug is a tedious, complex, and expensive process, entrenched with a high degree of uncertainty that a drug will actually succeed. Prioritizing BP reduction with the use of appropriate and individualized dosages of current drugs will continue to be a crucial goal in the management of hypertension until new technology is ready for practical usage.

KEYWORDS: Novel drug, Hypertension, Blood pressure, Current trends.

INTRODUCTION

Hypertension is defined conventionally as a persistent elevation of arterial blood pressure (BP) ≥140/90 mm Hg; a criterion identifies a group of people whose risk of cardiovascular

illness associated with hypertension is significant enough to require medical attention.[1] Hypertension is one of the most important public health issues. It is identified as having the greatest impact on the worldwide burden of disease. The number of adults with hypertension increased from 594 million in 1975 to 1.13 billion in 2015, with the hike seen largely in low- and middle-income countries but just 14% have it under control.[2] Epidemiological data have shown that hypertension prevalence is increasing steadily in India, with rates ranging from 4–15% in urban areas and 2-8% in rural areas.[3] All of these findings imply that it is critical to overcome the recent stasis in hypertension management and develop a novel approach to lessen the burden of high blood pressure globally. Hypertension is widely recognized as the most prevalent modifiable risk factor for cardiovascular diseases (CVD), stroke, and renal failure. It is the second most common cause of chronic kidney disease (CKD) leading to early disability and dependency, reducing the life expectancy in patients, and increasing the cost of care.[4] Effective hypertension management will undoubtedly have one of the biggest contributions on saving lives in the upcoming years.[5]

Several national and international guidelines have been published for the treatment of hypertension. However, many medical professionals use their own prescribing practices to manage hypertension patients based on their individual clinical requirements. The main goal of antihypertensive medication is to lower the risk of morbidity and mortality related to hypertension. Often, two or more antihypertensive drugs are needed to effectively manage this condition.[6] The global control of hypertension has advanced slowly, despite the significant cost to public health and ongoing research efforts. To manage this situation, transformation is urgently required.[7]

Blood Pressure Monitoring

"True" blood pressure is referred as the average level over a prolonged period of time.[8] High blood pressure is often asymptomatic, mainly in the early stages, leading to its description as a 'silent killer'.[9] Regular blood pressure measurements are necessary due to the asymptomatic nature of hypertension and the medical impact it carries. The US Preventive Services Task Force (USPSTF) suggests screening for hypertension in adults of 18 years or older with office blood pressure measurements. It also recommends to obtain blood pressure measurements outside of the clinical setting for diagnostic confirmation before starting treatment.[10] Developments in non-physician-based blood pressure measurements utilising new technologies may make it possible to diagnose hypertension earlier.[11] Auscultatory or

oscillometric semiautomatic or automatic sphygmomanometers are the recommended method for measuring BP in the doctor's office.[12] Self-screening enables patients to measure their own blood pressure outside of physician consultations. Home BP is the average of all BP measurements taken with a semiautomatic, validated BP monitor, that require no training, just simple instructions for at least 3 days and preferably for 6–7 consecutive days before each clinic visit, with readings in the morning and the evening.[13]

Ambulatory monitors typically involve portable, automated cuffs worn continuously so that the readings are taken every 15 to 30 minutes for 24 hours, with around 50 to 100 readings in total. Data from the device are downloaded into software and can be translated into a report.[14]

Advances in technology have allowed for the development of new 'cuff-less' BP monitoring devices that will permit continuous blood pressure measurement and monitoring for a wide range of patients, allowing them to perform their daily activities without being interrupted.[15]

Wearable blood pressure monitors allow frequent blood pressure measurements with minimal strain on the patient. It is anticipated that wearable devices will significantly change the quality of detection and management of hypertension by increasing the accurate detection of phenotypes that have a negative impact on cardiovascular prognosis, such as masked hypertension and aberrant blood pressure fluctuation.[16] However, the validation of these devices must follow standardized criteria and techniques.[17]

Current Trends in Hypertension

It is widely accepted that BP targets should be customized to the person based on the tolerability of treatment, age and comorbidities, although targets differ between guidelines.[18] Different complications and issues have been arising as a result of an increase in the number of medications available for the treatment of hypertension.[19] To address the issue, 39 significant professional, public, and seven government departments, established a committee known as the Joint National Committee (JNC).[20] JNC- 8 recommendations state that in patients aged ≥60 years pharmacologic treatment may be started to lower systolic BP (SBP) ≥150 mm Hg or diastolic BP (DBP) ≥90 mm Hg.[21] In the population, aged 18 years (and those younger or older than 60 years with either diabetes or CKD) always initiate pharmacological treatment to lower SBP≥140mmHg or DBP ≥ 90mmHg.[22]

The JNC- 7 Guideline recommended considering thiazide-type diuretics as first-line therapy for the majority of patients; however, now a day, thiazide diuretics were not the most widely used drug class. This might be an indication of the JNC 8 guideline's emphasis on thiazide, calcium channel blockers, Angiotensin-converting enzyme inhibitors, or Angiotensin receptor blockers as first-line medications.[23] Additional drugs may also be required for the effective management of hypertension.

Discover, develop and marketing of a novel drug requires huge financial and time investment. With this in mind, recent focus has turned to re-evaluate the efficacy of older, less commonly used antihypertensive agents, and agents approved for indications other than hypertension, particularly for individuals at high risk of cardiovascular disease (CVD).[18]

Novel Drug Therapy in Hypertension

Due to intolerance to the existing antihypertensive medications, a large number of hypertensive patients remain uncontrolled. Hence, new therapeutic targets and treatments are required to control hypertension and may provide additional BP-lowering and broader cardiovascular disease (CVD) protection, especially if used in the context of comorbidities such as chronic kidney disease (CKD) and diabetes.[24]

Sodium glucose cotransporter -2 inhibitors (SGLT -2 Inhibitors)

The SGLT -2 Inhibitors are a class of drugs that hinders glucose reabsorption by suppressing the sodium-glucose co-transporter 2 found on the apical membrane of the proximal convoluted tubules.[25] A randomized crossover phase IIIb study demonstrated that BP control (via improved hemodynamic and volume control) appears likely to be one of the most important physiological mechanisms of the CVD benefits of SGLT2i.[26] A recent randomized, placebo-controlled, multicentre trial confirmed that Dapagliflozin has been shown to lower systolic blood pressure up to 5mmHg in studies whether administered alone or as an add-on therapy and the similar effect is seen with Canagliflozin.[27,28,29] Despite their obvious advantages, these agents have recognized side effects. The key side effect associated with SGLT2 inhibitors appears to be non-sexually transmitted mainly mycotic, genito-urinary infection linked to increased glucose levels in the urine.[30]

Aldosterone synthase inhibitors

The significance of aldosterone in hypertension had first been recognized in 1954 by Conn and Louis, who successfully treated a case of hypertension by removing an adrenal adenoma

which secreted excess aldosterone.[31] Although Spironolactone and Eplerenone successfully reduce blood pressure, they have the potential to unintentionally elevate levels of renin and aldosterone in the blood, which would lessen the effectiveness of the therapy. Aldosterone synthase is encoded by the CYP11B2 gene, and its transcription is largely responsible for controlling aldosterone production.[32] The first orally active aldosterone synthase inhibitor to undergo human testing is LC1699; which has greater selectivity for inhibition of CYP11B2 over CYP11B1, so that having less of an influence on cortisol. LY3045697 is an effective and highly selective aldosterone synthase inhibitor with selectivity for CYP11B2, gives a significant potential advantage over other aldosterone synthase inhibitors tested in the trials.[33]

RO6836191 as a potent competitive inhibitor of AS, shows that it is possible to reduce aldosterone production completely in humans without altering cortisol production.[34] A new drug called Baxdrostat reduces blood pressure in a dose-dependent manner in patients with treatment-resistant hypertension.[35] Clinic and ambulatory blood pressure were considerably reduced by aldosterone synthase inhibition with LCI699. Fewer participants reported reduced cortisol release in response to adrenocorticotropic hormone stimulation. These findings encourage further investigation into the effectiveness of aldosterone synthase inhibition in the treatment of primary hypertension.[36]

Dual angiotensin receptor–neprilysin inhibitors

Inhibition of neprilysin prevents natriuretic peptide degradation resulting in natriuresis, vasodilatation and reduced sympathetic tone thereby exerts beneficial cardiovascular and renal effects in heart failure, while RAAS blockers target the angiotensin receptor these combined effect lowers BP.[37] LCZ696 is a novel single molecule comprising molecular moieties of Valsartan and Neutral endopeptidase inhibitor prodrug AHU377 in the ratio of 1:1.[38] The Sacubitril-Valsartan combination is currently authorized in more than 57 nations, including India. A double-blind trial confirmed that ARNI treatment is superior to Enalapril alone in lowering the risks of death and of hospitalization for heart failure.[39]

Soluble guanylate cyclase stimulators

Soluble guanylate cyclase (sGC) is a prime enzyme in the nitric oxide (NO) signaling pathway. sGC catalyzes the synthesis of the secondary messenger cyclic guanosine monophosphate (cGMP) on binding of NO to its haem group, which promotes vasodilation.[40] Impaired NO and cGMP signaling has been linked to the pathogenesis of

cardiovascular disease, including systemic arterial and pulmonary hypertension.[41] The first sGC stimulator discovered was the benzylindazole chemical YC-1, which served as a model for the design of new sGC stimulators with increased potency and specificity for sGC, such as CFM-1571, BAY 41-2272, BAY 41-8543, and BAY 63-2521.[42] Studies on the therapeutic potential of sGC stimulators in animal models of hypertension have been very informative regarding its pharmacological efficacy. Oral BAY 41–2272 and BAY 41–8543 also resulted in antiplatelet activity, a significant drop in blood pressure, and an improvement in mortality in a low-NO rat model of hypertension.[43,44] Many trials are going on sGC stimulators. If successful, these studies will herald a new generation of treatments for cardiopulmonary disease.[45]

Phosphodiesterase- 5 inhibitors

The enzyme PDE- 5 catalyzes the hydrolysis of cyclic guanosine monophosphate (cGMP), a potent vasodilator and nitric oxide (NO) donor, to its corresponding metabolites (monophosphates). It is widely distributed in heart and blood vessels. Based on its distribution, it was hypothesized that enzyme PDE- 5 inhibition could lead to significant coronary vasodilation, which would benefit patients with hypertension. Phosphodiesterase- 5 (PDE- 5) inhibitors are selective inhibitors of the enzyme PDE- 5.[46] PDE- 5Is have improved a number of hemodynamic and clinical parameters in significant randomized studies, which led to their approval for the treatment of pulmonary arterial hypertension.[47] The effectiveness of sildenafil as a treatment for people with pulmonary arterial hypertension has been verified by recent human evidence. Others are under investigation.[48] Sildenafil and Tadalafil markedly improve clinical status, exercise ability, and hemodynamic of pulmonary arterial hypertension patients. The third PDE- 5 inhibitor Vardenafil, is presently being investigated in pulmonary arterial hypertension. The most common minor side effects include headache, flushing, nasal congestion, stomach issues, and myalgia.[49]

Table 1: Antihypertensive drugs in current trials.

DRUG CLASS	COMPOUND NAMES	STATUS
Sodium glucose co-transporter- 2 inhibitors	Canagliflozin Dapagliflozin	Approved Approved
Aldosterone synthase inhibitors	Nonselective CYP11B2 inhibitor: LCI699 Selective CYP11B2 inhibitors: LY3045697 RO6836191	Phase II Phase I Phase I

Dual-acting angiotensin receptor-neprilysin inhibitor	LCZ696	Phase III
Soluble guanylate cyclase stimulators	Riociguat (BAY 63–2521) Vericiguat Praciliguat	Phase I Phase II Phase I
Phosphodiesterase 5 inhibitors	Sildenafil PF-00489791	Phase II Phase II
Aminopeptidase A inhibitors	Firibastat (RB150) QGC001	Phase I/II Phase II
Aminopeptidase N inhibitors	PC18	Preclinical
Vasoactive intestinal peptide receptor agonists	Vasomera (PB1046)	Phase I
Mineralo corticoid receptor antagonist	Finerenone (BAY 94–8862) Esaxerenone (CS-3150)	Phase IIb Phase III
Advanced glycation end product (AGE) breakers	Alagebrium (ALT-711)	Phase II
Intestinal Na^+/H^+ exchanger 3 inhibitor	Tenapanor (AZD1722)	Phase I
Dual acting endothelin-converting enzymes-neprilysin inhibitor	Daglutril (SLV-306)	Phase II
Natriuretic peptide A agonist	PL-3994	Phase II
Dopamine β-hydroxylase inhibitor	Etamicastat	Phase I

CONCLUSION

The increased prevalence of hypertension has necessitated the development of a new class of safe and effective therapeutic agents because the currently available medications, while effective at lowering blood pressure, have noticeable adverse effects when used for a long period of time. In comparison to current medications, several novel drugs have demonstrated greater safety and efficacy in clinical studies and may end up being a preferable alternative due to minimal adverse effects and the prevention of end organ damage. Several novel pharmaco-therapeutic strategies hold promise and those with further widespread cardiovascular and renal protection are especially compelling. Although just a few hypertension therapies have recently received clinical approval, the medications covered in this review are still promising therapy alternatives in future. Prioritizing BP reduction with the use of appropriate and individualized dosages of current drugs, enhancing patient compliance to medications, and expanding access to healthcare will continue to be crucial goals in the management of hypertension until this technology is ready for practical usage.

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