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Evolution of Pharmacotherapy of Hypertension: A Brief Review

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ABSTRACT- Hypertension is a significant risk factor for cardiovascular mortality and morbidity, also an emerging cause of premature death worldwide. The pathogenesis of hypertension is complex and requires more in-depth studies and exploration of pharmacotherapy. In this review, we demonstrated important pathogenesis areas of hypertension. We highlighted new treatments proposed in these areas according to recent guidelines, hoping to provide insight into the prevention and treatment of essential hypertension.

Key Words- Hypertension, antihypertensive therapy, systolic blood pressure, arterial stiffness.

INTRODUCTION-

Hypertension (HTN) is a pervasive disorder, particularly in middle age, associated with cardiovascular mortality and morbidity. The cutoff manometric reading between normotensives and hypertensives is arbitrary. An estimated 1.28 billion adults aged 30–79 years worldwide have hypertension, most 2/3rd living in low- and middle-income countries.[1]

Hypertension is diagnosed when a person's systolic blood pressure (SBP) is ≥140 mm Hg and diastolic blood pressure (DBP) is ≥90 mm Hg following repeated examination.[1]

Essential hypertension adds to more than 90% of all hypertensive patients. [2] The most commonly applied method of controlling hypertension is pharmacological treatment along with lifestyle intervention. Many antihypertensive medication groups are available among them, renin-angiotensin-aldosterone system (RAAS) inhibitors, calcium channel blockers, and diuretics, from which a variety of fixed-dose combinations have been formulated, are primarily used. [3-5] many new findings about essential hypertension have emerged, and these provide important theoretical evidence to help develop a better understanding and treatment of essential hypertension.[6]

In this review, we briefly reviewed pathogenesis and advances in treatment methods of hypertension in recent years.

The pathogenesis of hypertension is based on both decreased vasodilation and increased blood volume. Arterial stiffness directly causes a decrease in vasodilation, and water-sodium retention directly leads to an increase in blood volume. Arterial stiffness, salt-water retention, Renin-angiotensin-aldosterone system (RAAS) activation, Genetics, and sympathetic dysregulation are the factors that are major contributors to hypertension pathophysiology.[6]

The European Society of Cardiology and the European Society of Hypertension (ESC/ESH) defines hypertension as office Blood pressure (BP) levels ≥140 mmHg systolic or 90 mmHg diastolic.[7]

According to **Joint National Committee (JNC) guidelines** for hypertension- 8th revision, Hypertension has been classified as per the following:

Blood pressure Classification	**Systolic blood pressure SBP (mm Hg)**	**Diastolic blood pressure DBP (mm Hg)**
Normal	< 120	< 80
Pre-hypertension	120-139	80-89
Stage I Hypertension	140-159	90-99
Stage II Hypertension	≥ 160	≥ 100

JNC-8th revision: Hypertension classification [Hernandez-Vila E. A review of the JNC 8 Blood Pressure Guideline. Tex Heart Inst J. 2015 Jun 1;42(3):226-8. doi: 10.14503/THIJ-15-5067. PMID: 26175633; PMCID: PMC4473614.]

The American Heart Association (AHA), and the American College of Cardiology (ACC) have endorsed a more 'aggressive' definition based on office BP values ≥130 mmHg systolic or 80 mmHg diastolic.[8] In addition, the International Society of Hypertension (ISH) adopted the 140/90 mmHg definition. [8,9]

According to the US guidelines not to imply that all the patients with office BP in the range of 130–139/80–89 mmHg require drug treatment. Instead, the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines suggest applying more appropriate lifestyle measures (weight control, smoking cessation, low-sodium diet, etc.) for these subjects, and reserve drug treatment for cases of inefficacy of non-pharmacologic measures.[10]

All guidelines share the recommendation that drug treatment should be started immediately for:

(a) Patients with office BP ≥ 160/100 mmHg regardless of other considerations [7-9]

(b) Patients with BP ≥ 140/90 mmHg in the presence of ischemic heart disease, cerebrovascular disease, or heart failure. [7-9]

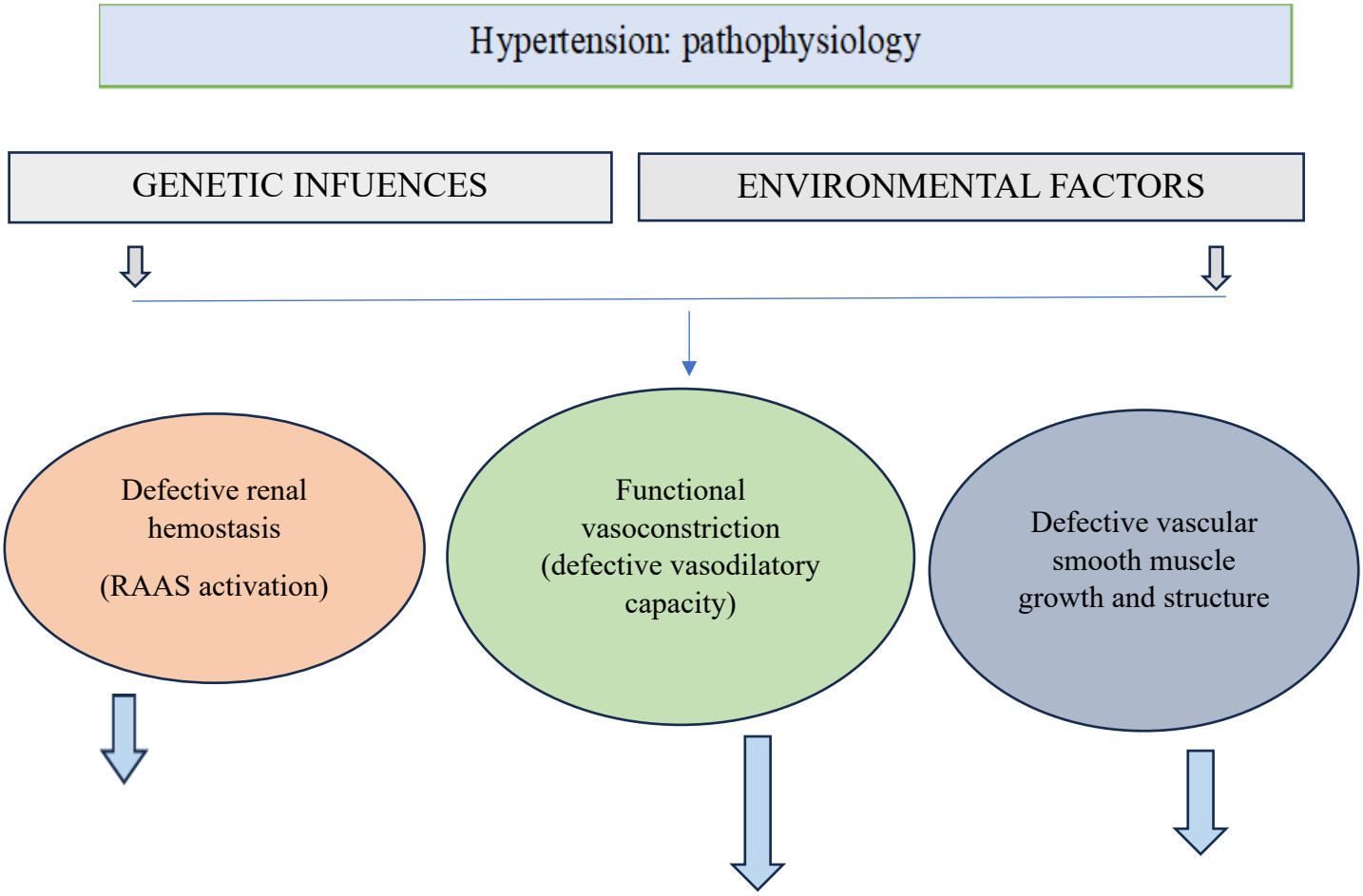
All guidelines suggest that drug treatment should be initiated, regardless of other considerations, in patients with BP persistently ≥ 140/90 mmHg in case of inefficacy of lifestyle measures. [7-9] In the case of a BP between 130/80 and 140/90 mmHg, the AHA guidelines recommend drug treatment in patients with overt cardiovascular disease (i.e., secondary prevention), as well as in patients without overt cardiovascular disease (i.e., primary prevention) if their 10-year risk of cardiovascular disease is ≥10% according to the Atherosclerotic Cardiovascular Disease (ASCVD) calculator. [9,10]

Available guidelines provide different recommendations in terms of BP targets and definitions of BP control. The Indian Society of Hypertension (ISH) and the European Society of Cardiology/ European Society of Hypertension (ESC/ESH) guidelines recommend a uniform BP target should be a reasonable target, with the main goal to prevent the most closely BP-related adverse complication of hypertension, which include stroke and heart failure. [10,11]

High blood pressure is largely asymptomatic, especially in the early stages, leading to its description as a 'silent killer'. [12] The asymptomatic nature of hypertension in conjunction with its disease burden necessitates routine blood pressure screening.[13] Despite such impressive growth, the proportion of treated hypertensive subjects with normal blood pressure ('controlled hypertension') remains very low worldwide. It has been estimated that such a proportion approaches 23% in women and 18% in men. [14]

Hypertension: Pathophysiology

Elevated blood pressure is a serious medical condition that significantly increases the risk of diseases of the heart, brain, kidneys, and other organ damage. An estimated 1.4 billion people worldwide have high blood pressure, but just 14% of patients have it under control.[15] (who guide.)



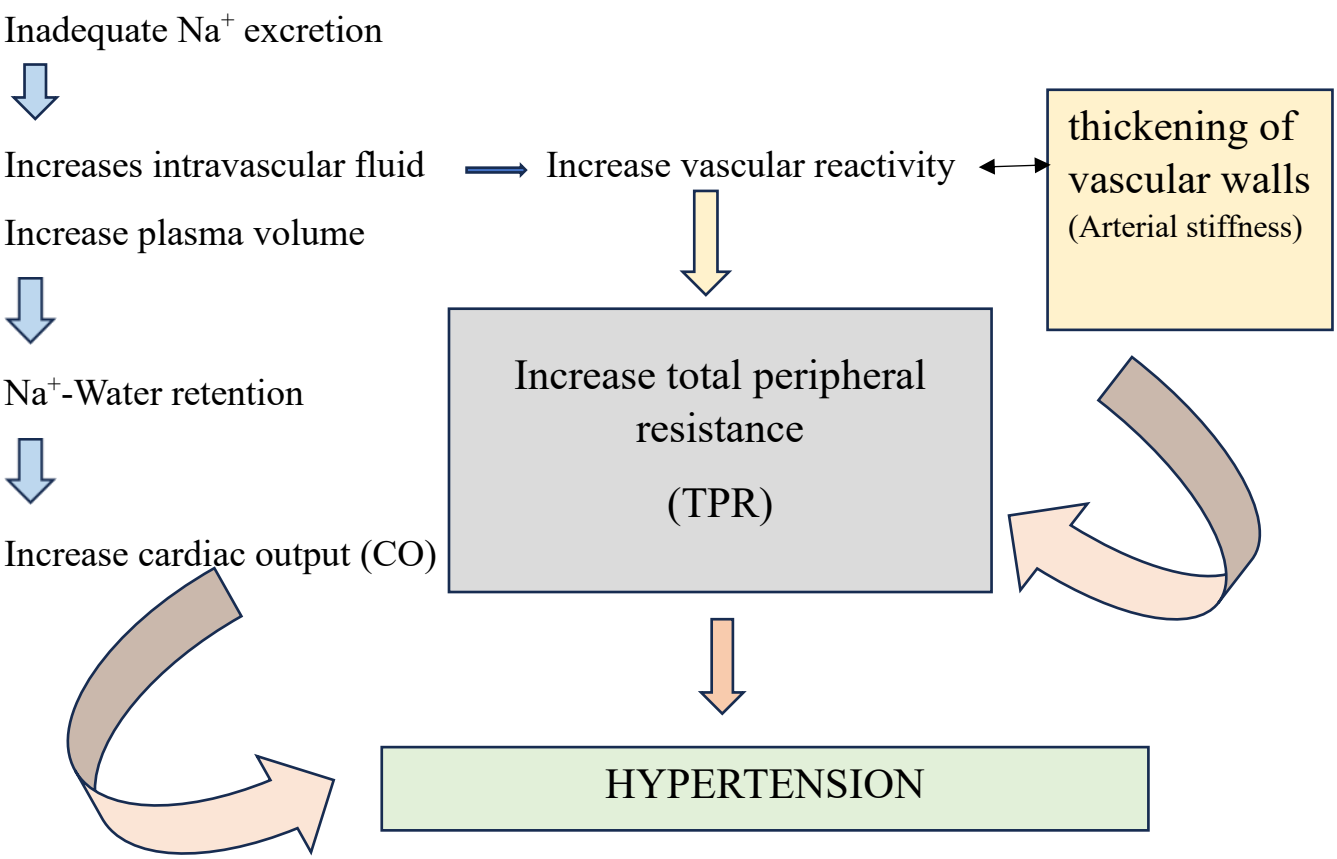


Fig.1: Pathophysiology of hypertension

Arterial stiffness

Reduction in elasticity and distensibility of arteries, and for that Pulse wave velocity (PWV) is used to represent the degree of stiffness in large arteries. An increase in PWV indicates severe impairment in arterial dilatation capacity.[16] Arterial stiffness has been closely associated with an increased risk of hypertension [17,18] and majorly with isolated systolic hypertension. [19] Systolic blood pressure (SBP) is also associated with a clinically significant progression of arterial stiffness. [20] Arterial stiffness is categorized into functional arterial stiffness and structural arterial stiffness. [21]

Functional arterial stiffness is mainly related to the contractile dysfunction of vascular smooth muscle cells (VSMCs), while Structural arterial stiffness is majorly correlated with age, hyperlipidaemia, and diabetes mellitus, and is characterized by elastin disruption, collagen deposition, and altered extracellular matrix composition. [19-21]

Water-sodium retention-

High salt intake is an important trigger factor in essential or primary hypertension caused by water-sodium retention, causing abnormal increases in intravascular fluid volume and plasma.[22] Multiple factors may contribute to the development of salt-sensitive hypertension, including age, obesity, genetic background, and maternal conditions during foetal life, etc. [23]

Low potassium activates the system by hyperpolarizing the membrane, leading to Cl^- efflux from the inhibitory binding site on WNK (with no lysine [K]) kinases. Once disinhibited, WNK kinases phosphatidate SPAK (STE20/SPS1-related proline/alanine-rich kinase), which in turn phosphor-activates nine–rich kinase co-transporter (NCC), and this is called the Potassium Switch theory [24-26] which is one of the important theories on the pathogenesis of salt-sensitive hypertension.

Renin-angiotensin-aldosterone system (RAAS)-

It regulates blood pressure mainly by affecting arterial constriction and water-sodium retention in the body. Several components of axis cascade have been identified in the RAAS, including angiotensinogen, renin, angiotensin-converting enzyme, angiotensin with various subtypes (Ang I, Ang II, Ang III, Ang IV, Ang 1-7), aldosterone, and aldosterone receptors.[27]

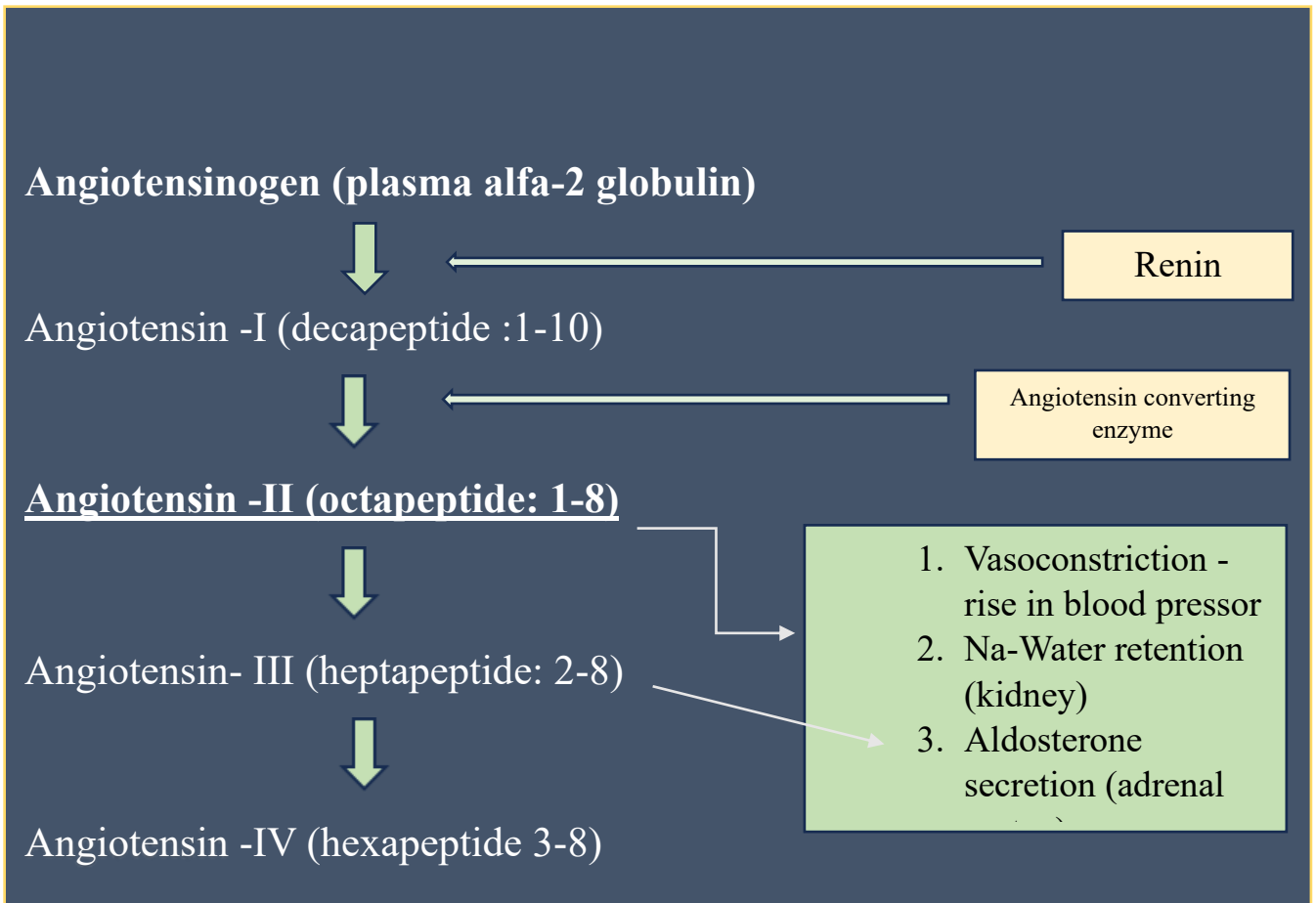


Fig. 2: Physiological regulation of electrolyte balance, plasma volume, and blood pressure by the renin-angiotensin system.

Angiotensinogen is cleaved by renin secreted from the kidney to form angiotensin I. Angiotensin I (1-10) is then cleaved in the circulatory system by enzymes (e.g., Angiotensin-converting enzyme) to form different peptides that eventually act in various organs.[28] Among these cleavage peptides, the function of angiotensin II (1-8) has been elucidated the most. Angiotensin II binds to the angiotensin II receptor in several organs and directly leads to vasoconstriction, water-sodium retention, and myocardial remodeling. In addition, when angiotensin II acts on the kidney, it further stimulates aldosterone secretion and exacerbates water-sodium retention.[29]

Renin-angiotensin-aldosterone system (RAAS) blockades, including angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor (subtype-1 receptor, AT1R) blockers (ARBs), Angiotensin receptor-neprilysin inhibitor (ARNI), and mineralocorticoid receptor blockers (MRAs), contributes to the prevention of hypertension as well as the protection of target organs.[30]

Sympathetic dysregulation-

Sympathetic dysregulation is also an important cause of essential hypertension, [31] which leads to increased cardiac output, systemic vascular tone, and plasma catecholamine levels. Patients with hypertension can present with greater muscle sympathetic nerve activity (MSNA) and lower baroreflex response.[32] Muscle sympathetic nerve activity (MSNA) plays a significant role in determining total peripheral resistance and vasoconstrictive function by controlling skeletal muscle.[33]

The manifestations of BP changes in sympathetic hypertension are also complex, including morning hypertension, nocturnal hypertension, sleep apnoea–related hypertension, orthostatic hypertension, resistant hypertension, etc. [34] Sympathetic overdrive not only contributes to the progression of BP elevation but also promotes hypertension-related target organ damage, such as left ventricular hypertrophy and dysfunction, congestive heart failure, renal insufficiency. [34] Beta-blockers are drugs commonly used clinically, which can inhibit the increase in blood pressure and heart rate caused by sympathetic excitation.

By modifying posterior hypothalamus activity, the renal sensory afferent nerve directly influences sympathetic outflow to the kidneys and other strongly innervated organs involved in cardiovascular regulation, such as the heart and peripheral blood vessels. In some experimental models, suppression of sensory afferent neurons lowers blood pressure and the damage chronic sympathetic overactivity causes to certain organs.[35] Currently, a popular method for renal artery radiofrequency denervation (RDN), catheter-based RDN is gradually gaining recognition for its antihypertensive and safe properties. [36-40]

Genetics

Genes also have a close relationship with hypertension. Genome-wide association studies have identified over 500 loci related to blood pressure regulation, bringing the total number of blood pressure genetic loci to over 1,000. [41–45] Human susceptibility to hypertension has been linked to genome-wide doxy-ribose nucleic acid (DNA) and RNA methylation. [45, 46] It has also been demonstrated in animal models that DNA methylation affects many genes important for blood pressure regulation. [47,48]

Although single nucleotide polymorphisms (SNPs) have the potential to be a pathogenic mechanism for essential hypertension, they primarily reside in nonprotein coding regions of the genome and have minimal effect on blood pressure since they do not change protein function. According to recent research, N6-methyladenosine (m6A) is enriched among the SNPs linked to blood pressure, and 10% of the BP-associated m6A SNPs are linked to coronary artery disease or stroke.[49]

Hypertension: Pharmacotherapy

Controlling blood pressure is proportionate to reduction in mortality and adverse cardiovascular outcomes, [50,51], and non-pharmacological and pharmacological interventions are essential for treatment.[52] non-pharmacological interventions

include reducing dietary sodium intake, increasing consumption of fruits and green vegetables, [53,54] a high-protein low-carbohydrate diet,[55] and weight loss,[56] all of which should be included throughout the treatment period.

Antihypertensive drug therapy has been remarkably improved in the last 60 years. Different classes of drugs have received prominence with time in this period.

1930-1940s	Veratrum alkaloids, Sod. Nitrocynate, catecholamine depilators (Rauwolfia derivatives)
1950s	Ganglionic blockers, Reserpine Vasodilators (Hydralazine), Monoamine oxidase inhibitors
1961	Guanethidine
1960-1970s	Methyldopa, Alpha blockers, Beta blockers, high celling diuretics, thiazides
1971	Prazosin introduced
1980-1990s	Angiotensin II converting enzymes (ACE) inhibitors, Calcium channel blockers (CCBs), Aliskiren (direct renin inhibitor)

History of Treatment evaluation for hypertension.

RECENT DEVELOPMENTS

SGLT2 Receptor inhibitor:

The selective sodium-glucose cotransporter-2 (SGLT2) receptor inhibitors (empagliflozin, canagliflozin, dapagliflozin) demonstrated BP-lowering effects through various mechanisms including natriuresis, osmotic diuresis, and reduction of the sympathetic tone.[57] The degree of actual BP reduction was quantified in the range of 2 mm Hg to 3 mm Hg in the meta-analysis evaluation of available randomized clinical trials, a modest but sizable impact.[58]

The cardiovascular benefits of these medications are well proven, especially in the treatment and prevention of heart failure, and the additional effect on blood pressure (BP) should be taken into consideration for patient-specific strategy.[59] Glucagon-like peptide 1 receptor agonists (GLP1-RA), revolutionary drugs in

medical management of obesity, positively impact BP in multiple ways above and beyond the expected positive effects of weight loss on hypertension. Indeed, the reduction in BP shown in clinical trials with GLP1-RA was observed early in the treatment, before significant weight loss occurred, suggesting independent action of these medications on hypertension.[60]

The effect of Liraglutide and Semaglutide demonstrated a reduction in systolic BP in the range of 3.5 to 5.6 mm Hg and 3.9 to 6.2 mm Hg, respectively in their pivotal randomized clinical trials.[61] The proposed mechanisms for these antihypertensive effects might include natriuresis and increased urinary output, direct vasodilation via receptors in blood vessels, decreased sympathetic activity, or improve endothelial function through the resolution of negative effects of hyperglycaemia.[62]

These classes represent an important ancillary medical strategy to optimize blood pressure control in high-risk populations in which multiple comorbidities such as obesity, type 2 diabetes mellitus, and metabolic syndrome might be adequately addressed at the same time.[63]

Endothelin Receptor Antagonists:

Endothelin regulates vascular tone and BP, producing a powerful vasoconstrictor effect and contributing to the pathogenesis of hypertension. It causes neurohormonal and sympathetic activation, hypertensive end-organ damage, fibrosis, endothelial dysfunction, and increased aldosterone synthesis and secretion. [64,65]

Aprocinentan

A blocker of both endothelin-A and endothelin-B receptors with a very long pharmacological half-life (about 44 hours), proved more effective than placebo and lisinopril. [66]

This antihypertensive agent seems to exert additional mechanisms beyond the expected beneficial effects of sustained BP-lowering action (including a decrease in renal vascular resistance and left ventricular hypertrophy) supporting the hypothesis that this new agent could expand our antihypertensive arsenal against resistant hypertension.[65,67] Indeed, Aprocinentan in patients with resistant hypertension is currently under investigation in the PRECISION phase III trial (Clinical Trials identifier: NCT03541174)

Renal Denervation:

Renal sympathetic overactivity contributes to the development and progression of hypertension. Renal denervation in experimental models of hypertension has been shown to reduce BP and improve renal function. Renal artery denervation has a strong physiological rationale to justify a strong BP-lowering effect. [68-70]

Recently, several new antihypertensive drugs have been developed, such as the angiotensin receptor neprilysin inhibitor, sacubitril/valsartan[71,72], new mineralocorticoid receptor blockades with a nonsteroidal structure such as Esaxerenone [73] and Finerenone [74] and SGLT2 inhibitor [75], which have been introduced in clinical practice to reduce the risk for cardiovascular outcomes including heart failure and effectively reduces 24-hour Blood pressure including nighttime and morning BP readings [76]. In addition, an aminopeptidase A inhibitor that has central effects on vasopressin, a combined endothelin A and B receptor blocker, and an aldosterone synthase inhibitor devoid of glucocorticoid activity, are involved in the ongoing recruitment of Phase III trials. [77,78]

Conclusion:

Hypertension is a major cause of premature death worldwide. One of the main causes of death and morbidity in the world is hypertension. 15% of people worldwide suffer from hypertension, and the majority of these persons either don't get any therapy at all or, if they do, don't meet their blood pressure goals. Many studies have demonstrated, and many guidelines consistently advises, that the primary factor influencing the decrease of adverse cardiovascular events is the total degree of blood pressure drop rather than the usage of a particular class of antihypertensive medications. Blood Pressure control that is more consistent can be achieved by using multiple drug therapy as the initial approach and strategies to improve patient compliance, such as one-time dosing, using well-tolerated medications, or switching to generic versions of more affordable medications.

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