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New Drugs in the Treatment of Hypertension and Resistant Hypertension: A Review of Therapies

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Abstract
Advancements in pharmacotherapy for hypertension (HTN) have led to the development of new drug classes and innovative supportive treatments. Aprocitentan, an endothelin receptor antagonist, has demonstrated promising effects in managing resistant hypertension, as evidenced by the PRECISION study [1]. Another notable innovation is firibastat, an aminopeptidase A inhibitor, which reduces the activity of the renin-angiotensin system by modulating angiotensin II conversion in the brain. Studies on firibastat suggest its potential in reducing blood pressure in primary hypertensive patients [2].
In the treatment of resistant HTN, newer forms of aldosterone inhibitors, such as esaxerenone, have shown greater selectivity compared to spironolactone, reducing the risk of side effects [3]. Additionally, baxdrostat, a potassium salt of aldosterone synthase inhibitor, decreases aldosterone production and improves blood pressure control [1].
Adjunctive therapies, including renal denervation and baroreceptor stimulation, are being investigated for their efficacy in reducing resistance to medication in patients with resistant HTN. Research suggests that these interventions may be particularly beneficial for patients who do not respond to standard pharmacological treatments [4].
Further research into these pharmacological and procedural therapies is crucial for optimizing hypertension management strategies.

Keywords: hypertension, aprocitentan, resistant hypertension, aminopeptidase a, endothelin antagonists. NHE.

Introduction

Hypertension (HT) is one of the most common cardiovascular conditions and represents a significant risk factor for the development of cardiovascular diseases. In Poland, the prevalence of hypertension is estimated to affect approximately 30-40% of the adult population [5].
The treatment of hypertension is critical for reducing the risk of cardiovascular complications.

Current guidelines published after 2020, by both the European Society of Cardiology (ESC) and other international organizations, emphasize the importance of a personalized approach to therapy. This approach should not only consider blood pressure values but also take into account the presence of other risk factors, such as diabetes, dyslipidemia, and kidney disease [6].
In recent years, there has been significant progress in the development of therapeutic strategies for the treatment of hypertension. New classes of medications, such as SGLT-2 inhibitors, have been incorporated into standard treatment regimens. Additionally, non-pharmacological therapies, including lifestyle modifications, have gained increasing importance in the management of hypertension. These modifications encompass a reduction in salt intake, increased physical activity, and weight reduction, all of which play a crucial role in managing blood pressure effectively [7].
The aim of this review article is to discuss the latest advancements in the treatment of hypertension, with a particular focus on pharmacological strategies, newly introduced medications, and non-pharmacological approaches. The article will also present the current guidelines and future prospects for the development of hypertension therapies.

Epidemiology
Hypertension is a significant global health issue. According to 2024 estimates, around 1.28 billion adults aged 30-79 worldwide are affected by hypertension [8]. In the United States, according to the American Heart Association, approximately 122.4 million adults, or 47% of the adult population, have hypertension [9].
The increasing prevalence of hypertension is closely associated with various risk factors, including age, obesity, physical inactivity, and a diet high in salt [8]. It is important to note that the majority of individuals with hypertension do not experience symptoms, which complicates the early detection and treatment of this condition [8], [10].

Etiology
Hypertension (HT) is a multifactorial condition, with its etiology involving genetic, environmental, and physiological factors. The etiology of hypertension can be categorized into two main types: primary (essential) hypertension and secondary hypertension. Primary hypertension accounts for approximately 90-95% of all cases, while secondary hypertension results from underlying diseases or disorders.

Primary hypertension has a complex etiology, involving the interaction of several factors. These include:
Genetic predispositions: Meta-analytic studies suggest that certain genetic variants are associated with the risk of developing hypertension. Genetic factors may include polymorphisms that affect the regulation of the renin-angiotensin-aldosterone system (RAAS) and sodium metabolism [5], [7], [11], [12].

Environmental factors: A diet high in salt, excessive alcohol consumption, smoking, and lack of physical activity contribute to the development of hypertension.

In particular, meta-analyses indicate that reducing salt intake by 1 gram per day can lower mean blood pressure by 5-7 mmHg in patients with hypertension [5], [13], [14].
Obesity and insulin resistance: Obesity is strongly correlated with hypertension. The underlying mechanisms include an increase in plasma volume, heightened sympathetic nervous system activity, and alterations in kidney function [7], [15].

Dysfunction of the nervous and hormonal systems: Increased sympathetic nervous system activity and disturbances in the renin-angiotensin-aldosterone system (RAAS) can lead to an elevation in blood pressure through mechanisms such as sodium retention, increased blood volume, and vasoconstriction [7], [11], [1].

Secondary hypertension is a result of existing conditions, such as:
Kidney diseases: Chronic kidney disease (CKD) is the most common cause of secondary hypertension. The mechanisms involved include impaired filtration and sodium retention. Additionally, kidney dysfunction can activate the renin-angiotensin-aldosterone system (RAAS), further exacerbating hypertension by promoting vasoconstriction and sodium retention [17], [18].

Endocrine disorders: Secondary hypertension may result from conditions such as hyperaldosteronism (e.g., Conn's syndrome), Cushing's disease, or pheochromocytomas [13], [16], [19].

Medications and substances: Certain medications, such as corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and illicit substances (e.g., cocaine), can contribute to elevated blood pressure.
Meta-analytic studies confirm that the treatment of hypertension, including both pharmacological therapy and lifestyle modifications, significantly reduces the risk of cardiovascular complications, such as strokes and heart attacks [5], [7].

Pathophysiology
The mechanism of hypertension is complex and involves multiple physiological systems. One of the key elements in the pathophysiology of hypertension is arterial stiffness, where changes in the structure and function of the arterial walls play a major role [20]. Chronic high blood pressure increases collagen production while degrading elastin in the arterial walls, significantly impairing the artery's ability to stretch and contract [21], [22].
Another crucial mechanism in the pathophysiology of hypertension is the excessive activity of the sympathetic nervous system (SNS). Research suggests that heightened SNS activity contributes to elevated blood pressure through several mechanisms: vasoconstriction, increased heart rate and renin release [23]. Sympathetic activation during sleep leads to a morning increase in blood pressure, raising cardiovascular risk in patients with hypertension [23], [24].
Activation of the renin-angiotensin-aldosterone system (RAAS) plays a key role in the mechanism of hypertension. Increased activity of this system leads to vasoconstriction and sodium retention.

Persistent RAAS activation can result in vascular remodeling and target organ damage, such as left ventricular hypertrophy (LVH) and renal dysfunction [5], [7], [16], [19], [21], [25].

Classical Antihypertensive Treatment

Angiotensin-converting enzyme inhibitors (ACE-I) & Angiotensin II receptor blockers (ARB)

Meta-analyses published in 2021 and later confirm that inhibitors of the renin-angiotensin-aldosterone system (RAAS), including both angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARBs), have a beneficial effect on blood pressure and other hemodynamic parameters. Studies have demonstrated that RAAS inhibitors effectively lower blood pressure in the arteries, which is directly associated with a reduced risk of cardiovascular complications such as stroke and heart attack. Furthermore, these medications have been shown to be more effective in reducing arterial stiffness, a critical marker of vascular health in individuals with hypertension [25], [26], [27], [28].

Calcium Channel Blockers (CCB)

Recent analyses have demonstrated that calcium channel blockers (CCBs), particularly when combined with other antihypertensive medications, effectively reduce the risk of cardiovascular events. A 2022 meta-analysis highlighted that CCBs, when used in conjunction with RAAS inhibitors (such as ACE inhibitors or ARBs), show significant improvement in managing resistant hypertension. This combination therapy not only lowers blood pressure but also positively affects central arterial pressure. Improved central blood pressure is associated with enhanced vascular function and a reduced risk of stroke [25], [26], [27], [29].

Thiazide diuretics & thiazide-like diuretics

Although thiazide diuretics are older-generation drugs, their effectiveness in lowering blood pressure is still supported by research. However, new data suggest that compared to newer medications such as ACE inhibitors (ACE-I), angiotensin II receptor blockers (ARB), and calcium channel blockers (CCB), diuretics have a lesser impact on blood pressure. This may explain somewhat poorer outcomes in reducing the risk of cardiovascular complications in certain patients [25], [26], [30], [31].

Beta-blockers

Recent meta-analyses suggest that, while beta-blockers are effective in treating patients with coronary artery disease, they may be less effective compared to other drug classes in reducing the risk of stroke and mortality in patients with hypertension. It is now considered that beta-blockers should primarily be used in patients with concomitant heart disease, rather than as first-line agents in the monotherapy of hypertension [25], [26], [32], [33], [34].

Aldosterone antagonists

Studies published after 2021 confirm that aldosterone antagonists, such as spironolactone, are effective in the treatment of resistant hypertension.

Spironolactone, when used in patients for whom other antihypertensive medications do not provide the desired effects, results in significant benefits in lowering blood pressure, especially when combined with other antihypertensive drugs. This approach has been shown to be particularly beneficial in patients with difficult-to-control hypertension, providing an additional therapeutic option in managing this condition effectively [25], [26], [35], [36].

New Drugs as Adjunctive Therapy for Hypertension and Resistant Hypertension

Endothelin antagonists

Endothelin is a potent vasoconstrictor peptide produced by endothelial cells in blood vessels. It exerts its effects primarily through the ET-A and ET-B receptors located on smooth muscle cells and endothelial cells. In the treatment of hypertension, especially resistant hypertension, medications such as aprocitentan, bosentan, ambrisentan, and macitentan have proven effective. For instance, in the PRECISION trial, aprocitentan reduced blood pressure by an average of 15.3 mmHg, compared to a reduction of 3.8 mmHg with placebo (97.5% CI -6.8 to -0.8, p=0.0042) [37]. Their action involves vasodilation, reduction in smooth muscle cell proliferation, and limitation of fluid retention. These medications are particularly effective in treating pulmonary hypertension. By blocking endothelin receptors, they help relax blood vessels, reducing blood pressure and improving circulation. Their therapeutic benefits extend to various forms of hypertension, especially in resistant cases [37], [38], [39].

Caffeine

According to multiple studies conducted before 2020, caffeine has been shown to raise blood pressure. This effect is believed to occur due to the stimulation of the nervous system, which leads to vasoconstriction (narrowing of the blood vessels) [40]. Recent studies suggest that caffeine may also have a diuretic effect, which can lead to a reduction in fluid retention and potentially contribute to lowering blood pressure [41]. Research has shown that caffeine, particularly from coffee, may reduce the development of hypertension by approximately 7% (95% CI: 0.88, 0.97; $I2$: 22.3%) [42]. Han M. and colleagues, in their analysis of 25 independent cohort studies, demonstrated that caffeine does not have a significant impact on the development of hypertension. (95% CI, 0.90–1.05; $I^2 = 58.0\%$; n = 13), recent research suggests that caffeine, especially when consumed through coffee, may actually lower blood pressure and reduce the risk of developing hypertension. (RR, 0.93; 95% CI, 0.87-0.98; $I^2 = 4.6\%$; n = 5) [43].

Phytotherapy

Phytotherapy, which involves the use of medicinal plants and their extracts, is increasingly considered as an alternative or complementary approach to conventional treatments for hypertension. Research suggests that certain herbs and plants possess the potential to lower blood pressure through various biological mechanisms [44].

The allicin in garlic helps to dilate blood vessels and improve blood flow. Meta-analyses have shown that garlic supplementation can reduce systolic blood pressure by approximately 8-10 mmHg and diastolic blood pressure by 6-8 mmHg in patients with hypertension [45].

Hibiscus flowers have diuretic and vasodilatory properties, which aid in the regulation of blood pressure. Hibiscus works by inhibiting the angiotensin-converting enzyme (ACE), similar to the action of ACE inhibitors used in hypertension treatment. Clinical studies suggest that drinking hibiscus tea can lead to a reduction in systolic blood pressure by 7-10 mmHg and diastolic blood pressure by 3-6 mmHg [46].

Flavonoids and catechins found in green tea may have a beneficial impact on blood pressure. The mechanism of action involves improving endothelial function, which promotes the relaxation of blood vessels and leads to a reduction in blood pressure. Some studies have shown that regular consumption of green tea can lower systolic blood pressure by approximately 2-3 mmHg [47].

Lemon balm (Melissa officinalis) is renowned for its calming properties. Due to its sedative effects, it can help lower blood pressure by promoting relaxation of the nervous system, which in turn leads to vasodilation (relaxation of the smooth muscle in blood vessels). In addition to its ability to reduce blood pressure, lemon balm has a variety of other health benefits, including anti-inflammatory, antioxidant, and antispasmodic actions [48].

Flaxseed oil is rich in omega-3 fatty acids, which have well-documented effects in reducing blood pressure. Regular consumption of flaxseed oil may aid in lowering blood pressure, particularly in patients with hypertension. Studies show that its use can decrease systolic blood pressure by approximately 2-3 mmHg and diastolic blood pressure by about 2 mmHg. These effects are attributed to the anti-inflammatory and vascular benefits of omega-3 fatty acids, which support the relaxation and dilation of blood vessels [49].

Extra virgin olive oil, particularly rich in polyphenols, has anti-inflammatory and antioxidant properties. Regular consumption of olive oil, especially within the context of the Mediterranean diet, is associated with lower blood pressure. Studies indicate that polyphenols in olive oil, such as oleuropein and hydroxytyrosol, help reduce oxidative stress and inflammation, which in turn promotes better vascular health and contributes to the reduction of systolic and diastolic blood pressure levels [50].

Depression Treatment

Antidepressant medications, while primarily used for mood regulation, can also impact the cardiovascular system, including blood pressure. Some antidepressants have been found to lower blood pressure, particularly those that affect neurotransmitters like serotonin and norepinephrine [51], [52], [53].

Tricyclic antidepressants (TCAs), such as amitriptyline and clomipramine, exert their effects on adrenergic, cholinergic, and histaminergic receptors. Specifically, their antagonistic action on alpha-adrenergic receptors results in vasodilation, which can lower blood pressure, particularly in the form of orthostatic hypotension [52], [53].

Mirtazapine acts as an antagonist of alpha-2 adrenergic receptors, which leads to increased release of norepinephrine and serotonin. Additionally, it blocks serotonin receptors 5-HT2 and 5-HT3. This combined action enhances the release of neurotransmitters, potentially alleviating symptoms of depression and anxiety. Furthermore, its sedative and vasodilatory effects can result in a reduction of blood pressure, particularly in individuals experiencing high levels of stress [51], [53], [54].

Monoamine oxidase inhibitors (MAOIs), such as phenelzine and tranylcypromine, inhibit the enzyme monoamine oxidase (MAO), which is responsible for breaking down catecholamines, including norepinephrine, dopamine, and serotonin. Their effect on blood pressure is complex and dual: by inhibiting MAO, these drugs increase the levels of neurotransmitters in the brain, leading to a reduction in the tone of blood vessels and a possible decrease in blood pressure. However, in specific conditions, such as the consumption of foods rich in tyramine (e.g., aged cheese, cured meats), MAOIs can lead to a dangerous increase in the release of norepinephrine, potentially triggering a hypertensive crisis. This can result in a rapid and severe increase in blood pressure, a condition known as "cheese reaction" or tyramine-induced hypertensive crisis [51], [54].

Trazodone is a serotonin receptor antagonist, specifically targeting 5-HT2 receptors, and acts as a serotonin reuptake inhibitor. Additionally, trazodone functions as an alpha-adrenergic receptor antagonist. This dual action can lead to vasodilation, or relaxation of the smooth muscle in blood vessels, which may contribute to a reduction in blood pressure [54], [55].

Agomelatine acts as an agonist at the melatonin receptors MT1 and MT2, and as an antagonist at the serotonin 5-HT2C receptors. Its effects on the circadian rhythm and stress reduction can indirectly contribute to lowering blood pressure. By improving sleep patterns and modulating the stress response, agomelatine may help to reduce factors that contribute to elevated blood pressure [52], [55].

Cognitive Behavioral Therapy (CBT)

Cognitive Behavioral Therapy (CBT) is a well-established psychotherapy method that is effective in reducing stress, anxiety, and depression-factors that contribute to increased blood pressure. Research increasingly shows that CBT may also have direct benefits in lowering blood pressure, especially in individuals with hypertension who also experience emotional difficulties [56], [57].

Research suggests that Cognitive Behavioral Therapy (CBT) is effective in reducing both systolic and diastolic blood pressure in patients with hypertension who also suffer from depression or anxiety. For example, a systematic review found that CBT interventions are comparable to pharmacological therapies in alleviating psychological symptoms and have a significant positive impact on blood pressure outcomes, especially in short-term studies.

Furthermore, CBT applied over a period of 8-10 weeks has been shown to lead to marked improvements in blood pressure parameters, particularly in individuals experiencing high levels of stress and anxiety. This underscores CBT's potential as a valuable non-pharmacological approach for managing hypertension in patients with emotional distress [56], [57], [58].

Aminopeptidase A

Aminopeptidase A (APA) plays a crucial role in the regulation of blood pressure through its involvement in the renin-angiotensin system (RAS) in the brain. This enzyme converts angiotensin II into angiotensin III, which activates AT1 angiotensin receptors, thereby increasing sympathetic nervous system activity and raising blood pressure.

Inhibiting APA with drugs like firibastat reduces the production of angiotensin III, leading to a decrease in sympathetic nervous system overactivity and a subsequent reduction in blood pressure [59], [60]. Recent studies on firibastat, a selective inhibitor of aminopeptidase A (APA), have demonstrated its efficacy in normalizing blood pressure in patients with hypertension. In phase II clinical trials, firibastat was shown to lower blood pressure in patients of diverse ethnic backgrounds. Furthermore, animal model studies revealed that firibastat reduced the activity of the renin-angiotensin system (RAS), which is involved in blood pressure regulation. Additionally, it helped prevent cardiac hypertrophy and fibrosis, common complications associated with prolonged high blood pressure [59], [61].

Sodium - Hydrogen Exchanger (NHE)

The sodium-hydrogen exchanger (NHE), particularly the NHE3 isoform, plays a crucial role in the regulation of sodium and water balance in the kidneys, which is directly involved in the pathophysiology of hypertension. NHE3 primarily mediates the reabsorption of sodium in the proximal tubules of the kidneys. By inhibiting NHE3, sodium reabsorption is reduced, which enhances natriuresis (sodium excretion) and ultimately lowers blood pressure. This mechanism is being explored as a potential therapeutic target for managing hypertension, especially in patients where conventional treatments are not sufficiently effective [62], [63], [64], [65].

Meta-analyses and clinical review studies emphasize that pharmacological inhibition of NHE3, such as with drugs used in the treatment of chronic kidney disease (CKD) or diabetes, leads to a moderate reduction in blood pressure. Particularly noteworthy are the studies on sodium-glucose cotransporter 2 (SGLT2) inhibitors, which also affect NHE3 activity. These mechanisms contribute to a reduction in blood pressure, typically by 2-4 mmHg, in trials involving patients with type 2 diabetes and chronic kidney disease [62], [63].

Sphingolipids

Sphingosine and its phosphorylated form, sphingosine-1-phosphate (S1P), play a complex role in the regulation of blood pressure. As a bioactive lipid, S1P exerts its effects through specific receptors (S1PR1, S1PR2, and S1PR3) located in endothelial cells and smooth muscle cells of blood vessels. Depending on which receptor is activated and the physiological conditions present, S1P can either lower or raise blood pressure. This dual action is linked to its influence on vascular tone, endothelial function, and inflammation, which are all key factors in blood pressure regulation [66], [67].

Although S1P has a protective effect on the endothelium, activation of other receptors (e.g., S1PR2, S1PR3) may lead to opposite effects, such as vasoconstriction and increased blood pressure. This suggests a complex regulatory role of S1P in vascular tone and blood pressure. Therefore, further research into balancing these signaling pathways is crucial for the development of effective therapies that can selectively modulate S1P receptor activity to achieve desired outcomes in blood pressure regulation [66], [68].

Studies suggest that modulating the activity of sphingosine and its derivatives could represent a promising new strategy for treating hypertension. However, further research is needed, especially regarding the specific roles of different receptor types and their functions in the body [67], [68].

Gut Microbiome

The gut microbiome has been increasingly recognized as a significant factor in the regulation of blood pressure, with emerging research suggesting a potential role in the development of hypertension. Studies have shown that dysbiosis, or an imbalance in gut microbial composition, is linked to elevated blood pressure and other cardiovascular risks. Specifically, changes in the abundance of certain bacterial species, such as reduced levels of *Lactobacillus* species, have been observed in individuals with hypertension, while the supplementation of these beneficial microbes may help alleviate high blood pressure [69], [70], [71].

The gut microbiota influences blood pressure through various mechanisms, including the production of short-chain fatty acids (SCFAs) like acetate and butyrate, which have been shown to have vasodilatory effects. These SCFAs can promote the production of beneficial metabolites that improve endothelial function and reduce inflammation, both of which are crucial in managing blood pressure [70], [71].

Summary

The text provides an overview of various adjunctive therapies for hypertension, focusing on both pharmaceutical and non-pharmaceutical options. Endothelin antagonists like aprocitentan and bosentan help lower blood pressure by blocking endothelin receptors, leading to vasodilation and reduced smooth muscle proliferation. These drugs are particularly useful in resistant hypertension and pulmonary hypertension. Caffeine, though traditionally thought to increase blood pressure, may have a diuretic effect and reduce hypertension risk when consumed through coffee. Phytotherapy, using herbs like garlic, hibiscus, and green tea, offers natural alternatives that can reduce blood pressure through vasodilation, antioxidant, and anti-inflammatory effects. Depression treatments such as certain antidepressants (e.g., tricyclics and mirtazapine) can also lower blood pressure by affecting vascular tone. Cognitive Behavioral Therapy (CBT) is shown to reduce both systolic and diastolic blood pressure, particularly in patients with emotional stress. Additional emerging treatments like aminopeptidase A inhibitors (e.g., firibastat), NHE inhibitors, and the modulation of sphingolipids provide promising new avenues for managing hypertension. Lastly, the gut microbiome plays a role in blood pressure regulation, with beneficial bacteria potentially reducing hypertension.

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