Review

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Pharmacological Research Progress of Novel Antihypertensive Drugs

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Cardiovascular disease stands as the leading cause of death globally, with hypertension emerging as an independent risk factor for its development. The worldwide prevalence of hypertension hovers around 30%, encompassing a staggering 1.2 billion patients, and continues to escalate annually. Medication plays a pivotal role in managing hypertension, not only effectively regulating blood pressure (BP) but also substantially mitigating the occurrence of cardiovascular and cerebrovascular diseases. This review comprehensively outlines the categories, mechanisms, clinical applications, and drawbacks of conventional antihypertensive drugs. It delves into the five primary pharmacological classifications, namely β-receptor blockers, calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and diuretics. The emphasis is placed on elucidating the mechanisms, advantages, and research progress of novel antihypertensive drugs targeting emerging areas. These include mineralocorticoid receptor antagonists (MRAs), atrial natriuretic peptides (ANPs), neutral endopeptidase inhibitors (NEPIs), sodium-dependent glucose transporter 2 inhibitors (SGLT-2Is), glucagon-like peptide-1 receptor agonists (GLP-1RAs), endothelin receptor antagonists (ERAs), soluble guanylate cyclase (sGC) agonists, brain aminopeptidase A inhibitors (APAIs), and small interfering ribonucleic acids (siRNAs) targeting hepatic angiotensinogen. Compared to conventional antihypertensive drugs, these novel alternatives exhibit favorable antihypertensive effects with minimal adverse reactions. This review serves as a valuable reference for future research and the clinical application of antihypertensive drugs.

Keywords: antihypertension; conventional antihypertensive drugs; novel antihypertensive drugs

Introduction

In 2019, the prevalence of hypertension among adults aged 30–79 years was 32% for women and 34% for men, totaling nearly 1.278 billion cases [1]. In China, the prevalence of hypertension among individuals aged 18 and above stands at approximately 27.9%, with the affected population reaching nearly 300 million. The total cost of hospitalization for cardiovascular and cerebrovascular diseases in China in 2019 amounted to 313.366 billion yuan. Of this, the cost attributed to hypertension alone was approximately 16.721 billion yuan, imposing a substantial economic burden on families, society, and the nation [2].

Hypertension has the potential to inflict damage on the arteries of vital organs such as the heart, brain, and kidneys, giving rise to a spectrum of cardio-cerebrovascular diseases. These include but are not limited to stroke, angina pectoris, myocardial infarction, heart failure, left ventricular hypertrophy, atrial fibrillation, and renal failure [3].

Currently, five types of antihypertensive drugs are commonly employed in clinical settings: β-receptor blockers, calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and diuretics [4] (Fig. 1). While these medications effectively regulate blood pressure (BP), they are not without their share of toxic side effects (Table 1, Ref. [5–9]). For instance, prolonged use of ACEIs (such as captopril and enalapril) may lead to dry cough, hyperkalemia, and dizziness [5]. ARBs (like losartan and valsartan) are associated with hyperkalemia [5,6], and CCBs (including nifedipine and amlodipine) can induce headaches, ankle edema, and facial flushing [5,7,8]. Long-term use of β-receptor blockers (such as propranolol and metoprolol) can result in sinus bradycardia, atrioventricular block, and bronchospasms [7], while diuretics (like hydrochlorothiazide and furosemide) may cause hypokalemia, hyperuricemia, and other adverse reactions [9].

Table 1. Antihypertensive mechanisms and adverse reactions of conventional antihypertensive drugs.

Drugs	Mechanism of antihypertensive action	Side effects	References
CCBs	inhibiting extracellular calcium influx	headaches, tachycardia, redness	[5,7,8]
ACEIs	inhibiting the angiotensin-converting enzyme	dry cough, hyperkalemia, and dizziness	[5]
ARBs	blocking the binding of angiotensin II and AT1 receptor	hyperkalemia	[5,6]
Diuretics	increasing urine volume	hypokalemia, hyperuricemia	[9]
β-receptor blockers	inhibiting the over-activation of the sympathetic nervous system	sinus bradycardia, atrioventricular block, and bronchospasms	[7]

ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers; ACEIs, angiotensin-converting enzyme inhibitors; AT1, angiotensin II receptor 1.

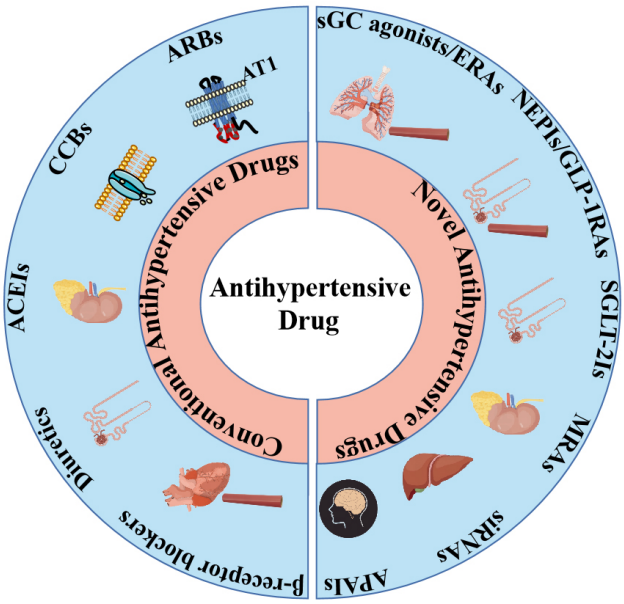

Fig. 1. Classification of conventional antihypertensive drugs and novel antihypertensive drugs. Fig. 1 was drawn with PhotoshopCS4 11.0, Adobe Systems Inc, San Jose, CA, USA. ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers; ACEIs, angiotensin-converting enzyme inhibitors; sGC, soluble guanylate cyclase; ERAs, endothelin receptor antagonists; NEPIs, neutral endopeptidase inhibitors; GLP-1RAs, glucagon-like peptide-1 receptor agonists; SGLT-2Is, sodium-dependent glucose transporter 2 inhibitors; MRAs, mineralocorticoid receptor antagonists; siRNAs, small interfering ribonucleic acids; APAIs, brain aminopeptidase A inhibitors.

Given these potential drawbacks, the development of novel hypertensive drugs holds significant importance for patients. Mineralocorticoid receptor antagonists (MRAs), atrial natriuretic peptides (ANPs), neutral endopeptidase inhibitors (NEPIs), sodium-dependent glucose transporter 2 inhibitors (SGLT-2Is), glucagon-like peptide-1 receptor agonists (GLP-1RAs), endothelin receptor antagonists (ERAs), soluble guanylate cyclase (sGC) agonists, brain aminopeptidase A inhibitors (APAIs), and small interfering ribonucleic acids (siRNAs) targeting hepatic angiotensinogen (AGT) represent the future direction of antihypertensive drug development (Fig. 1). These promising alternatives aim to not only sustainably and smoothly reduce BP but also exhibit certain protective effects on the heart, brain, kidneys, and blood vessels.

This review provides an extensive examination of the categories, mechanisms, disadvantages, and clinical applications of commonly used antihypertensive drugs. Furthermore, it underscores the latest advancements in novel antihypertensive drugs and their potential advantages over conventional counterparts. The information serves as a valuable reference for future research and clinical applications.

Conventional Antihypertensive Drugs

Calcium Channel Blockers (CCBs)

Calcium channel blockers (CCBs), exemplified by nifedipine and nicardipine, consist of dihydropyridine and non-dihydropyridine types. They predominantly exert antihypertensive effects by blocking calcium channels in the cell membrane of vascular smooth muscle cells (VSMCs), thereby inhibiting extracellular calcium influx, inducing blood vessel dilation, and reducing peripheral vascular resistance [10] (Table 1). CCBs offer the advantage of sustained action, enabling a 24-hour smooth reduction in BP or prompt and stable effects. However, they may lead to adverse reactions such as headaches, tachycardia, and facial flushing.

A randomized controlled trial has indicated that CCBs might elevate the incidence of cardiovascular events and congestive heart failure events when compared to diuretics [11]. Additionally, CCBs demonstrate a reduction in cardiovascular mortality compared to β-receptor blockers [11]. In comparison to ACEIs, CCBs can lower the risk of stroke and increase the occurrence of congestive heart failure events [11]. When compared with ARBs, CCBs exhibit a reduced incidence of myocardial infarction but an increased occurrence of congestive heart failure events [11]. Clinical recommendations often include the combined use of CCBs and folic acid, providing a more precise approach to BP reduction and cardiovascular disease prevention [12] (Fig. 2).

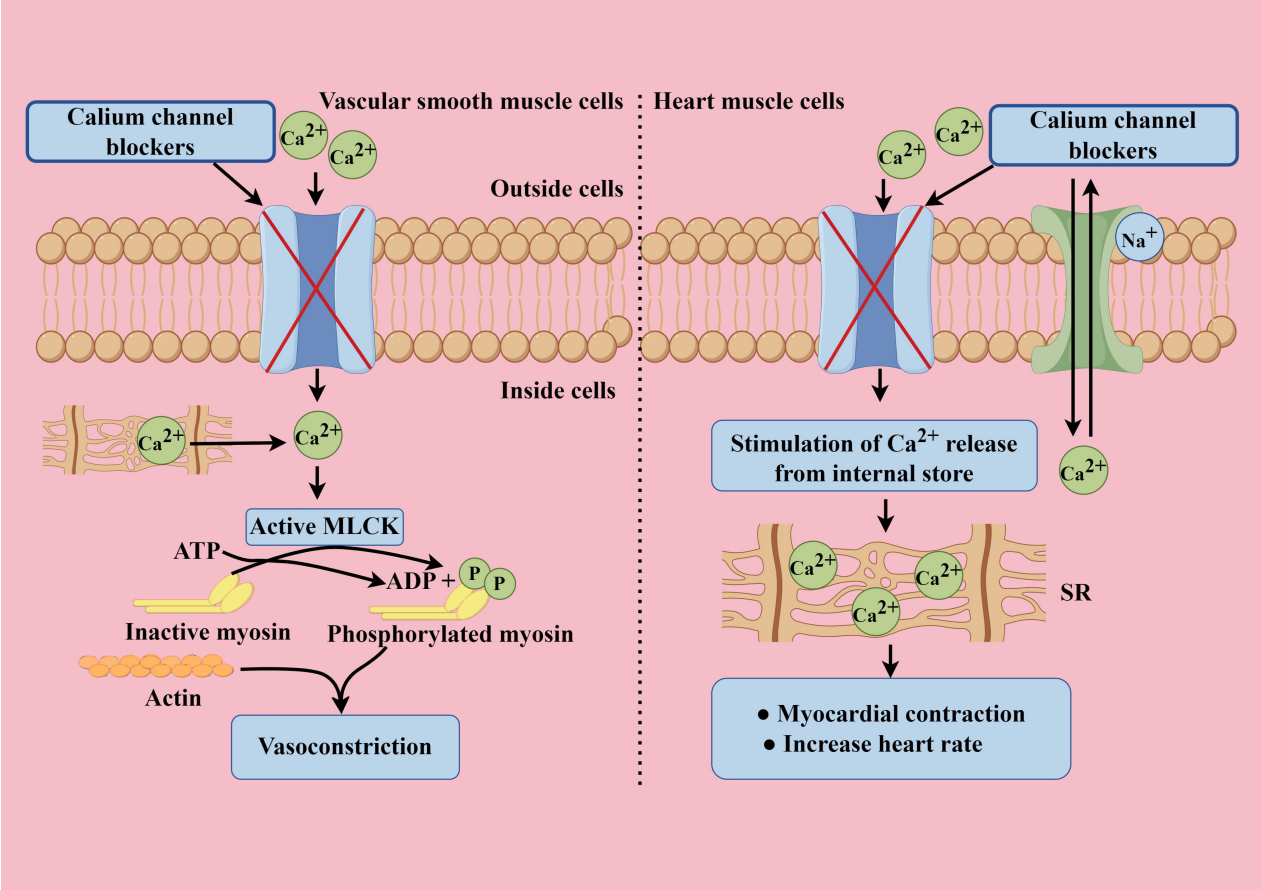

Fig. 2. Mechanism of calcium channel blockers (CCBs). CCBs mainly block the calcium channels on the membrane of myocardial and vascular smooth muscle cells (VSMCs), inhibit the influx of extracellular calcium ions, thus relax VSMCs, and finally reduce the blood pressure. Additionally, they weaken the myocardial contractility and reduce the heart rates. Fig. 2 was drawn with PhotoshopCS4 11.0, Adobe Systems Inc, San Jose, CA, USA. MLCK, myosin light chain kinase; ATP, adenosine triphosphate; ADP, adenosine diphosphate; SR, sarcoplasmic reticulum.

Angiotensin-Converting Enzyme Inhibitors (ACEIs)

ACEIs function by acting on the renin-angiotensin-aldosterone system (RAAS), inhibiting the angiotensin-converting enzyme (ACE), and thereby impeding the conversion of angiotensin I (AngI) to AngII, resulting in antihypertensive effects [13] (Table 1). Beyond their BP-lowering capabilities, ACEIs exhibit cardioprotective properties. They enhance ventricular remodeling by inhibiting vasoconstriction and reducing the preload and afterload of the heart. This makes ACEIs particularly suitable for patients with heart failure complicated by hypertension [13].

Commonly utilized ACEIs include captopril, enalapril, perindopril, and others. Each drug possesses distinct characteristics. Captopril, for instance, is a short-acting antihypertensive drug that rapidly lowers BP, making it suitable for acute increases in BP [14]. However, it may be associated with side effects such as an increase in creatinine or cough during treatment [5,14] (Table 1). Perindopril, with the longest half-life, offers prolonged antihypertensive effects, stability, and minimal blood pressure fluctuations. Notably, perindopril is a prodrug, necessitating hepatic metabolism to activate its antihypertensive components [14]. Enalapril, a potent ACEI, is commonly administered intravenously, providing persistent and effective hypertension reduction [14] (Fig. 3).

Research indicates that ACEIs used for antihypertensive purposes can contribute to a reduction in mortality among patients with hypertension. In a study by Lam *et al.* [15], the investigation focused on 614 hypertensive patients with coronavirus disease 2019 (COVID-19) during their hospitalization. The patients were categorized into two groups: the first group, comprising hypertensive patients who were not using ACEIs at home, and the second group, including those who were using ACEIs. Within the latter group, patients were further divided into those who discontinued ACEIs usage during hospitalization and those who continued ACEIs treatment.

The outcomes revealed notable differences in mortality rates between the two subgroups. Specifically, patients who stopped using ACEIs during hospitalization exhibited

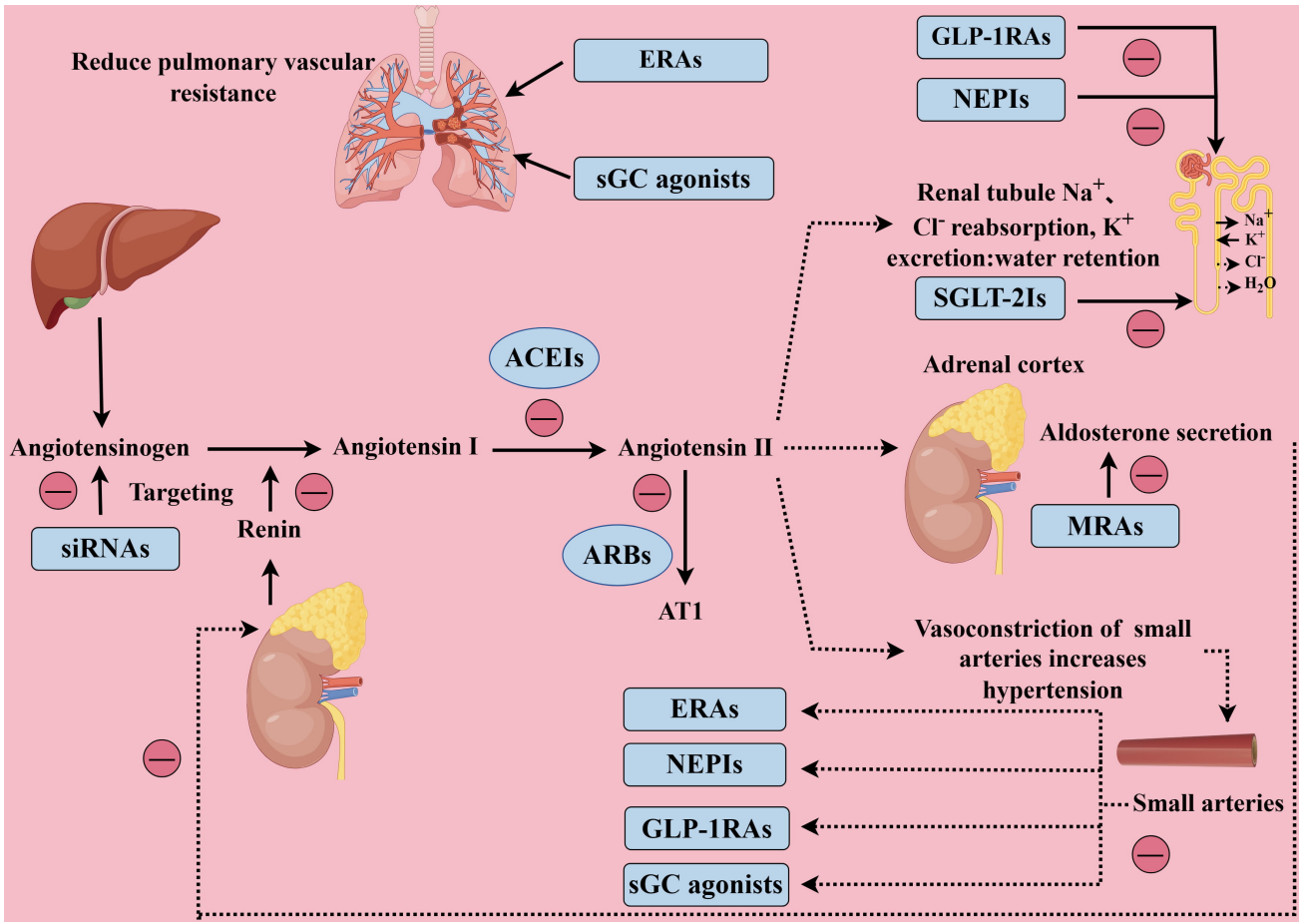

Fig. 3. Mechanism of drugs targeting the RAAS. Fig. 3 was drawn with PhotoshopCS4 11.0, Adobe Systems Inc, San Jose, CA, USA. ERAs, endothelin receptor agonists; sGC, soluble guanylate cyclase; GLP-1RAs, glucagon-like peptide-1 receptor agonists; NEPIs, neutral endopeptidase inhibitors; SGLT-2Is, sodium-dependent glucose transporter 2 inhibitors; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; MRAs, mineralocorticoid receptor antagonists; AT1, angiotensin II receptor 1; siRNAs, small interference ribonucleic acids; RAAS, renin-angiotensin-aldosterone system.

a mortality rate of 28%, while those who continued ACEIs treatment showed a significantly lower mortality rate of 6%. These findings suggest a substantial reduction in the mortality rate among hypertensive patients with COVID-19 who persist with ACEIs usage during their hospital stay.

Angiotensin Receptor Blockers (ARBs)

ARBs function as blockers of the angiotensin receptor, selectively inhibiting the binding of AngII to its receptor 1 (AT1 type). This action weakens the influence of angiotensin on vascular contraction, leading to vasodilation and a subsequent reduction in BP [16]. Moreover, ARBs can diminish aldosterone secretion by inhibiting the activation of RAAS, thereby reducing water and sodium retention and achieving an antihypertensive effect [16].

ARBs offer a sustained and significant BP-lowering effect. They demonstrate the ability to reverse damage to target organs caused by hypertension, such as reducing microalbuminuria, delaying cardiac wall thickening, minimizing ventricular overdilation, and decreasing the incidence of heart failure. Importantly, ARBs can address the adverse side effects associated with ACEIs, such as cough and angioedema. Commonly used ARBs include losartan, valsartan, candesartan, telmisartan, and irbesartan. Among these, candesartan stands out for its superior antihypertensive efficacy, achieving notable effects even at lower doses [16,17].

Studies, such as the one conducted by Jackson *et al.* [18], have explored the impact of sacubitril-valsartan on patients with refractory hypertension. In a randomized trial comparing sacubitril-valsartan and valsartan alone, after 16 weeks of treatment, the sacubitril-valsartan group exhibited a higher proportion of patients with controlled systolic blood pressure (47.9%) compared to the valsartan control group (34.3%). This suggests that for patients with refractory hypertension, sacubitril-valsartan proves more effective than valsartan alone [18].

Diuretics

The utilization of diuretics as antihypertensive agents has consistently been a primary choice in first-line treat-

ment. The principal mechanism of their antihypertensive action involves increasing urine volume, diminishing the retention of sodium ions and water in the body, thereby reducing blood volume and cardiac preload. This, in turn, alleviates the burden on the heart and leads to a lowering of BP [19] (Table 1).

Clinical diuretics commonly used can be categorized into various types. Loop diuretics, such as furosemide, predominantly exert antihypertensive and diuretic effects by inhibiting the reabsorption of sodium and chloride in the medullary loop. These are frequently employed in patients with heart failure [20]. Thiazide diuretics, like hydrochlorothiazide and indapamide, induce natriuretic diuresis by inhibiting the reabsorption of chloride and sodium in the distal convoluted tubules of the kidney. As standalone antihypertensive therapy, thiazide diuretics have been recommended as first-line drugs in national guidelines for an extended period [20].

Potassium-preserving diuretics, including triamterene and spironolactone, increase sodium ion and water excretion, thus lowering blood volume and lower BP. These diuretics achieve this by antagonizing aldosterone receptors and inhibiting sodium and potassium pumps on the renal tubular epithelial cell membrane, without causing potassium loss in the body [20]. Osmotic diuretics, such as mannitol and sorbitol, reduce water reabsorption by elevating solute concentration in renal tubules and collecting ducts, playing a diuretic role. Typically, they are well-tolerated and commonly used to treat conditions like brain edema and reduce intracranial pressure [20].

In recent years, certain scholars have introduced a novel class of diuretics known as renal outer medullary potassium inhibitors (ROMKIs). There is compelling evidence supporting the potential use of selective ROMKIs in the treatment of hypertension in the future [21,22]. ROMK channels are expressed in two distinct regions of the kidney: the thick segment of the ascending branch of the medullary loop of Henle and the cortical collecting duct (CCD) [21,23]. This channel functions as a highly permeable and weakly inward rectifier potassium channel, differing from typical voltage-gated channels. It plays a pivotal role in promoting the reabsorption of sodium ions and the secretion of potassium ions in the CCD [24].

In a study involving salt-sensitive hypertensive patients [22], participants were categorized into four groups: a high-salt diet control group, ROMKI B group (3 mg/kg/day), ROMKI B group (10 mg/kg/day), and a hydrochlorothiazide group (2 mg/kg/day). These groups were part of both prophylactic (high-salt diet from week 1 to week 9) and therapeutic studies (high-salt diet from week 5 to week 9). The results indicate that ROMKIs consistently lowered BP, and its antihypertensive efficacy surpassed that of hydrochlorothiazide. This suggests that ROMKIs may hold promise as a novel antihypertensive drug, particularly for patients with salt-sensitive hypertension.

β-Receptor Blockers

β-receptor blockers are widely employed in the clinical treatment of hypertension. They not only effectively control BP but also reduce myocardial contractility, myocardial oxygen consumption, and cardiac output [25,26]. Clinical study has identified sympathetic nervous system hyperactivity as a crucial factor in the pathogenesis of hypertension and the primary cause of target organ damage [25]. β-receptor blockers can efficiently inhibit the overactivation of the sympathetic nervous system, thereby contributing to BP reduction [25]. The specific mechanism encompasses the following aspects: (1) Blocking β-receptors in the central nervous system weakens the activity of excitatory neurons, thereby inhibiting peripheral sympathetic tension. This results in reduced peripheral vascular resistance and the manifestation of the antihypertensive effect. (2) Blocking renal β2-receptors decreases the release of renin, thereby inhibiting the RAAS and achieving an antihypertensive effect. (3) Blocking β-adrenoceptors in the heart reduces heart rate and myocardial contractility, leading to a decrease in cardiac output and subsequently lowering BP. (4) Diminishing peripheral sympathetic activity, β-receptor blockers block the β-receptors on the presynaptic membrane of norepinephrine (NE) nerve terminals. This action reduces the release of NE, contributing to a reduction in BP [26–28] (Fig. 4) (Table 1).

Because β-receptor blockers primarily reduce BP by diminishing sympathetic activity, they are more appropriate for young and middle-aged individuals with diastolic hypertension. Research indicates that β-receptor blockers not only lower blood pressure but also contribute to the delay of ventricular remodeling. Consequently, they have the potential to reverse left ventricular hypertrophy caused by hypertension [25]. Representative drugs among β-receptor blockers include metoprolol, which is well-suited for young and middle-aged patients with a rapid heart rate, particularly those with hypertension and concurrent coronary heart disease, angina pectoris, or myocardial infarction. Nebivolol, on the other hand, is a selective β1-adrenoceptor antagonist with vasodilating activity. It finds application in the treatment of mild-to-moderate hypertension and is also suitable for managing angina pectoris and hypertrophic cardiomyopathy [26,28].

A study presented at the annual meeting of the American Society of Hypertension (ASH) revealed that, when compared to amlodipine/metoprolol (A/M), amlodipine/nebivolol (A/N) demonstrated an advantage in reducing mean 24-hour ambulatory blood pressure (ABP) and resulted in less ankle edema in patients. The study enrolled a total of 41 hypertensive adults, initiating four weeks of amlodipine monotherapy (10 mg/day). Subsequently, they received low-dose nebivolol (10 mg/day) or metoprolol (50 mg/day) for four weeks, followed by high-dose nebivolol (20 mg/day) or metoprolol (100 mg/day) in the subsequent four weeks. After 12 weeks of treatment, the A/N group ex-

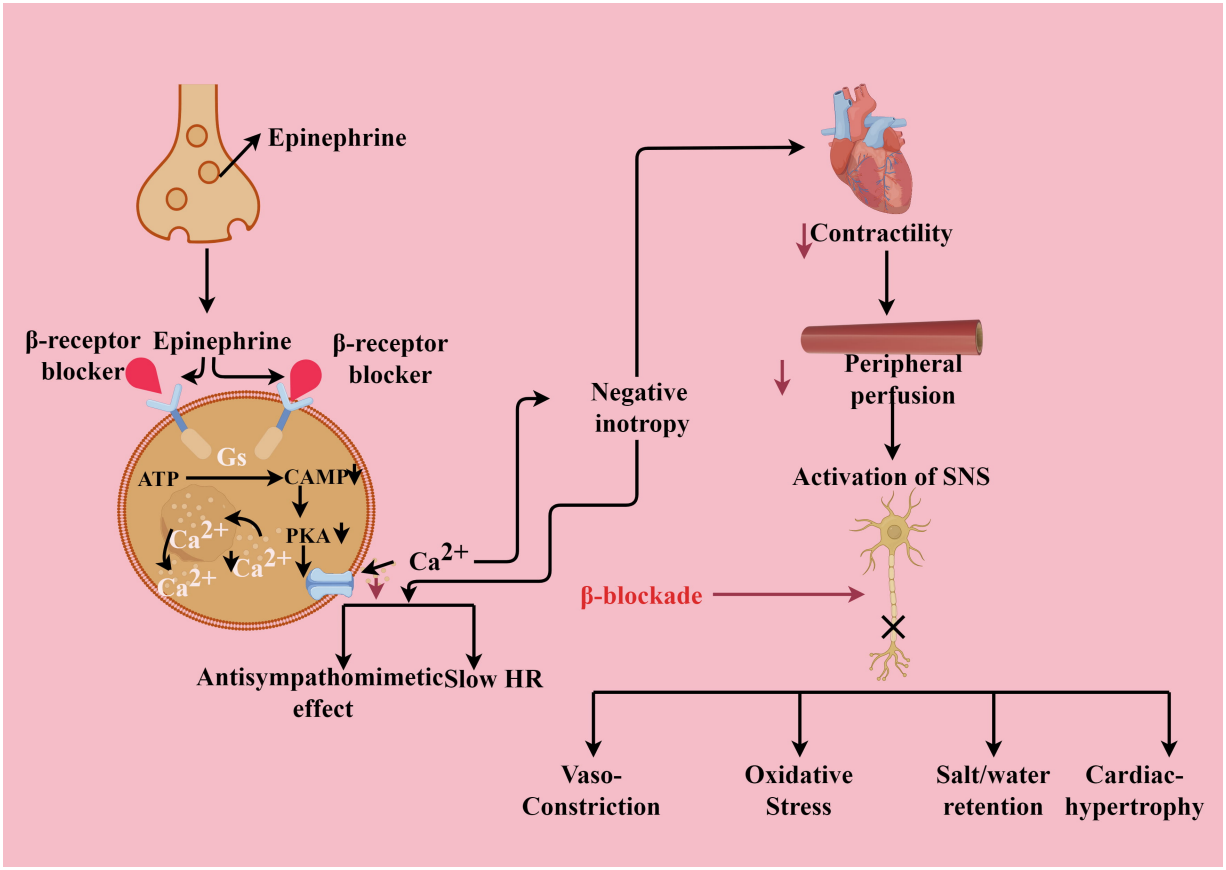

Fig. 4. Mechanism of β-receptor blockers. β-receptor blockers exert their antihypertensive effects mainly by blocking β-receptors in the sympathetic nervous system, heart and kidney. Fig. 4 was drawn with PhotoshopCS4 11.0, Adobe Systems Inc, San Jose, CA, USA. SNS, sympathetic nervous system; HR, heart rate; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A.

hibited a reduction of 27 mmHg and 16 mmHg in mean 24-hour dynamic systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively, with a mean difference of 133.8 gms in measurements of leg edema. In the A/M group, mean 24-hour dynamic SBP and DBP decreased by 24 mmHg and 13 mmHg, respectively, with a mean difference of 148.5 gms in measurements of leg edema [29]. Consequently, it appears that nebivolol may offer superior efficacy and safety compared to metoprolol in the treatment of hypertension.

Novel Antihypertensive Drugs

Mineralocorticoid Receptor Antagonists (MRAs)

The mineralocorticoid receptor (MR) is widely distributed in various cells, including cardiomyocytes, vascular endothelial cells, and VSMCs [30]. Research indicates that an abnormal increase in plasma aldosterone and a high salt load can lead to the excessive activation of MR, resulting in water and sodium retention. This, in turn, contributes to elevated BP and the development of cardiovascular and renal fibrosis [31]. Previous studies have reported similar findings, demonstrating that MR in mouse VSMCs can directly regulate BP. Mice with specific MR deletion in vascular smooth muscle cells exhibited decreased BP, reduced vascular myogenic tension, AngII-induced vasoconstriction, and decreased expression and activity of L-type calcium channels in VSMCs, with no change in renal sodium treatment [31]. These findings underscore that blocking the excessive activation of MR can effectively regulate BP and protect cardiac and renal function [30,31] (Table 2, Ref. [30–42]). In recent years, MRAs have been frequently utilized in the treatment of essential hypertension and aldosteronism. MRAs commonly used in clinical practice can be categorized into steroids, such as spironolactone and eplerenone, and non-steroids, such as finerenone. Steroidal glucocorticoid receptor antagonists competitively inhibit the binding of aldosterone and salt corticosteroid receptors, exerting a potassium-preserving and diuretic effect. Spironolactone, a first-generation MRA, can partially reverse cardiac remodeling during diuresis and is suitable for patients with hypertension and heart failure. Its more prevalent side effects include hyperkalemia and decreased BP [30] (Table 2).

Eplerenone, a second-generation steroid corticosteroid receptor antagonist, exerts its effects by antagoniz-

Table 2. Antihypertensive mechanisms and adverse reactions of novel antihypertensive drugs.

Drugs	Mechanism of action	Adverse reactions	References
MRAs	blocking the excessive activation of MR	hyperkalemia and decreased blood pressure	[30,31]
NEPIs	prolong the biological half-life of ANP	angioedema	[31,32]
SGLT-2Is	resulting in enhanced osmotic diuresis and enhanced urinary sodium excretion	increasing the risk of urinary and genital infections	[33]
GLP-1RAs	inhibiting the RAAS, increasing urine output and urinary sodium excretion	headache, dizziness, nausea and vomiting	[34,35]
ERAs	inhibiting ET-1 receptor	mild-to-moderate fluid retention	[36,37]
sGC agonists	increasing the sensitivity of sGC to NO, reducing systemic blood pressure	headache, flushing, orthostatic hypotension, nasal congestion	[38,39]
APAIs	inhibiting aminopeptidase	headaches and skin reactions	[40]
siRNAs	targeting AGT	minor skin injection site reactions	[41,42]

MR, mineralocorticoid receptor; ANP, atrial natriuretic peptides; ET-1, Endothelin-1; NO, nitric oxide; AGT, angiotensinogen.

ing aldosterone receptors. It has demonstrated clear efficacy in the treatment of hypertension, heart failure, and myocardial infarction, characterized by minimal adverse reactions and good tolerance. One notable advantage is its ability to significantly reduce severe hypertension that remains uncontrolled by various antihypertensive drugs, with a more pronounced decrease in SBP [43,44]. Research indicates that eplerenone is particularly effective in essential hypertension patients who have not experienced benefits from ACEIs and ARBs [43]. It is important to note that both eplerenone and similar drugs carry the risk of hyperkalemia and potential deterioration of renal function, which limits their widespread use. Additionally, the success of eplerenone has paved the way for the development of third-generation MRAs based on non-steroidal dihydropyridines.

In recent years, new non-steroidal mineralocorticoid receptor antagonists, namely finerenone and esaxerenone, have gained prominence. In comparison to MRAs, these non-steroidal counterparts exhibit the capability to lower both blood glucose and BP, while simultaneously preventing inflammation and fibrosis in the heart and kidneys [45,46].

A review has indicated that finerenone exhibits higher selectivity and activity compared to spironolactone and eplerenone. Its ability to inhibit the overactivation of glucocorticoid receptors is noteworthy, contributing to the reduction of remodeling, fibrosis, and inflammation, particularly in the cardiovascular and renal systems. Due to its high selectivity, finerenone does not significantly increase serum potassium levels when decreasing proteinuria, brain natriuretic peptide (BNP), and N-terminal pro-B-type natriuretic peptide [45].

In a study by Kolkhof *et al.* [46], the combination of the non-steroidal mineralocorticoid receptor antagonist finerenone and SGLT-2Is, as opposed to their respective low-dose monotherapy, significantly reduced plasma creatinine and serum uric acid. After seven weeks, the survival rates in the placebo group and the low-dose combination groups were 50% and 93%, respectively. Additionally, after five weeks, the combination of finerenone and low-dose therapy significantly reduced the SBP of rats [46]. These findings further validate the protective effect of finerenone on the cardiovascular and renal systems.

Esaxerenone, a novel nonsteroidal mineralocorticoid receptor antagonist, effectively and specifically inhibits the receptor activity of excess corticosteroids. It has received approval for the treatment of essential hypertension and diabetic nephropathy in Japan. In a phase 3 clinical trial involving patients with type 2 diabetes (T2D) and microalbuminuria, the addition of esaxerenone to the hypertension treatment regimen resulted in a reduction in the progression of albuminuria [44].

Research has demonstrated that when esaxerenone was used as a monotherapy, the sitting BP decreased by an average of –18.5/–8.8 mmHg from baseline to the end of treatment. Additionally, when esaxerenone was used as an adjunct therapy alongside renin-angiotensin system inhibitors, the average reduction was –17.8/–8.1 mmHg. In summary, whether used as a single treatment or in combination, esaxerenone exhibits a significant antihypertensive effect with acceptable tolerability in hypertensive patients, whether they have moderate renal insufficiency or normal renal function. Notably, no patients discontinued treatment due to elevated blood potassium levels or decreased renal function during esaxerenone treatment, indicating its suitability for hypertensive patients with moderate renal insufficiency [47].

In general, novel non-steroidal mineralocorticoid receptor antagonists exhibit superior characteristics when compared to conventional drugs targeting the RAAS system. Firstly, they can act more selectively on aldosterone receptors, reducing unnecessary pharmacological side effects. Simultaneously, these agents demonstrate commendable cardiovascular and kidney protective effects. Moreover, the use of such drugs does not induce excessive adverse effects on the metabolism and regulation of the normal human body. Consequently, they can be considered as effective options for the treatment of hypertension [44–47].

Atrial Natriuretic Peptides (ANPs) and Neutral Endopeptidase Inhibitors (NEPIs)

ANP, also known as atrial peptide, is a recently discovered polypeptide. It is primarily synthesized, stored, and released by cardiomyocytes and is widely distributed in peripheral tissues and organs such as the heart, pituitary, lung, adrenal gland, among others [48]. Numerous researchers have identified ANP's potent antihypertensive effects, although there is no consistent conclusion regarding its antihypertensive mechanism. Possible mechanisms of action include the following [48] (Table 2): (1) ANP inhibits the release of Ca^{2+} from the sarcoplasmic reticulum and the inflow of Ca^{2+}, thereby suppressing the vasoconstrictive effects of AngII; (2) ANP reduces circulating blood volume and cardiac output through natriuresis and diuresis; (3) ANP increases the content of cyclic guanosine monophosphate in tissue and plasma, acting as the mediator for vasodilation induced by various chemicals and hormones.

ANP is primarily degraded by neutral endopeptidase (NEP). Despite its short half-life, neutral endopeptidase inhibitors (NEPIs) can extend the biological half-life of ANP. Consequently, NEPIs hold promise as a new therapeutic drug class for patients with hypertension [32]. However, due to their limited efficacy when used alone, these inhibitors are often combined with drugs that inhibit the RAAS to achieve clinical benefits.

Omapatrilat, an AngII receptor-NEP dual inhibitor, stands out as one of the representative drugs in this category. Early clinical trials have confirmed its potent inhibitory effects on both ACE and NEP *in vitro* within a low dose range, showcasing a sustained and robust antihypertensive and cardioprotective effect [49]. Furthermore, a large randomized clinical trial involving over 25,000 patients with hypertension evaluated the efficacy and safety of omapatrilat, demonstrating a certain antihypertensive effect. However, it was disappointing to find that the incidence of angioedema was three times higher than that of enalapril (2.17% *vs* 0.68%), with angioedema occurring earlier and at higher severity in the omapatrilat group [49] (Table 2). These findings serve as a theoretical basis for the development of new AngII receptor-NEP dual inhibitors. Sacubitril/valsartan, for instance, exclusively inhibits enkephalinase without affecting other enzymes involved in bradykinin catabolism, thereby reducing the risk of angioedema.

Sacubitril/valsartan (LCZ696), developed by Novartis, is a novel antihypertensive drug classified as an AngII receptor-NEP dual inhibitor. Among the nine randomized controlled trials involving 6765 subjects, eight compared the efficacy and safety of LCZ696 with ARBs. Evidence suggests that LCZ696 achieves a superior BP control rate compared to ARBs (odds ratio (OR): 1.24; 95% confidence interval (CI): 1.14–1.35), particularly in reducing systolic and 24-hour average ambulatory SBP and 24-hour average static DBP. Additionally, there was no significant difference in the incidence of adverse events between the LCZ696 group and the control group [50]. Consequently, LCZ696 is recognized as a potential drug for the control of hypertension and its complications.

S086, a new AngII receptor-NEP dual inhibitor developed by Salubris Company, is aimed at treating hypertension and chronic heart failure. In a study conducted by Sun *et al.* [51], a rat hypertension model and telemetry system were utilized to investigate the circadian rhythm of BP in Dahl salt-sensitive hypertensive rats, evaluating the antihypertensive effect of S086. The results indicated that the antihypertensive effect of oral S086 was dose-dependent ($p < 0.001$) compared to LCZ696, and the antihypertensive effect of oral S086 was more significant than that of oral LCZ696. This study confirms that S086 can effectively reduce BP in DSS hypertensive rats, providing a reliable basis for further clinical research [51].

Sodium-Dependent Glucose Transporter 2 Inhibitors (SGLT-2Is)

SGLTs are widely distributed membrane proteins that facilitate the entry of Na^+ and glucose into cells through the Na^+/K^+ATPase, positioned on both sides of the proximal tubular endothelial cells and the plasma membrane at the base of the kidney [52]. Currently, six SGLT proteins have been identified, namely SGLT-1-6, with SGLT-1 and SGLT-2 primarily involved in glucose reabsorption in the kidney [52].

SGLT-2, situated mainly on the S1 and S2 segments of proximal convoluted renal tubules, is a low-affinity, high-load Na^+ glucose transporter. It plays a crucial role in reabsorbing 90% of glucose, making it the primary glucose transporter in the kidney [53]. Studies have demonstrated that SGLT-2Is can lower blood pressure by inhibiting the reabsorption of sodium ions and glucose in the original urine, leading to increased osmotic diuresis and enhanced urinary sodium excretion [33] (Table 2). Furthermore, SGLT-2Is can impact the pathogenesis of hypertension in diabetic patients, improve arterial stiffness and endothelial dysfunction, reduce oxidative stress, and enhance circadian rhythm and blood pressure variability [33,54]. Previous research has indicated that the antihypertensive efficacy of these hypoglycemic drugs is significantly greater than that of GLP-1RAs. A meta-analysis of data from seven randomized controlled trials (2381 patients) revealed that SGLT-2Is reduced 24-hour dynamic systolic/diastolic blood pressure (3.62/1.70 mmHg) irrespective of the SGLT-2Is dose. Its antihypertensive effect is comparable to that of a low dose of hydrochlorothiazide [55]. Consequently, the inhibition of SGLT-2 emerges as a potential strategy for hypertension treatment.

Currently, five types of SGLT-2Is are widely utilized in the treatment of diabetes. These include Bexagliflozin (Brenzavvy), Canagliflozin (Invokana), Dapagliflozin (Farxiga), Empagliflozin (Jardiance), Ertugliflozin

(Steglatro) [52]. Canagliflozin holds the distinction of being the first SGLT-2I approved by the Food and Drug Administration (FDA) for improving blood glucose in adult patients with T2D [52]. In a placebo-controlled phase 3 clinical trial involving 2250 patients with T2D, subjects were administered 100 mg and 300 mg doses of canagliflozin or a placebo once daily for 26 weeks. The average weight and SBP of patients in the 100 mg and 300 mg canagliflozin groups were more than 5% lower than those in the placebo group. Additionally, the SBP in the 300 mg canagliflozin group was 50% lower than that in the placebo group. This study affirms that weight loss induced by canagliflozin contributes to the reduction in SBP [56].

The antihypertensive mechanism of dapagliflozin is found to be multifaceted. On one hand, dapagliflozin reduces BP and improves cardiac function by directly lowering blood glucose levels. This reduction in hyperglycemia helps mitigate the toxic damage to blood vessels and myocardium, while also inhibiting the increase in arterial stiffness and myocardial fibrosis [33]. On the other hand, dapagliflozin directly inhibits the activity of the RAAS. By inhibiting the co-transport of sodium and glucose, it induces osmotic diuresis. Additionally, dapagliflozin indirectly inhibits RAAS activity, delays the process of atherosclerosis, improves vascular endothelial function, and exerts an antihypertensive effect. Notably, it significantly reduces both pre- and post-load myocardial oxygen consumption in patients [33]. A prospective, double-blind, placebo-controlled clinical study spanning 12 weeks found that dapagliflozin significantly reduced SBP, diminished vasoconstriction, and increased vasodilation in patients with T2D. These results suggest that dapagliflozin may contribute to improving outcomes in hypertension and congestive heart failure [57]. In a study on T2D patients with nocturnal hypertension, empagliflozin demonstrated a significant antihypertensive effect compared to placebo, leading to a steady decrease in 24-hour ambulatory BP [34].

The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME) study further revealed that empagliflozin effectively reduced both SBP and DBP. Moreover, it decreased the risk of primary endpoint events, cardiovascular death, and exacerbation of heart failure [34,58]. In a clinical trial, Packer *et al.* [59] found that empagliflozin not only did not increase the incidence of related adverse events such as hypovolemia or deterioration of renal function but also significantly reduced the risk of intensive diuretic therapy. The additional benefits of SGLT-2Is, particularly represented by empagliflozin in reducing BP, are noteworthy and are anticipated to provide new choices and hope for more hypertensive patients in the future.

Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs)

GLP-1RAs represent a class of new hypoglycemic drugs introduced to the market in recent years. Beyond their well-established hypoglycemic effects, these drugs demonstrate additional benefits such as weight reduction, BP-lowering, and protection of the cardiovascular and renal systems [60–62]. Presently, the exact antihypertensive mechanism associated with GLP-1RAs is not fully elucidated. However, studies have indicated that GLP-1RAs can reduce BP by inhibiting the RAAS, and increasing urine output and urinary sodium excretion in spontaneously hypertensive rats [35] (Table 2).

GLP-1RAs are also found to promote the secretion of ANP by elevating the level of cAMP-regulated guanine nucleotide exchange factor II. ANP, in turn, mediates various effects, including increased vascular permeability, induction of VSMCs relaxation, vasodilation, and enhanced renal sodium excretion, all contributing to a reduction in BP [60]. Additionally, other studies have demonstrated that GLP-1RAs possess an anti-proliferative effect on VSMCs and can elevate the level of nitric oxide (NO), dilating blood vessels by reducing oxidative stress, thus further lowering BP [35].

Research has indicated that continuous treatment with GLP-1RAs can lead to a reduction in SBP, with little impact on DBP. Liraglutide, exenatide, and semaglutide are clinically confirmed GLP-1RAs with well-established cardiovascular benefits.

Studies on liraglutide have suggested that it may reduce BP by decreasing body weight, increasing urinary sodium excretion, lowering free fatty acids, and improving endothelial function [61]. In a rat model of osmotic AngII infusion, liraglutide was found to reduce BP by upregulating the expression of endothelial nitric oxide synthase 3 [63]. In a 24-hour blood pressure trial with hypertensive patients having T2D, liraglutide treatment for 5 weeks showed average changes in 24-hour SBP and daytime SBP of –4.72 mmHg and –5.61 mmHg, respectively, compared to baseline. In contrast, the placebo group exhibited changes of 1.02 mmHg and 0.83 mmHg, respectively, suggesting a beneficial effect of short-term liraglutide treatment on SBP [34].

Long-term observational studies on semaglutide have demonstrated its ability to reduce the progression of major adverse cardiovascular events (MACE) and chronic kidney disease (CKD). In a trial involving 47 patients given semaglutide once daily, the drug significantly lowered SBP and improved cardiovascular risk factors after 3 and 6 months. Semaglutide also reduced indicators of renal damage, such as urinary albumin-to-creatinine ratio (UACR), indicating that oral semaglutide may reduce BP by improving the weight of obese patients with T2D [62].

In the Exenatide Study of Cardiovascular Event Lowering, the mean SBP of the exenatide group was 1.6 mmHg lower than that of the placebo group after 6 months of treatment, while the DBP value was 0.3 mmHg higher. Postmortem analysis of 6 randomized controlled trials in the duration series showed that SBP/DBP decreased by 2.8/0.8 mmHg at 24–30 weeks after exenatide treatment [64].

Overall, GLP-1RAs not only effectively reduce blood glucose and induce weight loss but also have a modest effect on BP reduction. They regulate lipid levels and improve renal function. Compared to conventional antihypertensive drugs, GLP-1RAs offer a significant advantage of comprehensive benefits, encompassing weight reduction, SBP reduction, improvement of dyslipidemia, effective blood sugar control, and positive cardiovascular and renal outcomes [35,62–64]. Future research should delve deeper into the physiological interaction mechanisms of GLP-1RAs, exploring their potential molecular mechanisms for improving BP.

Endothelin Receptor Antagonists (ERAs)

Endothelin-1 (ET-1) acts as a potent endogenous vasoconstrictor. Upon binding to its specific receptors, ET-A or ET-B, it triggers the release of calcium ions from the sarcoplasmic reticulum, promoting smooth muscle contraction and vasoconstriction [36]. The robust vasoconstrictive effects of ET-1 are believed to be associated with the pathogenesis of hypertension. Consequently, inhibiting the ET-1 receptor represents a potential therapeutic strategy for managing hypertension [36] (Table 2).

The antihypertensive effects of ERAs were recently confirmed in a meta-analysis comprising 4898 patients, including those endothelin receptor antagonists (ERAs) with selective ET-A and dual ET-A/ET-B. The results demonstrated that, compared with placebo, ERAs induced an average decrease in office SBP and DBP of –6.12 mmHg and –3.81 mmHg, respectively. The differences in 24-hour SBP and DBP were –7.65 mmHg and –5.92 mmHg, respectively. The analysis further affirmed that there was no significant difference in the antihypertensive effect between selective and non-selective antagonists [65].

Aprocitentan, a novel oral dual endothelin receptor antagonist, effectively blocks the binding of ET-1 to the ET-A/ET-B receptor. Previous studies have suggested that this drug could be a powerful tool in combating hypertension through the endothelin signaling pathway [66]. Clozel [66] conducted a study on the antihypertensive effect of aprocitentan in two rodent models: one with hereditary hypertension, normal renin levels, and normal/decreased ET-1 expression; the other simulating refractory hypertension with low renin, high salt, and increased ET-1 expression. In both models, aprocitentan not only decreased mean arterial BP in a long-term and dose-dependent manner but also reduced renal vascular resistance and the incidence of cardiomyopathy. The study also noted that compared with spontaneous hypertension rats (SHRs), the hemodynamic effects on low renin and high salt rats were more significant, suggesting that higher ET-1 production leads to a greater antihypertensive effect of endothelin receptor antagonists.

Phase 2 clinical trial data revealed that aprocitentan significantly reduced blood pressure in patients compared to placebo, and its efficacy was comparable to moderate-dose ACEIs in patients with essential hypertension [67]. The PRECISION study, a double-blind, randomized, multicenter, parallel-group phase 3 study, evaluated the antihypertensive efficacy and safety of aprocitentan in patients with refractory hypertension. The results indicated that the reduction in SBP in the aprocitentan group was significantly better than that in the placebo group, with a difference of –3.8 mmHg in the 12.5 mg group and –3.7 mmHg in the 25-mg group. SBP consistently decreased between weeks 36 and 40, with a difference of –5.8 mmHg between the aprocitentan group and the placebo group, lasting up to 48 weeks. Importantly, aprocitentan was well-tolerated, with the most common adverse event being mild-to-moderate fluid retention [37]. Therefore, aprocitentan holds promise as a new, effective, and well-tolerated antihypertensive agent for patients with refractory hypertension.

Soluble Guanylate Cyclase (sGC) Agonists

sGC is a key transduction enzyme in the nitric oxide-soluble guanylate cyclase-cyclic guanosine monophosphate (NO-sGC-cGMP) signaling pathway [38]. Activated by binding to NO, sGC catalyzes the conversion of guanosine triphosphate to cyclic guanosine monophosphate, acting as a second messenger to activate various downstream effector molecules, leading to vasodilation [38,68] (Table 2). Disruptions in the sGC-mediated signal transduction pathway can result in a range of cardiovascular diseases, including hypertension and heart failure. Some studies have indicated that sGC agonists can enhance the sensitivity of sGC to NO, thereby reducing SBP, pulmonary artery pressure, and pulmonary capillary wedge pressure, making them a promising class of effective antihypertensive drugs [38].

Riociguat and vericiguat are representative agents of sGC agonists. Animal experiments have confirmed that riociguat can reduce BP and protect target organs such as the heart and kidneys in both high-renin and low-renin hypertensive rats [69]. A clinical trial phase I evaluated the safety and efficacy of riociguat in healthy subjects. The results showed that, compared with the placebo group, the DBP and mean arterial BP of healthy subjects who received 1–5 mg riociguat decreased significantly, but the decrease in SBP was not significant [39].

Vericiguat is a widely used sGC agonists in heart failure. At present, it has been approved by the FDA for use alone or in combination with other heart failure treatments. The VICTORIA study confirmed that vericiguat can reduce the hospitalization rate or the composite risk of cardiovascular death in patients with high-risk heart failure with de-

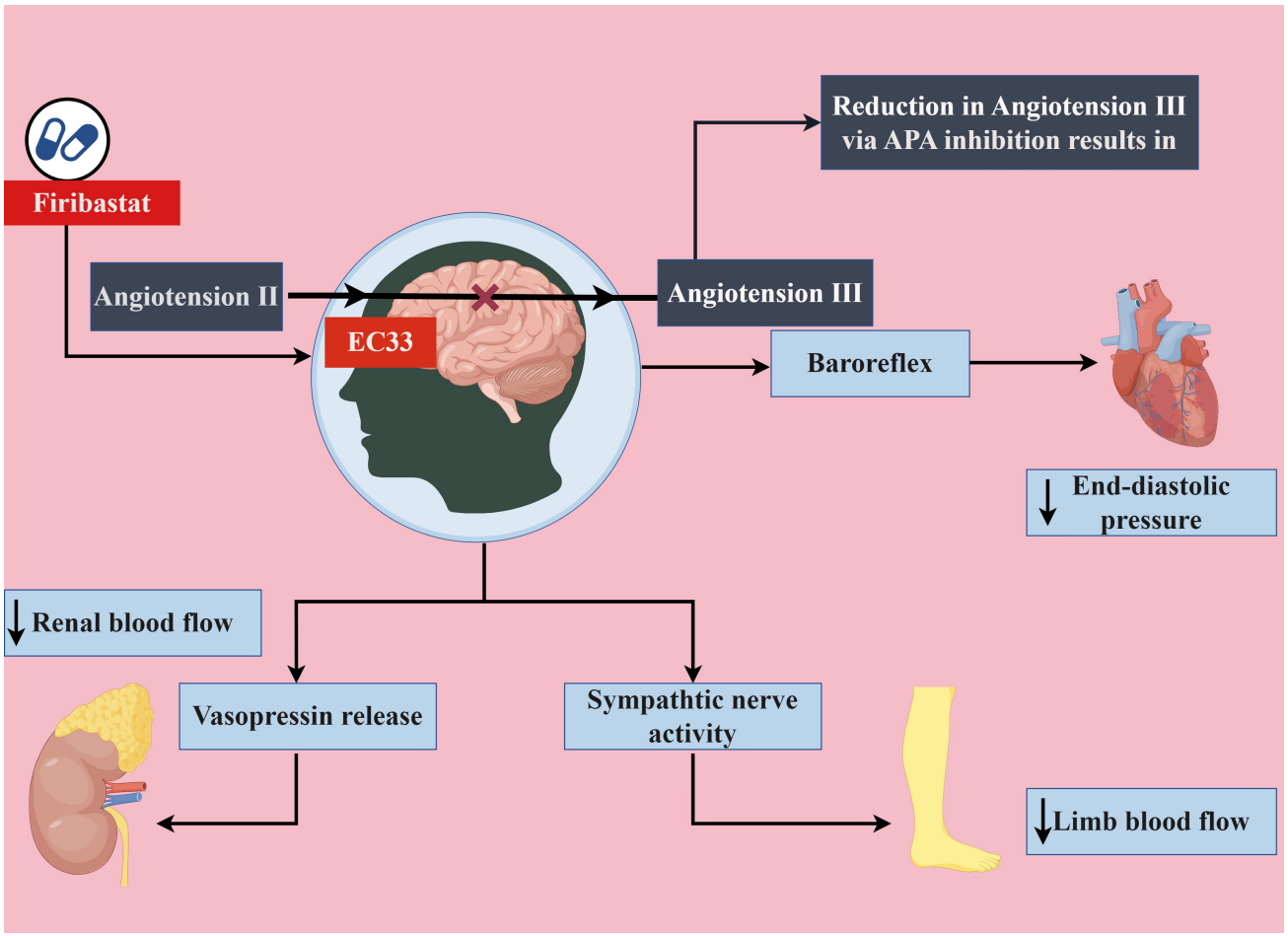

Fig. 5. Schematic diagram of the brain renin-angiotensin system. Fig. 5 was drawn with PhotoshopCS4 11.0, Adobe Systems Inc, San Jose, CA, USA. APA, aminopeptidase A; EC33, 3-amino-4-thio-butyl sulfonate.

creased ejection fraction, providing a new approach for the treatment of patients with heart failure complicated by hypertension [70].

BAY-747 is a highly effective second-generation sGC agonist. In an *in vivo* model of malignant and resistant hypertension, researchers found that BAY-747 could lead to a dose-dependent and persistent decrease in mean arterial BP in SHRs [68]. Additionally, BAY-747 provided additional benefits when administered in combination with traditional antihypertensive drugs. When used in combination with common antihypertensive drugs such as losartan, amlodipine, or spironolactone, or even on top of a triple combination of commonly used antihypertensive drugs, BAY-747 resulted in a further sustained decrease in mean arterial pressure [68]. In a dog model of resistant hypertension, administration of BAY-747 also led to a dose-dependent and sustained decrease in mean arterial BP. This suggests that BAY-747 is an effective sGC agonist with oral bioavailability, providing a new option for patients with hypertension who do not respond to standard treatment [68].

Brain Aminopeptidase A Inhibitors (APAIs)

RAAS is primarily composed of renin, angiotensinogen, ACE, angiotensin, and their respective receptors. This system is present not only in the humoral system but also in various tissues such as the kidney, heart, blood vessels, and brain tissues [71]. Research indicates that the brain's renin-angiotensin system can contribute to an increase in BP, stimulate thirst, encourage water consumption, and regulate pituitary hormone secretion, all of which play a role in the development of hypertension [71].

Mechanistic studies have identified AngIII as a key component of the brain RAAS. AngIII is formed from AngII through the action of aminopeptidase. In the brain, AngIII has the capacity to elevate sympathetic nerve activity, stimulate vasopressin release, and reduce baroreflex sensitivity, ultimately leading to an increase in blood pressure (Table 2). As a result, cerebral APA has been identified as a potential target for the treatment of hypertension [40] (Fig. 5).

RB150 is an orally active prodrug of APAI EC33 (3-amino-4-thio-butyl sulfonate), later renamed QGC001 or firibastat. This compound has the ability to increase urine

volume by reducing the release of antidiuretic hormone, consequently lowering peripheral vascular resistance and resulting in decreased BP [40].

A multicenter, open-label clinical study led by Professor Ferdinand and his team [72] assessed the effects of the brain APAIs firibastat on hypertensive patients who were overweight or obese. In this study, 256 patients were enrolled and received various treatments including firibastat alone or in combination with hydrochlorothiazide. After 8 weeks of treatment, compared with baseline, the subjects' SBP decreased by 9.5 $\pm$ 14.3 mmHg ($p < 0.0001$), and DBP decreased by 4.2 $\pm$ 9.4 mmHg ($p < 0.0001$). In patients treated with firibastat alone, ambulatory office SBP decreased by 9.4 $\pm$ 14.3 mmHg. The results indicated that RB150, either combined with diuretics or used alone, was effective in treating hypertensive patients who were overweight or obese, leading to a quick and significant reduction in BP. Importantly, there were no significant changes in the levels of serum potassium, sodium, and creatinine in the participants, suggesting that firibastat was well-tolerated. The study also highlighted the potential for further investigation of firibastat in patients with abnormal renal function [72].

AI929 is a novel APAI that demonstrates robust inhibitory activity against APA in mice, approximately 10 times more potent than EC33. Notably, AI929 requires only 1/10 of the dose of RB150, positioning it as a highly effective centrally acting APA inhibitory prodrug within the RB150 class [73]. Moreover, AI929 has shown effectiveness in reducing BP without inducing hypokalemia, suggesting potential advantages over traditional diuretics like hydrochlorothiazide and furosemide in maintaining electrolyte balance [73]. Previous research has indicated that APAIs selectively inhibited the RAAS in the brain, without affecting the RAAS in the systemic circulation. This selectivity suggests that APAIs do not induce renal damage, a side effect associated with ACEIs [74]. Studies conducted in the deoxycorticosterone acetate salt hypertensive rat model have further confirmed this property of APAIs. These findings imply that APAIs might be particularly well-suited for patients who are resistant to ACEIs and ARBs in the future [74].

siRNAs Targeting Hepatic Angiotensinogen

The RAAS is a crucial endocrine humoral regulatory system that plays a key role in maintaining BP. Hepatic angiotensinogen (AGT), which, under the influence of renin, generates AngI. AngI, in turn, is converted to AngII through the action of ACE [41]. AngII, being the most potent vasoconstrictor *in vivo*, activates angiotensin receptors, leading to vasoconstriction and, subsequently, an increase in BP. Liver-derived AGT serves as the sole precursor for angiotensin peptides [42]. In theory, inhibiting the production of AGT by hepatocytes could result in a substantial decrease in both AngI and AngII levels in the body. This approach might circumvent the potential escape phenomenon associated with the use of ACEIs or ARBs, potentially leading to a more pronounced reduction in BP compared to these two drug classes [41,42] (Table 2).

The study by Yuan *et al*. [75] demonstrated that the administration of Gal-PEG-Et (GPE) AGT shRNA nanocomplex significantly decreased the expression of mRNA and protein, as well as the levels of serum AGT and AngII in the liver of rats. The reduction in AGT expression occurred at both the gene and protein levels. Moreover, in SHRs treated with GPE-AGT shRNA nanocomplex, there was a significant decrease in caudal arterial pressure after the initial three injections, amounting to (28 $\pm$ 4) mm Hg compared to the pre-treatment levels ($p < 0.01$). This suggests that the nanocomplex effectively reduced AGT expression and resulted in a notable reduction in arterial pressure.

Zilebesiran is a siRNA that targets AGT mRNA. Phase I clinical trials of zilebesiran demonstrated significant, dose-dependent reductions in serum AGT levels compared to the placebo group. Additionally, zilebesiran led to a dose-dependent reduction in SBP. After a single administration of zilebesiran at a dose of 800 mg over 24 weeks, serum AGT levels remained reduced by more than 90%. The average 24-hour SBP consistently showed the largest reduction at –22.5 mmHg, and mean DBP displayed a similar improvement at –10.8 mmHg [42]. Importantly, zilebesiran exhibited good safety over the 24-week period, with only minor skin injection site reactions observed (Table 2). No adverse effects were reported in the heart, brain, or kidneys [42].

KARDIA-1 is a Phase II randomized, double-blind, placebo-controlled, multicenter global dose range exploration study designed to evaluate the efficacy and safety of zilebesiran monotherapy in the treatment of mild to moderate adult hypertension. The study successfully recruited 394 adult patients, and the results revealed that, in comparison to the placebo group, the 24-hour mean SBP of the zilebesiran group exhibited a clinically significant decrease by the third month. Furthermore, the reduction in both the 300 mg and 600 mg dose groups exceeded 15 mmHg ($p < 0.0001$).

The study also achieved a critical secondary endpoint, demonstrating a sustained decline in SBP over six months, supporting the feasibility of quarterly or semi-annual administration. Additionally, the research indicated that zilebesiran effectively and persistently reduced serum AGT levels within a six-month period, along with presenting promising safety and tolerability results [76].

Currently, widely used ACEIs for hypertension, such as pullipes and sartan drugs, often lead to a compensatory increase in renin over prolonged use. Over time, the receptor target of ACEIs action competitively recovers, resulting in RAAS escape, leading to drug resistance and a reduction in antihypertensive efficacy [77]. In contrast, zilebesiran nearly completely depleted hepatic AGT, preventing RAAS

escape and achieving long-term BP control. Furthermore, zilebesiran's antihypertensive effect remained effective for up to six months with a single administration, significantly enhancing adherence to hypertension treatment [78].

The demonstrated efficacy and safety of zilebesiran in hypertension treatment suggest that, as a siRNA formulation of antihypertensive drugs, zilebesiran has the potential to establish robust BP control over an extended period, making it a noteworthy candidate for a new hypertensive drug treatment option.

Summary and Prospect

The global population is experiencing a growing trend of aging, with an escalating proportion of individuals aged 65 years and above. Concurrently, the prevalence of hypertension, a quintessential geriatric ailment, is steadily rising each year. Given the substantial patient demographic and the sustained demand for long-term medication, antihypertensive drugs have garnered acknowledgment for possessing a vast market.

Certain conventional antihypertensive drugs, including β-receptor blockers, CCBs, ACEIs, ARBs, and diuretics, are associated with noticeable adverse reactions. Consequently, the development of new antihypertensive drugs holds significant importance. Existing evidence supports the exploration of novel antihypertensive drugs, such as MRAs, ANPs, NEPIs, SGLT-2Is, GLP-1RAs, ERAs, sGC agonists, APAIs, and siRNAs targeting hepatic AGT, through animal experiments, with some progressing to clinical phases I/II.

Compared to conventional antihypertensive drugs, these novel alternatives exhibit favorable antihypertensive effects with minimal adverse reactions. Post-administration, they seldom induce problems such as dry cough, edema, frequent urination, elevated uric acid, fatigue, or metabolic abnormalities. Simultaneously, they demonstrate the potential to delay renal function deterioration and effectively enhance the prognosis of myocardial infarction. This suggests the promising candidacy of novel drugs in hypertension treatment. Nevertheless, mechanistic reports on these novel antihypertensive drugs are not sufficiently specific, predominantly focusing on animal studies. Therefore, further clinical trials are imperative to comprehensively assess the medicinal value of these emerging drugs.

It is of importance to note that the array of antihypertensive drugs is diverse, and physicians may opt to combine different drug types based on the patient's specific circumstances and requirements to achieve optimal treatment outcomes.

In summary, significant progress has been achieved in the research field of antihypertensive drugs, transitioning from conventional medications to current targeted therapies. Despite these advancements, the treatment and control rates for patients with hypertension remain notably low. Numerous substantial challenges persist in hypertension management, including identifying antihypertensive targets for individuals with refractory hypertension, investigating novel mechanisms of antihypertensive drugs, and ensuring both effectiveness and safety.

Looking ahead, the future research and development direction for new antihypertensive drugs will encompass two key aspects. Firstly, there is a need to explore novel therapeutic targets and develop innovative drugs. Secondly, the focus should be on realizing individualized treatment approaches to enhance therapeutic effectiveness and mitigate potential side effects. Through ongoing and future research endeavors, the goal is to achieve better control of hypertension, addressing the existing challenges in its treatment.

Conclusion

Antihypertensive drugs can effectively control blood pressure to reduce the morbidity and mortality of cardiovascular diseases. Traditional antihypertensive drugs may cause various adverse reactions while effectively controlling blood pressure. New antihypertensive drugs not only focus on lowering blood pressure levels, but also aim to reduce the risk of cardiovascular complications, improve the quality of life of patients, and minimize adverse reactions, which has brought new hope for the treatment of hypertension patients. However, as the research continues to deepen, further clinical validation and long-term observation are needed to ensure the safety and effectiveness of these novel drugs and provide more reliable support for clinical practice.

Abbreviations

A/M, amlodipine/metoprolol; A/N, amlodipine/nebivolol; ABP, ambulatory blood pressure; ACEIs, angiotensin-converting enzyme inhibitors; Ang, angiotensin; ANPs, atrial natriuretic peptides; ARBs, angiotensin receptor blockers; ASH, American Society of Hypertension; BNP, brain natriuretic peptide; BP, blood pressure; CCBs, calcium channel blockers; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; EC33, 3-amino-4-thio-butyl sulfonate; EMPA-REG OUTCOME, The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose; ERAs, endothelin receptor antagonists; FDA, Food and Drug Administration; GLP-1RAs, glucagon-like peptide-1 receptor agonists; GPE, Gal-PEG-Et; MR, mineralocorticoid receptor; MACE, major adverse cardiovascular events; MRAs, mineralocorticoid receptor antagonists; NEPIs, neutral endopeptidase inhibitors; NO-sGC-cGMP, nitric oxide-soluble guanylate cyclase-cyclic guanosine monophosphate; PKA, protein kinase A; RAAS, renin-

angiotensin-aldosterone system; ROMK, renal outer medullary potassium; ROMKIs, renal outer medullary potassium inhibitors; SBP, systolic blood pressure; sGC, soluble guanylate cyclase; SGLT-2Is, sodium-dependent glucose transporter 2 inhibitors; SHRs, spontaneous hypertension rats; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio; VSMCs, vascular smooth muscle cells.

Availability of Data and Materials

Not applicable.

Author Contributions

All authors have contributed significantly. All authors made substantial contributions to conception and design. LH and YZ were responsible for the paper writing. LX, P-QL, H-QC focused on the reference review and analysis. C-XH devoted herself to the reference collection. WQ and H-LC committed themselves to the manuscript revision and polishing. All authors contributed to significant editorial changes in the manuscript. All the authorships are legitimate. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet. 2021; 398: 957–980.

[2] China Cardiovascular Health and Disease Report Writing Group. Summary of Chinese Cardiovascular Health and Disease report 2021. Chinese Journal of Circulation. 2022; 37: 553–578. (In Chinese)

[3] Revision Committee of Chinese Guidelines for Prevention and Treatment of Hypertension. Guidelines for Prevention and treatment of Hypertension in China (2018 revised Edition). Chinese Journal of Cardiology. 2019; 24: 24–56. (In Chinese)

[4] Hypertension Branch of China International Exchange and Promotive Association for Medical and Health Care. Chinese expert advice on the clinical application of Shakubatrizartan in patients with hypertension. Chinese Journal of Hypertension. 2021; 29: 108–114. (In Chinese)

[5] Laurent S. Antihypertensive drugs. Pharmacological Research. 2017; 124: 116–125.

[6] Pioli MR, de Faria AP. Pro-inflammatory Cytokines and Resistant Hypertension: Potential for Novel Treatments? Current Hypertension Reports. 2019; 21: 95.

[7] Sinha AD, Agarwal R. Clinical Pharmacology of Antihypertensive Therapy for the Treatment of Hypertension in CKD. Clinical Journal of the American Society of Nephrology. 2019; 14: 757–764.

[8] Weber MA, Schiffrin EL, White WB, Mann S, Lindholm LH, Kenerson JG, *et al*. Clinical practice guidelines for the management of hypertension in the community a statement by the American Society of Hypertension and the International Society of Hypertension. Journal of Hypertension. 2014; 32: 3–15.

[9] Blowey DL. Diuretics in the treatment of hypertension. Pediatric Nephrology. 2016; 31: 2223–2233.

[10] Smith DK, Lennon RP, Carlsgaard PB. Managing Hypertension Using Combination Therapy. American Family Physician. 2020; 101: 341–349.

[11] Zhu J, Chen N, Zhou M, Guo J, Zhu C, Zhou J, *et al*. Calcium channel blockers versus other classes of drugs for hypertension. The Cochrane Database of Systematic Reviews. 2021; 10: CD003654.

[12] Bao H, Huang X, Li P, Sheng C, Zhang J, Wang Z, *et al*. Combined use of amlodipine and folic acid are significantly more efficacious than amlodipine alone in lowering plasma homocysteine and blood pressure among hypertensive patients with hyperhomocysteinemia and intolerance to ACEI: A multicenter, randomized, double-blind, parallel-controlled clinical trial. Journal of Clinical Hypertension. 2023; 25: 689–699.

[13] Strauss MH, Hall AS, Narkiewicz K. The Combination of Beta-Blockers and ACE Inhibitors Across the Spectrum of Cardiovascular Diseases. Cardiovascular Drugs and Therapy. 2023; 37: 757–770.

[14] Fischer K, Diec S. Once- Versus Twice-Daily Angiotensin-Converting Enzyme Inhibitors for Blood Pressure Control in Adult Patients With Hypertension. Cureus. 2021; 13: e17331.

[15] Lam KW, Chow KW, Vo J, Hou W, Li H, Richman PS, *et al*. Continued In-Hospital Angiotensin-Converting Enzyme Inhibitor and Angiotensin II Receptor Blocker Use in Hypertensive COVID-19 Patients Is Associated With Positive Clinical Outcome. The Journal of Infectious Diseases. 2020; 222: 1256–1264.

[16] Delaitre C, Boisbrun M, Lecat S, Dupuis F. Targeting the Angiotensin II Type 1 Receptor in Cerebrovascular Diseases: Biased Signaling Raises New Hopes. International Journal of Molecular Sciences. 2021; 22: 6738.

[17] Zhang JQ, Yang GH, Zhou X, Liu JX, Shi R, Dong Y, *et al*. Effects of allisartan isoproxil on blood pressure and target organ

injury in patients with mild to moderate essential hypertension. Medicine. 2019; 98: e14907.
[18] Jackson AM, Jhund PS, Anand IS, Düngen HD, Lam CSP, Lefkowitz MP, *et al*. Sacubitril-valsartan as a treatment for apparent resistant hypertension in patients with heart failure and preserved ejection fraction. European Heart Journal. 2021; 42: 3741–3752.
[19] Titko T, Perekhoda L, Drapak I, Tsapko Y. Modern trends in diuretics development. European Journal of Medicinal Chemistry. 2020; 208: 112855.
[20] Arumugham VB, Shahin MH. Therapeutic Uses of Diuretic Agents. StatPearls [Internet]. StatPearls Publishing: Treasure Island (FL). 2023.
[21] Tang H, Zhu Y, Teumelsan N, Walsh SP, Shahripour A, Priest BT, *et al*. Discovery of MK-7145, an Oral Small Molecule ROMK Inhibitor for the Treatment of Hypertension and Heart Failure. ACS Medicinal Chemistry Letters. 2016; 7: 697–701.
[22] Zhou X, Forrest MJ, Sharif-Rodriguez W, Forrest G, Szeto D, Urosevic-Price O, *et al*. Chronic Inhibition of Renal Outer Medullary Potassium Channel Not Only Prevented but Also Reversed Development of Hypertension and End-Organ Damage in Dahl Salt-Sensitive Rats. Hypertension. 2017; 69: 332–338.
[23] Mennitt PA, Wade JB, Ecelbarger CA, Palmer LG, Frindt G. Localization of ROMK channels in the rat kidney. Journal of the American Society of Nephrology. 1997; 8: 1823–1830.
[24] Araujo M, Welch WJ, Zhou X, Sullivan K, Walsh S, Pasternak A, *et al*. Inhibition of ROMK blocks macula densa tubuloglomerular feedback yet causes renal vasoconstriction in anesthetized rats. American Journal of Physiology. Renal Physiology. 2017; 312: F1120–F1127.
[25] Li H, Peng W, Wu S. The Use of β-blockers in the Management of Hypertension in Young and Middle-aged People. Chinese General Practice. 2023; 26: 248. (In Chinese)
[26] Ojha U, Ruddaraju S, Sabapathy N, Ravindran V, Worapongsatitaya P, Haq J, *et al*. Current and Emerging Classes of Pharmacological Agents for the Management of Hypertension. American Journal of Cardiovascular Drugs. 2022; 22: 271–285.
[27] AlHabeeb W, Mrabeti S, Abdelsalam AAI. Therapeutic Properties of Highly Selective β-blockers With or Without Additional Vasodilator Properties: Focus on Bisoprolol and Nebivolol in Patients With Cardiovascular Disease. Cardiovascular Drugs and Therapy. 2022; 36: 959–971.
[28] Vrablik M, Corsini A, Tůmová E. Beta-blockers for Atherosclerosis Prevention: a Missed Opportunity? Current Atherosclerosis Reports. 2022; 24: 161–169.
[29] Punzi HA. A randomized, open-label, blinded-endpoint, active-comparator, forced-titration study to compare nebivolol versus metoprolol as dual therapy with amlodipine in patients with hypertension: results of the tandem study. Journal of the American Society of Hypertension. 2014; 8: e27.
[30] Barrera-Chimal J, Bonnard B, Jaisser F. Roles of Mineralocorticoid Receptors in Cardiovascular and Cardiorenal Diseases. Annual Review of Physiology. 2022; 84: 585–610.
[31] Ferreira NS, Tostes RC, Paradis P, Schiffrin EL. Aldosterone, Inflammation, Immune System, and Hypertension. American Journal of Hypertension. 2021; 34: 15–27.
[32] Cai DY, Tang CS. The role of neutral endopeptidase and its inhibitors in the process of cardiovascular diseases. Advances in Physiological Science. 2005; 53–54. (In Chinese)
[33] Briasoulis A, Al Dhaybi O, Bakris GL. SGLT2 Inhibitors and Mechanisms of Hypertension. Current Cardiology Reports. 2018; 20: 1.
[34] Liakos A, Lambadiari V, Bargiota A, Kitsios K, Avramidis I, Kotsa K, *et al*. Effect of liraglutide on ambulatory blood pressure in patients with hypertension and type 2 diabetes: A randomized, double-blind, placebo-controlled trial. Diabetes, Obesity & Metabolism. 2019; 21: 517–524.
[35] Ma X, Liu Z, Ilyas I, Little PJ, Kamato D, Sahebka A, *et al*. GLP-1 receptor agonists (GLP-1RAs): cardiovascular actions and therapeutic potential. International Journal of Biological Sciences. 2021; 17: 2050–2068.
[36] Eroglu E, Kocyigit I, Lindholm B. The endothelin system as target for therapeutic interventions in cardiovascular and renal disease. Clinica Chimica Acta. 2020; 506: 92–106.
[37] Schlaich MP, Bellet M, Weber MA, Danaietash P, Bakris GL, Flack JM, *et al*. Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION): a multicentre, blinded, randomised, parallel-group, phase 3 trial. Lancet. 2022; 400: 1927–1937.
[38] Triposkiadis F, Xanthopoulos A, Skoularigis J, Starling RC. Therapeutic augmentation of NO-sGC-cGMP signalling: lessons learned from pulmonary arterial hypertension and heart failure. Heart Failure Reviews. 2022; 27: 1991–2003..
[39] Frey R, Mück W, Unger S, Artmeier-Brandt U, Weimann G, Wensing G. Single-dose pharmacokinetics, pharmacodynamics, tolerability, and safety of the soluble guanylate cyclase stimulator BAY 63-2521: an ascending-dose study in healthy male volunteers. Journal of Clinical Pharmacology. 2008; 48: 926–934.
[40] Llorens-Cortes C, Touyz RM. Evolution of a New Class of Antihypertensive Drugs: Targeting the Brain Renin-Angiotensin System. Hypertension. 2020; 75: 6–15.
[41] Mirabito Colafella KM, Bovée DM, Danser AHJ. The renin-angiotensin-aldosterone system and its therapeutic targets. Experimental Eye Research. 2019; 186: 107680.
[42] Desai AS, Webb DJ, Taubel J, Casey S, Cheng Y, Robbie GJ, *et al*. Zilebesiran, an RNA Interference Therapeutic Agent for Hypertension. The New England Journal of Medicine. 2023; 389: 228–238.
[43] Wu NN, Zhang YY, Zhao D. Eplerenone-A novel Mineralocorticoid receptor antagonist for the clinical application. Environmental Disease. 2022; 7: 1–11.
[44] Agarwal R, Kolkhof P, Bakris G, Bauersachs J, Haller H, Wada T, *et al*. Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. European Heart Journal. 2021; 42: 152–161.
[45] Przezak A, Bielka W, Pawlik A. Hypertension and Type 2 Diabetes-The Novel Treatment Possibilities. International Journal of Molecular Sciences. 2022; 23: 6500.
[46] Kolkhof P, Hartmann E, Freyberger A, Pavkovic M, Mathar I, Sandner P, *et al*. Effects of Finerenone Combined with Empagliflozin in a Model of Hypertension-Induced End-Organ Damage. American Journal of Nephrology. 2021; 52: 642–652.
[47] Ito S, Itoh H, Rakugi H, Okuda Y, Iijima S. Antihypertensive effects and safety of esaxerenone in patients with moderate kidney dysfunction. Hypertension Research. 2021; 44: 489–497.
[48] McKie PM, Ichiki T, Burnett JC, Jr. M-atrial natriuretic peptide: a novel antihypertensive protein therapy. Current Hypertension Reports. 2012; 14: 62–69.
[49] Arendse LB, Danser AHJ, Poglitsch M, Touyz RM, Burnett JC, Jr, Llorens-Cortes C, *et al*. Novel Therapeutic Approaches Targeting the Renin-Angiotensin System and Associated Peptides in Hypertension and Heart Failure. Pharmacological Reviews. 2019; 71: 539–570.
[50] Li Q, Li L, Wang F, Zhang W, Guo Y, Wang F, *et al*. Effect and safety of LCZ696 in the treatment of hypertension: A meta-analysis of 9 RCT studies. Medicine. 2019; 98: e16093.
[51] Sun JC, Xiao Y, Xu WJ, Xing W, Du F, Tian MZ, *et al*. Antihypertensive effect of a novel angiotensin II receptor neprilysin inhibitor (ARNi)-S086 in DSS rat model. Frontiers in Cardiovascular Medicine. 2024; 11: 1348897.
[52] Gu GY, Zheng SX. Sodium-glucose cotransporter 2 inhibitor-

A new approach to the treatment of diabetes mellitu. Chinese Journal of Practical Internal Medicine. 2014; 34: 962–968. (In Chinese)

[53] Hediger MA, Rhoads DB. Molecular physiology of sodium-glucose cotransporters. Physiological Reviews. 1994; 74: 993–1026.

[54] Kowalska K, Wilczopolski P, Buławska D, Młynarska E, Rysz J, Franczyk B. The Importance of SGLT-2 Inhibitors as Both the Prevention and the Treatment of Diabetic Cardiomyopathy. Antioxidants. 2022; 11: 2500.

[55] Georgianos PI, Agarwal R. Ambulatory Blood Pressure Reduction With SGLT-2 Inhibitors: Dose-Response Meta-analysis and Comparative Evaluation With Low-Dose Hydrochlorothiazide. Diabetes Care. 2019; 42: 693–700.

[56] Cefalu WT, Stenlöf K, Leiter LA, Wilding JPH, Blonde L, Polidori D, *et al*. Effects of canagliflozin on body weight and relationship to HbA1c and blood pressure changes in patients with type 2 diabetes. Diabetologia. 2015; 58: 1183–1187.

[57] Ghanim H, Batra M, Green K, Hejna J, Abuaysheh S, Makdissi A, *et al*. Dapagliflozin reduces systolic blood pressure and modulates vasoactive factors. Diabetes, Obesity & Metabolism. 2021; 23: 1614–1623.

[58] Lee HC, Shiou YL, Jhuo SJ, Chang CY, Liu PL, Jhuang WJ, *et al*. The sodium-glucose co-transporter 2 inhibitor empagliflozin attenuates cardiac fibrosis and improves ventricular hemodynamics in hypertensive heart failure rats. Cardiovascular Diabetology. 2019; 18: 45.

[59] Packer M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ, *et al*. Empagliflozin in Patients With Heart Failure, Reduced Ejection Fraction, and Volume Overload: EMPEROR-Reduced Trial. Journal of the American College of Cardiology. 2021; 77: 1381–1392.

[60] Heuvelman VD, Van Raalte DH, Smits MM. Cardiovascular effects of glucagon-like peptide 1 receptor agonists: from mechanistic studies in humans to clinical outcomes. Cardiovascular Research. 2020; 116: 916–930.

[61] Zhao D, Liu H, Dong P. Liraglutide reduces systolic blood pressure in patients with type 2 diabetes mellitus: A meta-analysis of randomized trials. Clinical and Experimental Hypertension. 2020; 42: 393–400.

[62] Yanai H, Hakoshima M, Adachi H, Katsuyama H. A Significant Effect of Oral Semaglutide on Cardiovascular Risk Factors in Patients With Type 2 Diabetes. Cardiology Research. 2022; 13: 303–308.

[63] Vandemark C, Nguyen J, Zhao ZQ. Cardiovascular Protection with a Long-Acting GLP-1 Receptor Agonist Liraglutide: An Experimental Update. Molecules. 2023; 28: 1369.

[64] Liakos CI, Papadopoulos DP, Sanidas EA, Markou MI, Hatziagelaki EE, Grassos CA, *et al*. Blood Pressure-Lowering Effect of Newer Antihyperglycemic Agents (SGLT-2 Inhibitors, GLP-1 Receptor Agonists, and DPP-4 Inhibitors). American Journal of Cardiovascular Drugs: Drugs, Devices, and Other Interventions. 2021; 21: 123–137.

[65] Burnier M. Update on Endothelin Receptor Antagonists in Hypertension. Current Hypertension Reports. 2018; 20: 51.

[66] Clozel M. Aprocitentan and the endothelin system in resistant hypertension. Canadian Journal of Physiology and Pharmacology. 2022; 100: 573–583.

[67] McCoy EK, Lisenby KM. Aprocitentan (a Dual Endothelin-Receptor Antagonist) for Treatment-Resistant Hypertension. Journal of Cardiovascular Pharmacology. 2021; 77: 699–706.

[68] Wunder F, Stasch JP, Knorr A, Mondritzki T, Brockschnieder D, Becker-Pelster EM, *et al*. Identification and characterization of the new generation soluble guanylate cyclase stimulator BAY-747 designed for the treatment of resistant hypertension. British Journal of Pharmacology. 2023; 180: 2500–2513.

[69] Azizi M, Rossignol P, Hulot JS. Emerging drug classes and their potential use in hypertension. Hypertension. 2019; 74: 1075–1083.

[70] Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, *et al*. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. The New England Journal of Medicine. 2020; 382: 1883–1893.

[71] Urmila A, Rashmi P, Nilam G, Subhash B. Recent Advances in the Endogenous Brain Renin-Angiotensin System and Drugs Acting on It. Journal of the Renin-angiotensin-aldosterone System. 2021; 2021: 9293553.

[72] Ferdinand KC, Balavoine F, Besse B, Black HR, Desbrandes S, Dittrich HC, *et al*. Efficacy and safety of Firibastat, a first-in-class brain aminopeptidase A inhibitor, in hypertensive overweight patients of multiple ethnic origins: A Phase 2, open-label, multicenter, dose-titrating study. Circulation. 2019; 140: 138–146.

[73] Keck M, Hmazzou R, Llorens-Cortes C. Orally Active Aminopeptidase A Inhibitor Prodrugs: Current State and Future Directions. Current Hypertension Reports. 2019; 21: 50.

[74] Marc Y, Boitard SE, Balavoine F, Azizi M, Llorens-Cortes C. Targeting Brain Aminopeptidase A: A New Strategy for the Treatment of Hypertension and Heart Failure. The Canadian Journal of Cardiology. 2020; 36: 721–731.

[75] Yuan LF, Cao S, Sun T. Effect of targeted angiotensinogen RNA interference on spontaneously hypertensive model rats. Journal of Tissue Engineering. 2021; 25: 5626–5631. (In Chinese)

[76] Ranasinghe P, Addison ML, Webb DJ. Small Interfering RNA Therapeutics in Hypertension: A Viewpoint on Vasopressor and Vasopressor-Sparing Strategies for Counteracting Blood Pressure Lowering by Angiotensinogen-Targeting Small Interfering RNA. Journal of the American Heart Association. 2022; 11: e027694.

[77] Laghlam D, Jozwiak M, Nguyen LS. Renin-Angiotensin-Aldosterone System and Immunomodulation: A State-of-the-Art Review. Cells. 2021; 10: 1767.

[78] Addison ML, Ranasinghe P, Webb DJ. Novel Pharmacological Approaches in the Treatment of Hypertension: A Focus on RNA-Based Therapeutics. Hypertension. 2023; 80: 2243–2254.