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History of Development, Classification, Mechanism of Action and Rational Application of Major Anti-Hypertensive Drugs

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ABSTRACT

With the rise of the aging population, the number of people with high blood pressure is increasing. Hypertension can cause cerebral hemorrhage, cerebral infarction, heart failure, coronary atherosclerotic heart disease and renal failure. One of the most common treatments for hypertension is drug therapy. Common anti-hypertensive drugs include angioplasty-converting enzyme inhibitors, calcium channel blockers, adrenergic receptor antagonists, diuretics, central anti-hypertensive drugs and vasodilation. The types of drugs used vary depending on the individual's condition. This article reviews the development history, classification, mechanism of action and rational application of the major anti-hypertensive drugs, so that more people can understand hypertension and provide more choices of drugs for hypertensive people.

KEYWORDS

Angioplasty-converting enzyme inhibitors; Calcium channel blockers; Adrenergic receptor antagonists; Diuretics; Central anti-hypertensive and vasodilation agents

1. INTRODUCTION

The prevalence of hypertension is increasing year by year due to the aging of the population and the prevalence of obesity [1]. The morbidity and mortality of cardiovascular diseases have continued to increase and become the first cause of death in the Chinese population, and the prevalence of hypertension as a major risk factor for cardiovascular diseases is increasing [2]. The vast majority of hypertensive patients have an undetermined cause, called primary hypertension, and secondary hypertension only accounts for about 10%, the main complication in China's hypertensive population is stroke, and other complications include coronary artery disease, heart failure, left ventricular hypertrophy, atrial fibrillation, and end-stage renal disease [3]. Usually, drugs are one of the most commonly used means of treating hypertension, and anti-hypertensive drugs can effectively control blood pressure, prevent or reduce damage to vital organs such as the heart, brain, and kidneys, thus improving the quality of life of patients and prolonging life expectancy [3]. However, the awareness, control and treatment of hypertension in our population are far from adequate.6 In this paper, we summarize and summarize the development history, classification, mechanism of action and rational application of the main anti-hypertensive drugs, hoping that it will be helpful for the study of the treatment of hypertension and the use of medication.

2. HISTORY OF ANTI-HYPERTENSIVE DRUG DEVELOPMENT

Pharmacological treatment of hypertension began in the 1940s, the application of thiocyanates for the treatment of hypertension, but the anti-hypertensive effect is short-lived and unstable. 1950s began

to apply ganglionic blocking drugs such as hexamethylene bromide, camphor mifepristone, mecamylamine, etc., this kind of drug selective antagonism of ganglionic post-synaptic membrane of the N_1 receptors, antagonism of sympathetic activity and reduce peripheral vascular resistance, anti-hypertensive effect is powerful, but at the same time, block the parasympathetic ganglion adverse effects are more frequent. Blocking the parasympathetic ganglion, more adverse reactions, is currently mainly used in hypertensive crisis, aortic coarctation aneurysm and surgical control of blood pressure reduction. During this period, several other important anti-hypertensive drugs were found: Hydroplane is a vasodilation, with powerful anti-hypertensive effect; thiazides excrete sodium and diuretics, reduce cardiac output and peripheral vascular resistance, used alone or in combination with other anti-hypertensive drugs, and still remain as the basic drugs for the treatment of hypertension; guanethidine and rifampicin, both belong to the nor-epinephrine-generic nerve endings blocker, and their mechanism of action is to influence the release and storage of nor-epinephrine, and the release of nor-epinephrine, and the release of norepinephrine. Guanethidine and rifampicin, both nor-epinephrine nerve endings blocking drugs, its mechanism of action is to affect the storage and release of nor-epinephrine, leading to depletion of nor-epinephrine nerve endings vesicles in the depletion of transmitters to lower blood pressure, but due to the neurological and gastrointestinal system adverse effects are more, soon to be replaced by the subsequent introduction of the adverse effects of the drug less, is now mainly used as a tool for the study of sympathetic activity. Rifampicin has a weaker effect and more adverse reactions, and is no longer used alone, but as a component of the compound preparation is still the basic anti-hypertensive drug.The anti-hypertensive drugs developed in the 1960s include central anti-hypertensive drugs (methyl-dopa, coleopterist), vasodilation (diazepam), β-receptor antagonists (propranolol, etc.), and calcium channel blocking drugs (nifedipine, etc.). Since then, selective α1 receptor antagonists (prazosin, etc.), potassium channel openers (minoxidil, etc.), and selective imidazoline receptor agonists (moxonidine, rilmenidine) have been introduced, which have greatly enriched the variety of anti-hypertensive drugs. 1980s, the emergence of ACEIs and ARBs (chlorsartan, etc.) has brought the pharmacological treatment of hypertension into a new era, which not only effectively reduce blood pressure, but also prevent and control hypertension. These drugs are not only effective in lowering blood pressure, but also in preventing and reversing the reconstruction of cardiovascular configuration caused by hypertension [3].

In addition to the above anti-hypertensive drugs, many new anti-hypertensive drugs have been developed in recent years. For example, the dual inhibitors of neutral endopeptidase and ACE, such as omadacycline, fasidotril, and sambazolol, can inhibit ACE and neutral endopeptidase activity at the same time, reduce the activity of the renin-angiotensin system, and increase the levels of bradykinin and cardiac natriuretic peptide, thus producing anti-hypertensive effects; the prostaglandin synthesis-promoting drug, sicloxacillin, can promote prostaglandin synthesis to produce anti-hypertensive effects; the 5-hydroxytryptamine receptor agonist, uraldehydes The 5-hydroxytryptamine receptor agonist uradil agonizes the central 5-HT_{1A} receptor, reduces peripheral sympathetic nerve activity and produces anti-hypertensive effects; the 5-HT receptor antagonist ketanserin antagonizes the 5-HT_{2A} receptor and mildly antagonizes theα1 receptor, reduces peripheral vascular resistance and produces anti-hypertensive effects; and the endothelin receptor antagonist bosentan, cetanserin, and enlasentan antagonize the binding of endothelin and endothelin receptor to produce a potent anti-hypertensive effect [4, 5]. The effects of these drugs on cardio-cerebral canal events have yet to be evaluated in large-scale clinical trials.

With the deeper understanding of the pathogenesis of hypertension, many new anti-hypertensive drugs are being studied, such as vasoactive peptidase inhibitors, aldosterone synthase inhibitors, soluble epoxide hydrolase inhibitors, natriuretic peptide A agonists, vasoactive intestinal peptide type 2 receptor agonists, as well as salicylated corticosteroid receptor antagonists aminopeptidase A inhibitors, dopamine β-hydroxylase inhibitors, small intestinal Na^+/H^+ exchanger 3 inhibitors as well as angiotensin-converting enzyme II/angiotensin (1-7)/Mas receptor axis component agonists, enkephalinase inhibitors, and purinergic P2X3 receptor inhibitors [3].

3. CURRENT MAJOR CLINICAL ANTI-HYPERTENSIVE DRUGS AND THEIR MECHANISMS OF ACTION

3.1. Renin-angiotensin System Inhibitors

Angiotensin II in plasma is a very potent vasoconstrictor substance, with a presser-raising potency 40-50 times more potent than equimolar concentrations of nor-epinephrine, [6] and its presser-raising mechanism is shown in Fig. 1.

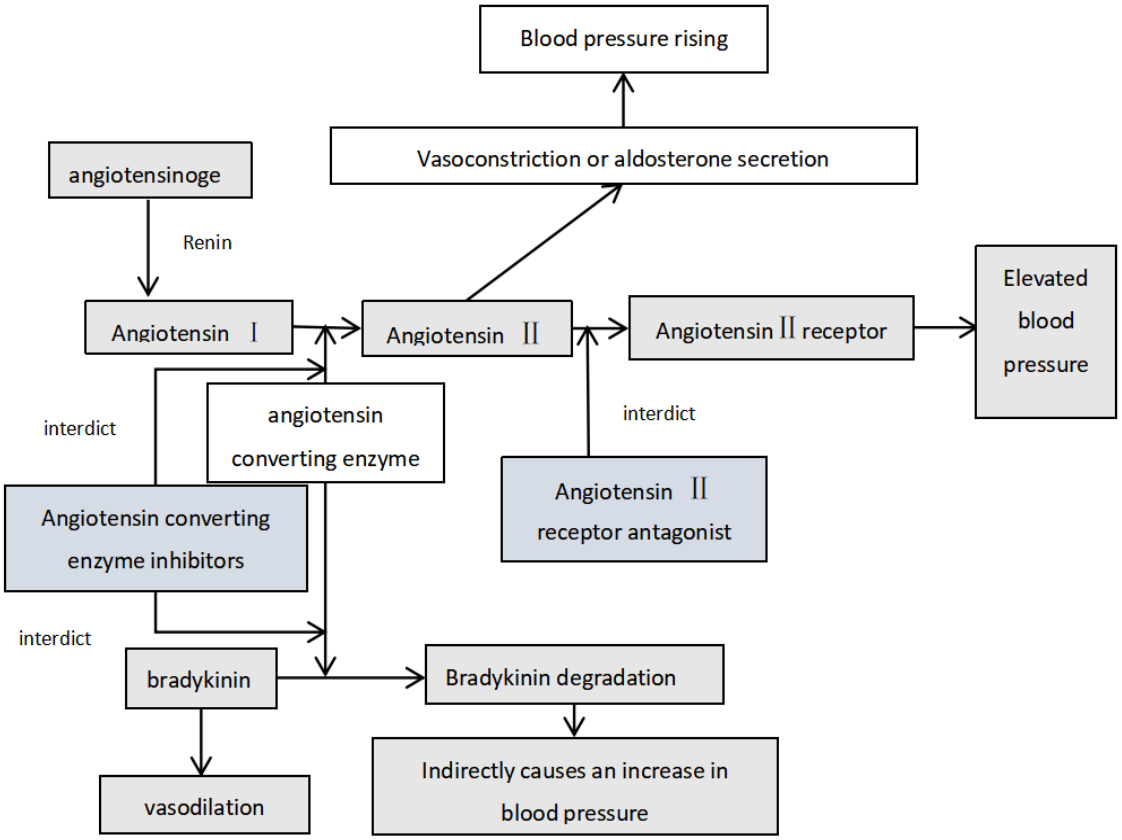


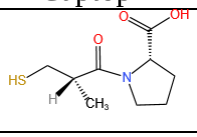
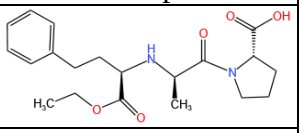
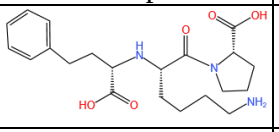
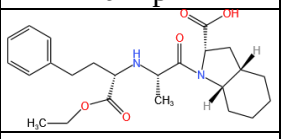
Figure 1. Regulation of blood pressure by angiotensin II

The components of the renin-angiotensin system mainly include renin, angiotensin-converting enzyme (ACE), angiotensinogen, and angiotensin II, and angiotensin-converting enzyme and angiotensin II receptor are enriched in a variety of organs and tissues, including cardiac muscle, vascular smooth muscle, skeletal muscle, brain, kidney, and gonads. The renin-angiotensin system is found both in the circulatory system and in tissues such as the vascular wall, heart, center, kidney, and adrenal glands. In addition to the systemic renin-angiotensin system, a relatively independent local renin-angiotensin system exists in cardiovascular and other organ tissues, and this local renin-angiotensin system can regulate cardiovascular activity more directly and importantly by paracrine and/or autocrine means.

3.1.1. Angiotensin-converting enzyme inhibitor

Captopril, also known as mercaptopropyl proline, was the first ACEI that could be taken orally, but some patients developed dry cough and loss of taste as side effects after using the drug, and it was hypothesized that the side effects might be related to the sulfhydryl group it produces, and thus the sulfhydryl group was formed into an ester or sulfhydryl group-free ACE inhibitors were synthesized, such as enalapril, lynacipril, ramipril, etc., in order to reduce some of the adverse effects [7], and its chemical structure and pharmacokinetics are shown in Table 1.

Table 1. Chemical structure and pharmacokinetics of common ACEIs

Name of drug	Captopril	Enalapril	Lenopril	Ramipril
chemical structure				
antecedent	No	Yes	No	Yes
Peak time/h	1	1	2-4	1
Plasma half-life/h	2.3	11 h	12 -24	9-18
metabolic organ	pancreas	pancreas	Prototype Discharge	kidney
Protein binding rate/%	30	50	A Little	36
Absolute bioavailability/%	70	40	25	50-60

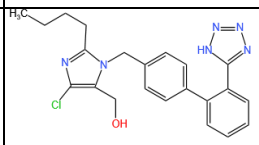
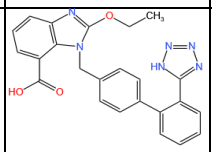
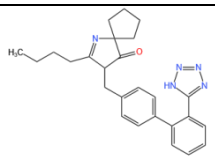
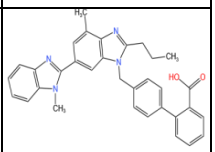
Mechanism of action: ACE is a protease that shears and hydrolyzes Ang I into Ang II, and ACE inhibitors reduce the production of Ang II by inhibiting ACE, which results in the inhibition of RAAS [8]. In addition, ACE is a key protease in the degradation of bradykinin, therefore, ACE inhibitors can lead to increased levels of bradykinin in circulation and tissues [6].

Adverse reaction:The most common adverse reaction is dry cough.The major adverse reactions include hyperkalemia, hypotension, rash, renal impairment, and occasionally angioneurotic edema and taste disturbance [3].

3.1.2. Angiotensin II inhibitors

Chlorosartan, its potassium salt chlorosartan potassium was first approved by the U.S. FDA in April 1995 for the treatment of hypertension, and became the first non-peptide and selective Ang II receptor inhibitor [7], which will inhibit the renin-angiotensin cycle, so that the human intestinal, renal membrane vascularization for constriction, the growth of vascular smooth muscle indirectly regulate the growth of effective blood vessels, and enhance the effect of coronary vasoconstriction in the body. Enhancement of coronary vasoconstriction in the body, in favor of good regulation of glomerular filtration, renal blood flow, better inhibition of the aldosterone release process, which in turn leads to a reduction in the level of blood pressure [9]. Similar drugs include candesartan, irbesartan, timosartan and others. Their chemical structure and pharmacokinetics are shown in Table 2.

Table 2. Chemical structure and pharmacokinetics of common Ang II receptor inhibitors

Name of drug	Chlorosartan	Candesartan	Irbesartan	Timosartan
chemical structure				
Bioavailability/%	33	42	60-80	42-57
Onset time/h	1	2-4	2	1
Peak time/h	6	6-8	3-6	3-9
Duration of action/h	24	≥24	24	≥24
Protein binding rate/%	>98	99.6	96	99.5
Distribution volume/L	34	10	500	53-96
Clearance of t1/2/h	2	9-13	11-15	18-24
Excretion/(urine/feces %)	35/60	33/67	20/80	1/97

Mechanism of action: Ang II receptor inhibitors directly block Ang II and the corresponding receptor binding to achieve the effect of anti-hypertension.

Adverse effects: less than angiotensin-converting enzyme inhibitors, do not cause cough, can cause hypotension, renal dysfunction, hyperkalemia, etc. [3].

3.1.3. Direct renin inhibitor

Aliskiren is the first non-peptide oral direct renin inhibitor, which inhibits the production of angiotensin I and II by decreasing the activity of plasma renin, thus blocking RAAS activation more completely from the root [10,11]. Numerous clinical studies have demonstrated that aliskiren can effectively lower blood pressure with a safety profile comparable to that of placebo, and that it is also well synergized and tolerated in combination with other types of anti-hypertensive drugs. In addition to effectively lowering blood pressure, aliskiren also reduces proteinuria, protects the kidneys and cardiovascular, and is an ideal anti-hypertensive drug for hypertensive patients [12], with mild adverse effects [3].

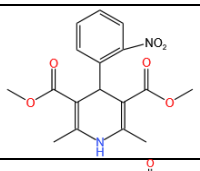
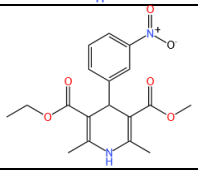
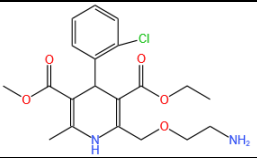
3.2. Calcium Channel Blockers

Calcium channel antagonists are clinically used in the treatment of arrhythmia, hypertension, angina pectoris, chronic new insufficiency and other diseases, with a wide range of applicability, especially for elderly patients with simple systolic hypertension, with good tolerability and no absolute contraindications [3]. Representative drugs are dihydropyridines (nifedipine, etc.), phenylalkanes (verapamil, etc.) and benzothiazepines (diltiazem, etc.), of which dihydropyridines have stronger effects on blood vessels [13]. A comparison of the anti-hypertensive effects of short-, medium-, and long-acting dihydropyridine calcium channel blockers is shown in Table 3.

Mechanism of action: By interfering with the intracellular $Ca2^{+}$ concentration, they have an obstructive effect on vascular smooth muscle as well as on calcium channels on cardiac cell membranes, inhibiting the inward flow of extracellular calcium ions, thus greatly attenuating the concentration of intracellular $Ca2^{+}$ to achieve vasorelaxation, which then leads to a decrease in intravascular resistance, and a simultaneous decrease in blood pressure [13].

Adverse reactions: headache, palpitations, edema, flushing, etc.[3]

Table 3. Comparison of anti-hypertensive effects of short-, medium- and long-acting dihydropyridine calcium channel blockers

Categorization	Representative drugs	chemical structure	T1/2/h	Characteristics of action
Short effect	Nifedipine		3-4	Fast and short
Medium effect	Nigtundipine		7-8	Mild and long-lasting, inhibits aldosterone secretion
Lasting effect	Amlodipine		40-50	Slow-acting, smooth and long-lasting, reduces or reverses left ventricular hypertrophy

3.3. Adrenergic Receptor Antagonists

3.3.1. Beta receptor antagonists

According to the selectivity of β_1-adrenergic receptors, β-blockers can be divided into selective β_1-blockers and non-selective β-blockers, the former mainly includes metoprolol, atenolol and bisoprolol, etc., and the latter includes propranolol, etc., The anti-hypertensive benefit of β-blockers mainly comes from the blockage of β_1-receptor, and the affinity of highly selective β_1-blockers for β_1-receptor is much higher than that of β_2-receptor, which can more accurately exert the therapeutic effect of cardiovascular diseases and reduce the incidence of adverse effects. [14] receptors, which can more accurately exert the therapeutic effects of cardiovascular disease and reduce the incidence of adverse effects [14].

Mechanisms of action: slowing heart rate, decreasing cardiac output, inhibiting renin release and angiotensin II production, blocking presynaptic membrane β-receptors and thus decreasing the release of nor-epinephrine from sympathetic nerve endings, decreasing central vasoconstrictor activity, decreasing venous reflux, and attenuating the elevated blood pressure response induced by the release of catecholamines during exercise and stress [14].

Adverse effects: non-selective β-receptor antagonists such as propranolol can elevate triglyceride levels, and non-selective β-receptor antagonists can delay the recovery of blood glucose levels after insulin [3].

3.3.2. α-receptor antagonists

The common non-selective α receptor antagonist is phentolamine, but the long-term anti-hypertensive effect is poor, more adverse reactions, mostly used to control the hypertensive crisis in patients with pheochromocytoma, not as a long-term application of anti-hypertension; selective α_1 receptor antagonist is prazosin, terazosin, and doxazosin, etc [3], with lower side effects.

Mechanism of action: α receptor antagonists can antagonize the contractile effect of catecholamines on vascular smooth muscle, so that the constricted state of small arteries diastole, resulting in anti-hypertensive effect [3].

3.3.3. α and β receptor antagonists

Labetalol, can antagonize α and β receptors, its antagonism of its antagonism of β receptors is stronger than the antagonism of α_1 receptors, no effect on α_2 receptors, its antagonism of α_1, β receptors, reduce peripheral vascular resistance and produce anti-hypertensive effect; carvedilol, can selectively antagonize the a_1 receptors and non-selective antagonism of the β receptor, reduce peripheral resistance. Adverse effects are similar to propranolol, but do not affect lipid metabolism [3].

3.4. Diuretics

Diuretics can be divided into thiazides, represented by hydrochlorothiazide, chlorothiazide, etc.;the class of labeled diuretics, represented by furosemide, etanercept, etc.; potassium-preserving diuretics, represented by spironolactone, aminopterin, etc.. Various types of diuretics have anti-hypertensive effects when used alone and can enhance the effects of other anti-hypertensive drugs.[15] Thiazide anti-hypertensive drugs are mild, long-lasting, and have anti-hypertensive effects in both the upright and prone positions, and are commonly used in the clinic.

Mechanism of action: thiazide diuretics can inhibit the proximal and distal distal convoluted tubules, increase the reabsorption of Na^+ and Cl^- in the convoluted tubules, play the role of sodium excretion and diuresis, and promote K^+ excretion. In addition, thiazide diuretics can inhibit phosphodiesterase activity, reduce the uptake of fatty acids in renal tubules, reduce mitochondrial oxygen consumption, and induce vasodilatation of the vascular wall, which not only reduces the blood volume, but also

reduces the peripheral vascular resistance and is suitable for prolonged blood pressure lowering [16, 17].

Adverse effects: hypokalemia, altered glucose and lipid metabolism, increased renin activity [3].

3.5. Other anti-hypertensive agents

3.5.1. Central anti-hypertensive drugs

Central anti-hypertensive drugs include methyldopa, colistin, rilmenidine, and moxonidine. Among them, methyldopa produces anti-hypertensive effect by agonizing the α_2 receptor in the nucleus tractus solitarius; the anti-hypertensive effect of colistin is also related to agonizing the imidazoline I_1 receptor in the ventral lateral area of the medulla oblongata in addition to the α_2 receptor mediation; rimenidine and moxonidine mainly act on the imidazoline I_1 receptor [3].

3.5.2. Vasodilators

Vasodilator drugs include direct vasodilator smooth muscle drugs and potassium channel opening drugs, of which direct vasodilator smooth muscle drugs are divided into small artery dilation drugs, representative drugs are hydralazine, minoxidil and diazepam, etc. and drugs with diastolic effect on arteries and veins, representative drugs are sodium nitroprusside [3].

4. RATIONAL APPLICATION OF ANTI-HYPERTENSIVE DRUGS

Anti-hypertensive drugs are diverse, each with its own characteristics, and there are great individual differences in efficacy, so they should be used rationally according to the condition and combined with the characteristics of the drug.

4.1. Principles of Hypertension Drug Treatment

(1) Effective treatment, lifelong treatment: blood pressure control below 140/90mmHg;

(2) Protect target organs (heart, brain and kidney): ACEI, ARB, CCB;

(3) Smoothing blood pressure: long-acting agents to reduce blood pressure fluctuations;

(4) Combination of drugs: diuretics, CCB, β-blockers, RAS inhibitors;

(5) Individualized treatment: degree of hypertension, drug sensitivity, affordability, etc.

4.2. Drug Selection According to the Degree of Hypertension

(1) Mild: low-fat, low-salt diet, weight control; hydrochlorothiazide is preferred;

(2) Moderate: β-blocker, calcium antagonist, ACEI, ARB, α_1 receptor blocker;

(3) Severe: combination drugs;

(4) Critical hypertension: sodium nitroprusside/furosemide/labetalol IV.

4.3. Preferred Indications

(1) left ventricular hypertrophy preferred CCB, ACEI or ARB;

(2) asymptomatic atherosclerosis patients may prefer ACEI, ARB or CCB;

(3) nifedipine is preferred for variant angina.

4.4. Selection of Drugs According to Commodities

(1) ACEI, ARB, CCB, methyldopa, colistin, prazosin are preferred for patients with renal dysfunction;

(2) In combination with sinus tachycardia, β-blockers, non-dihydropyridine CCBs are preferred;

(3) Combined bronchial asthma, should not use beta-blocking drugs;

(4) Thiazide diuretics are not suitable for those with underlying diabetes mellitus or gout.

(5) For peptic ulcer, colistin should be used instead of reserpine.

(6) ACEI and ARB should not be used in combination with renal artery stenosis.

(7) Risperdal and methyldopa should not be used in combination with mental depression.

4.5. Selection of Drugs According to Comorbidities

(1) ACEI and hydrochlorothiazide

(2) ARB and hydrochlorothiazide

(3) ACEI and CCB

(4) ARB and CCB

(5) α_1-receptor antagonists and β-receptor antagonists

5. CONCLUSION

The prevalence of hypertension is increasing year by year due to population aging and the obesity epidemic; therefore, it is important to understand the history of development, classification, mechanism of action and rational application of anti-hypertensive drugs. Currently, the commonly used anti-hypertensive drugs in clinical practice include angiotensin-converting enzyme inhibitors, calcium channel blockers, adrenergic receptor antagonists, diuretics, central anti-hypertensive agents and vasodilators. At the same time, in order to effectively control hypertension, in addition to adhering to individualized medication, diet control and moderate exercise should also be carried out. It is believed that by understanding the background, controlling diet and reasonable medication, our hypertensive population can be effectively controlled.

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