

Unit 3 Drug Affecting the Cardiovascular System

Chapter 1 Antihypertensive

Hypertension is defined as either a sustained systolic blood pressure of greater than 140 mm Hg or a sustained diastolic blood pressure of greater than 90 mm Hg.

The drugs used in the treatment of hypertension

ANGIOTENSIN II RECEPTOR BLOCKERS

Azilsartan medoxomil EDARBI
Candesartan ATACAND
Eprosartan TEVETEN
Irbesartan AVAPRO
Losartan COZAAR
Olmесartan BENICAR
Telmisartan MICARDIS
Valsartan DIOVAN

RENIN INHIBITORS

Aliskiren TEKTURNА

CALCIUM CHANNEL BLOCKERS

Amlodipine NORVASC
Clevidipine CLEVIPREX
Diltiazem CARDIZEM, CARTIA, DILACOR
Felodipine PLENDIL
Isradipine DYNACIRC CR
Nicardipine CARDENE
Nifedipine ADALAT, NIFEDIAC, PROCARDIA
Nisoldipine SULAR
Verapamil CALAN, ISOPTIN, VERELAN

α-BLOCKERS

Doxazosin CARDURA
Prazosin MINIPRESS
Terazosin HYTRIN

OTHERS

Clonidine CATAPRES, DURACLON
Fenoldopam CORLOPAM
Hydralazine APRESOLINE
Methyldopa ALDOMET
Minoxidil LONITEN
Nitroprusside NITROPRESS

ACE INHIBITORS

Benazepril LOTENSIN
Captopril CAPOTEN
Enalapril VASOTEC
Fosinopril MONOPRIL
Lisinopril PRINIVIL, ZESTRIL
Moexipril UNIVASC
Quinapril ACCUPRIL
Perindopril ACEON
Ramipril ALTACE
Trandolapril MAVIK

DIURETICS

Amiloride MIDAMOR
Bumetanide BUMEX
Chlorthalidone HYGROTON
Eplerenone INSPRA
Ethacrynic acid EDECRIN
Furosemide LASIX
Hydrochlorothiazide MICROZIDE
Indapamide LOZOL
Metolazone MYKROX, ZAROXOLYN
Spironolactone ALDACTONE
Triamterene DYRENIUM
Torsemide DEMADEx

β-BLOCKERS

Acebutolol SECTRAL
Atenolol TENORMIN
Betaxolol KERLONE
Bisoprolol ZEBETA
Carvedilol COREG, COREG CR
Esmolol BREVIBLOC
Labetalol TRANDATE
Metoprolol LOPRESSOR, TOPROL-XL
Nadolol CORGARD
Nebivolol BYSTOLIC
Penbutolol LEVATOL
Pindolol VISKEN
Propranolol Inderal LA, INNOPRAN XL
Timolol BLOCADREN

Etiology of Hypertension

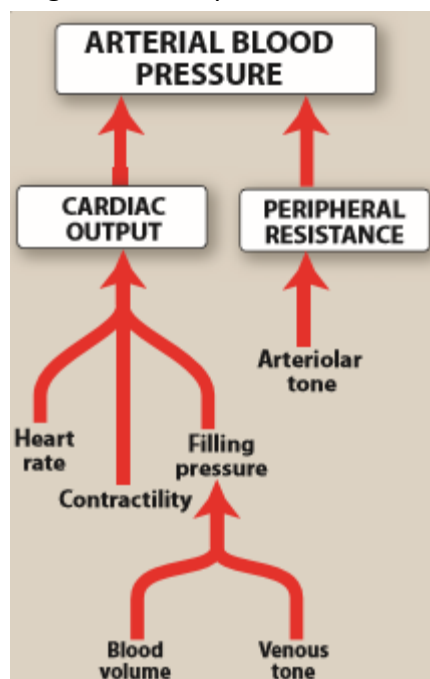
- **Primary hypertension (Essential)** a disorder of unknown origin that is not related to another medical condition. (more in black than in white)
- **Secondary:** Another medical condition that causes high blood pressure, usually occurring in the kidneys, arteries, heart or endocrine system.

There are four stages of high blood pressure or hypertension:

- STAGE 1 or Prehypertension is 120/80 to 139/89.
- STAGE 2 or Mild Hypertension is 140/90 to 159/99.
- STAGE 3 or Moderate Hypertension is 160/100 to 179/109.
- STAGE 4 or Severe Hypertension is 180/110 or higher.

Mechanism for controlling Blood Pressure

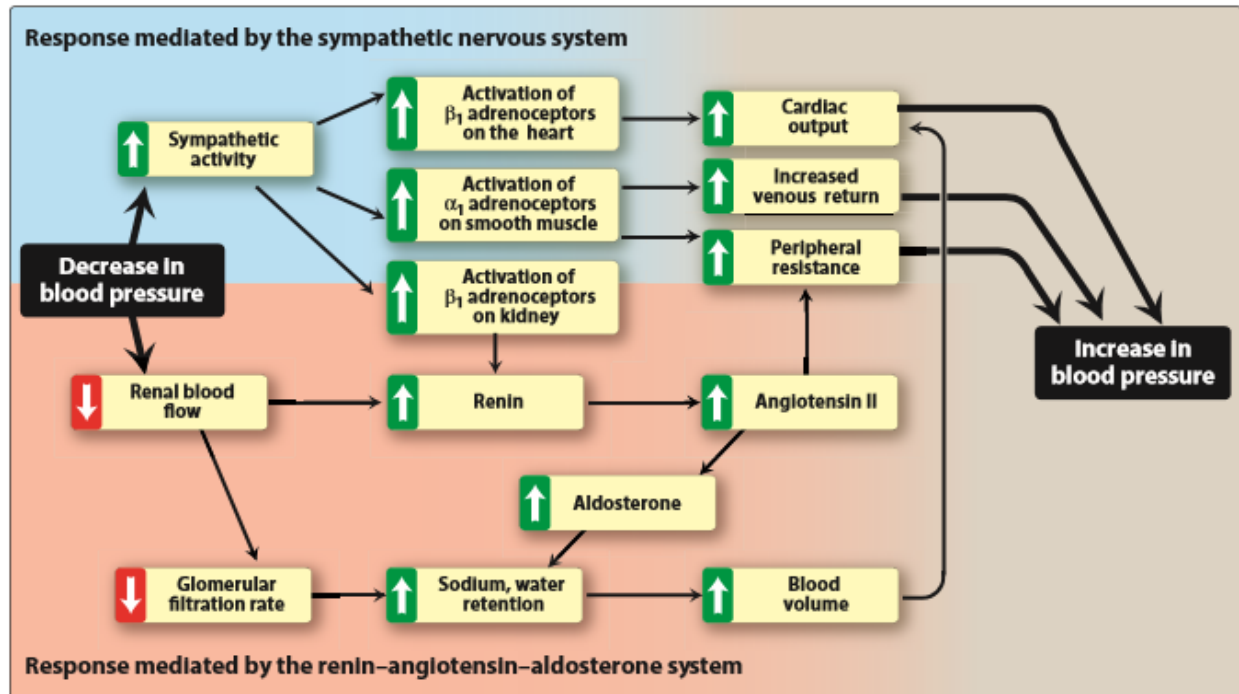
Arterial blood pressure is regulated within a narrow range to provide adequate perfusion of the tissues without causing damage to the vascular system. Arterial blood pressure is directly proportional to cardiac output and peripheral vascular resistance. Cardiac output and peripheral resistance, in turn, are controlled mainly by two overlapping control mechanisms: the baroreflexes and the renin–angiotensin–aldosterone system. Most antihypertensive drugs lower blood pressure by reducing cardiac output and/or decreasing peripheral resistance.



A. Baroreceptors and the sympathetic nervous system

Baroreflexes act by changing the activity of the sympathetic nervous system. Therefore, they are responsible for the rapid, moment-to-moment regulation of blood pressure. A fall in blood pressure

causes pressure-sensitive neurons to send fewer impulses to cardiovascular centers in the spinal cord. This prompts a reflex response of increased sympathetic and decreased parasympathetic output to the heart and vasculature, resulting in vasoconstriction and increased cardiac output. These changes result in a compensatory rise in blood pressure



B. Renin–angiotensin–aldosterone system

The kidney provides long-term control of blood pressure by altering the blood volume. Baroreceptors in the kidney respond to reduced arterial pressure (and to sympathetic stimulation of β_1 -adrenoceptors) by releasing the enzyme renin. Low sodium intake and greater sodium loss also increase renin release. Renin converts angiotensinogen to angiotensin I, which is converted in turn to angiotensin II, in the presence of angiotensin-converting enzyme (ACE). Angiotensin II is a potent circulating vasoconstrictor, constricting both arterioles and veins, resulting in an increase in blood pressure. Angiotensin II exerts a preferential vasoconstrictor action on the efferent arterioles of the renal glomerulus, increasing glomerular filtration. Furthermore, angiotensin II stimulates aldosterone secretion, leading to increased renal sodium reabsorption and increased blood volume, which contribute to a further increase in blood pressure. These effects of angiotensin II are mediated by stimulation of angiotensin II type 1 (AT1) receptors.

Treatment strategies

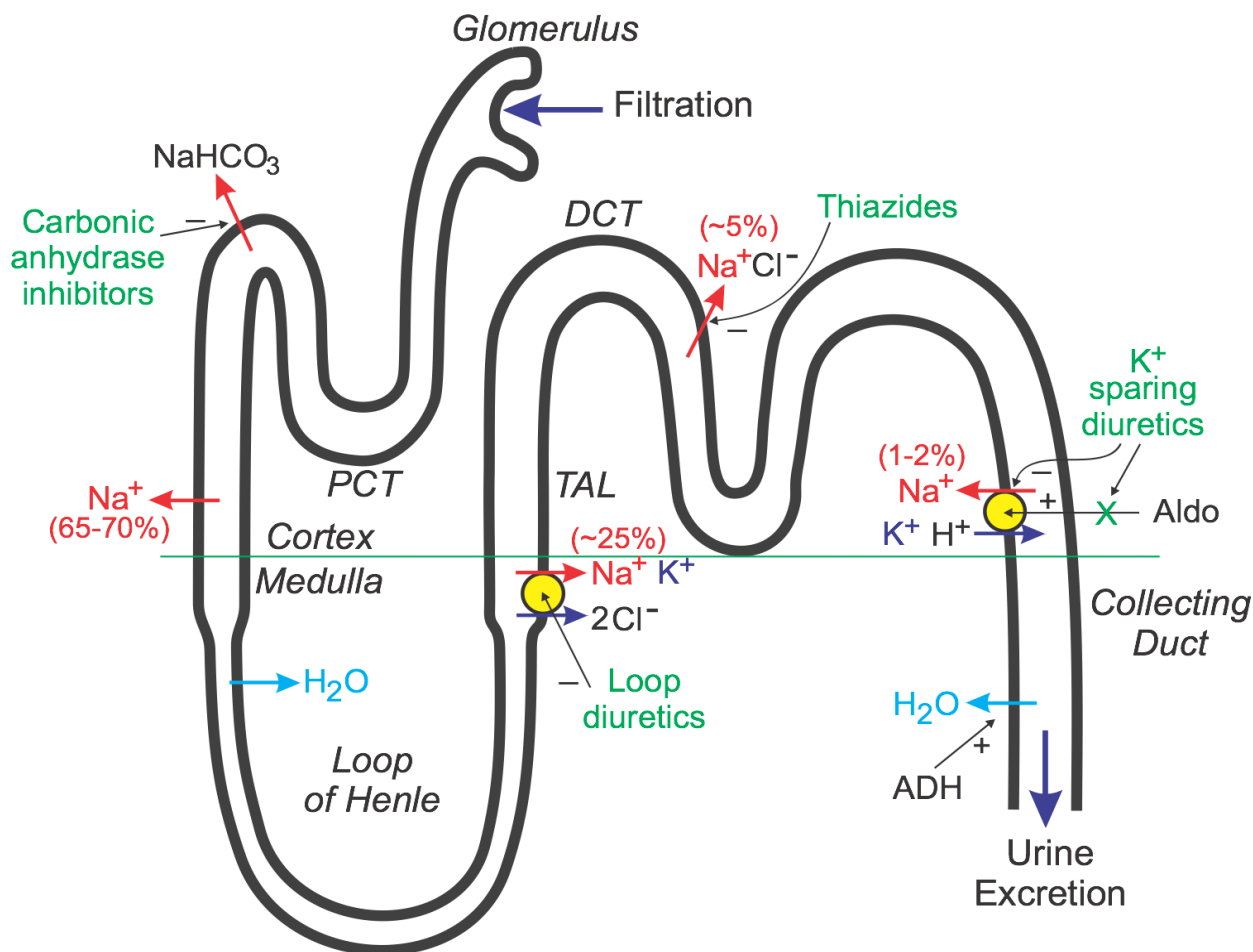
The goal of antihypertensive therapy is to reduce cardiovascular and renal morbidity and mortality. The relationship between blood pressure and the risk of cardiovascular events is continuous, and, thus, lowering of even moderately elevated blood pressure significantly reduces cardiovascular disease. For most patients, the blood pressure goal when treating

hypertension is a systolic blood pressure of less than 140 mm Hg and a diastolic blood pressure of less than 90 mm Hg. Mild hypertension can sometimes be controlled with monotherapy, but most patients require more than one drug to achieve blood pressure control. Current recommendations are to initiate therapy with a thiazide diuretic, ACE inhibitor, angiotensin receptor blocker (ARB), or calcium channel blocker.

➤ Diuretics

Thiazide diuretics can be used as initial drug therapy for hypertension unless there are compelling reasons to choose another agent. Drugs that increase urine flow are called diuretics. Diuretics play an important role in the management of high blood pressure. They are often used in combination with other classes of antihypertensive drugs. Diuretic can be used as first line drug therapy for hypertension. Low doses diuretics therapy is safe inexpensive and effecting in preventing stroke.

Mechanisms of diuretic drugs



Diuretic drugs increase urine output by the kidney (i.e., promote diuresis). This is accomplished by altering how the kidney handles sodium. If the kidney excretes more sodium, then water

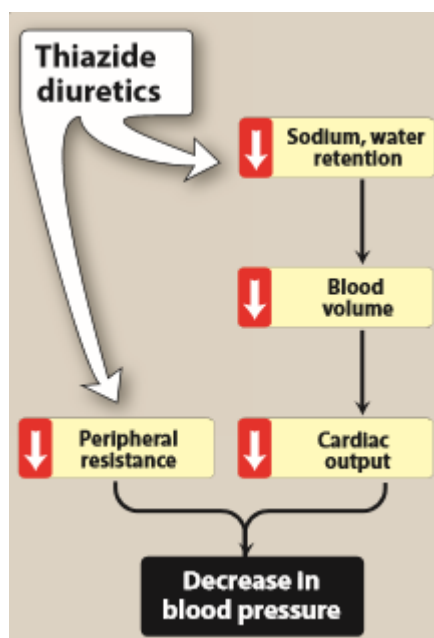
excretion will also increase. Most diuretics produce diuresis by inhibiting the reabsorption of sodium at different segments of the renal tubular system. (Sometimes a combination of two diuretics is given because this can be significantly more effective than either compound alone (synergistic effect).

Loop Diuretic

Inhibit the sodium-potassium-chloride cotransporter in the thick ascending limb (see above figure). This transporter normally reabsorbs about 25% of the sodium load; therefore, inhibition of this pump can lead to a significant increase in the distal tubular concentration of sodium, , and less water reabsorption in the collecting duct leads to diuresis (increased water loss) and natriuresis (increased sodium loss).

Thiazide diuretics

Thiazide diuretics, such as hydrochlorothiazide and chlorthalidone lower blood pressure initially by increasing sodium and water excretion. This causes a decrease in extracellular volume, resulting in a decrease in cardiac output and renal blood flow



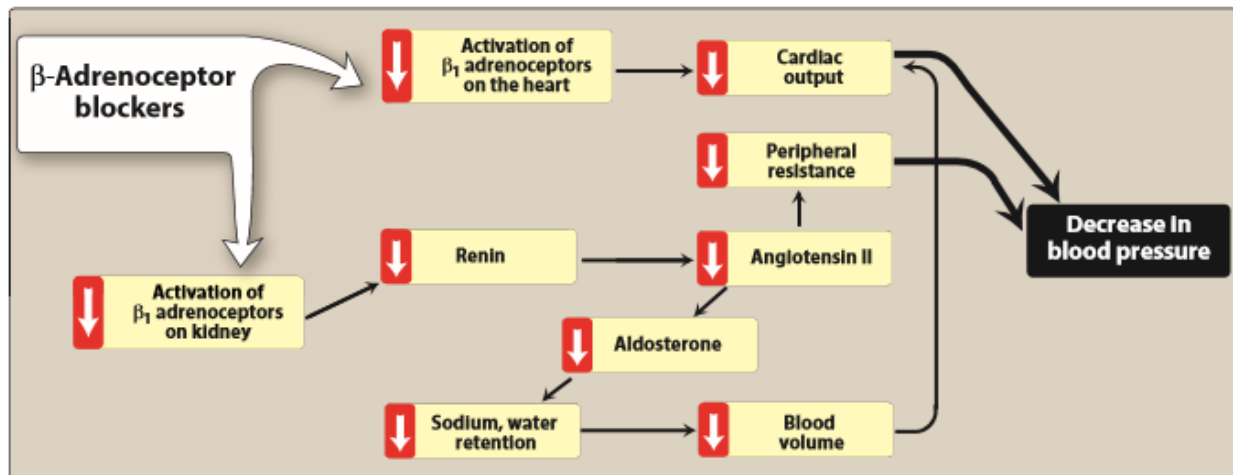
potassium-sparing diuretics.

Unlike loop and thiazide diuretics, some of these drugs do not act directly on sodium transport. Some drugs in this class antagonize the actions of aldosterone (aldosterone receptor antagonists) at the distal segment of the distal tubule. This causes more sodium (and water) to pass into the collecting duct and be excreted in the urine. They are called K⁺-sparing diuretics because they do not produce hypokalemia like the loop and thiazide diuretics. The reason for this is that by inhibiting aldosterone-sensitive sodium reabsorption, less potassium and

hydrogen ion are exchanged for sodium by this transporter and therefore less potassium and hydrogen are lost to the urine.

➤ **β- Adrenoceptor blocking agent**

The β-blockers reduce blood pressure primarily by decreasing cardiac output .They may also decrease sympathetic outflow from the central nervous system (CNS) and inhibit the release of renin from the kidneys, thus decreasing the formation of angiotensin II and the secretion of aldosterone.



The prototype β-blocker is propranolol which acts at both β₁ and β₂ receptors. Selective blockers of β₁ receptors, such as metoprolol and atenolol are among the most commonly prescribed β-blockers. Nebivolol is a selective blocker of β₁ receptors, which also increases the production of nitric oxide, leading to vasodilation.

Therapeutic uses

The primary therapeutic benefits of β-blockers are seen in hypertensive patients with concomitant heart disease, such as supraventricular tachyarrhythmia (for example, atrial fibrillation), previous myocardial infarction, angina pectoris, and chronic heart failure. Conditions that discourage the use of β-blockers include reversible bronchospastic disease such as asthma, second- and third-degree heart block, and severe peripheral vascular disease.

Adverse effect



➤ ACE Inhibitors

The ACE inhibitors, such as enalapril and lisinopril], are recommended as first-line treatment of hypertension in patients with a variety of compelling indications, including high coronary disease risk or history of diabetes, stroke, heart failure, myocardial infarction, or chronic kidney disease.

Action

The ACE inhibitors lower blood pressure by reducing peripheral vascular resistance without reflexively increasing cardiac output, heart rate, or contractility. These drugs block the enzyme ACE which cleaves angiotensin I to form the potent vasoconstrictor angiotensin II

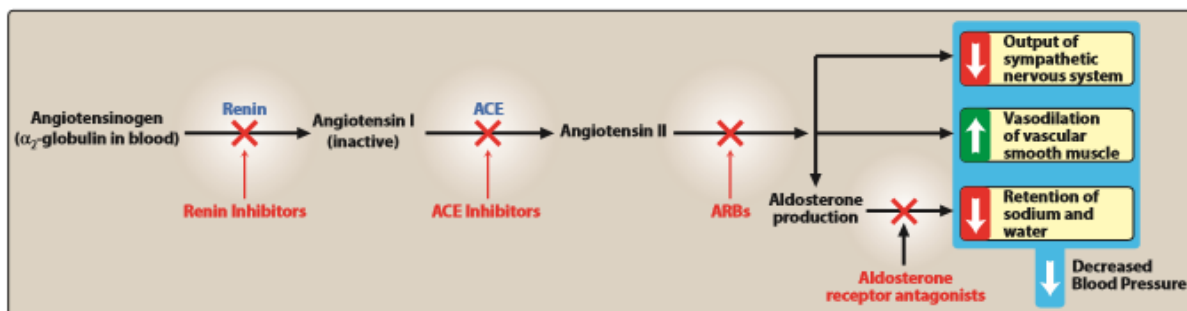


Figure 17.10

Effects of various drug classes on the renin–angiotensin–aldosterone system. Blue = drug target enzymes; red = drug class.

ACE is also responsible for the breakdown of bradykinin, a peptide that increases the production of nitric oxide and prostacyclin by the blood vessels. Both nitric oxide and prostacyclin are potent vasodilators. ACE inhibitors decrease angiotensin II and increase bradykinin levels. Vasodilation of both arterioles and veins occurs as a result of decreased vasoconstriction (from diminished levels of angiotensin II) and enhanced vasodilation (from increased bradykinin). By reducing circulating angiotensin II levels, ACE inhibitors also decrease the secretion of aldosterone, resulting in decreased sodium and water retention. ACE inhibitors reduce both cardiac preload and afterload, thereby decreasing cardiac work.

Therapeutic uses

Like the ARBs, ACE inhibitors slow the progression of diabetic nephropathy and decrease albuminuria and, thus, have a compelling indication for use in patients with diabetic nephropathy. Beneficial effects on renal function may result from decreasing intraglomerular pressures, due to efferent arteriolar vasodilation. ACE inhibitors are a standard in the care of a patient following a myocardial infarction and first-line agents in the treatment of patients with systolic dysfunction. Chronic treatment with ACE inhibitors achieves sustained blood pressure reduction, regression of left ventricular hypertrophy, and prevention of ventricular remodeling after a myocardial infarction. ACE inhibitors are first-line drugs for treating heart failure, hypertensive patients with chronic kidney disease, and patients at increased risk of coronary artery disease. All of the ACE inhibitors are equally effective in the treatment of hypertension at equivalent doses.

Adverse effect

Dry cough , Hyperkalemia , skin rash, Hypotension