Chapter 10

Blood Pressure and Antithrombotic Agents

Objectives

Upon completion of this chapter, you will be able to

- Understand the variables that affect blood pressure.
- Define key terms related to blood pressure and antithrombotic agents.
- Relate cardiovascular physiology to pharmacologic treatments.
- Describe indications and pharmacologic effects of various types of antihypertensive agents.
- Relate renal physiology to diuretic treatment.
- Describe indications and pharmacologic effects of anticoagulants, antiplatelet agents, and fibrinolytic agents.

Key Terms

afterload
anticoagulant
antiplatelet
baroreceptor
compliance
essential hypertension
fibrinolytic
hypertension
preload
thromboembolism

Abbreviations

ACE	angiotensin-converting enzyme
ACEI	ACE inhibitor
ACT	activated clotting time
ADH	antidiuretic hormone
ADP	adenosine diphosphate
aPTT	activated partial thromboplastin time
ARB	angiotensin II receptor blocker
BP	blood pressure
CCB	calcium channel blocker
CO	cardiac output
DTI	direct thrombin inhibitor
DVT	deep vein thrombosis
GP	glycoprotein
HIT	heparin-induced thrombocytopenia
ICP	intracranial pressure
INR	international normalized ratio
JNC	Joint National Committee
LMWH	low-molecular-weight heparin
PCI	percutaneous coronary intervention
PT	prothrombin time
TE	thromboembolism
TOD	target organ disease
tPA	tissue plasminogen activator
TPR	total peripheral resistance
UFH	unfractionated heparin

Chapter 9 focused on drugs that affect the heart. This chapter focuses on regulating pressure within the cardiovascular system. The drugs that regulate pressure in the cardiovascular system primarily affect sympathetic tone, the diameter of the blood vessels, or the actual blood volume. Diuretics work on the renal system and affect blood volume; therefore, they indirectly affect blood pressure. Although diuretics were mentioned in the previous chapter, they are discussed further in this chapter. In addition, this chapter discusses agents that ensure the blood itself flows freely through blood vessels and is not affected by intravascular blood clots. Anticoagulants prevent vascular clots from forming, extending, and/or breaking off, blocking vital blood flow to tissues and organs. In addition, this chapter discusses fibrinolytic agents that dissolve existing blood clots as well as antiplatelet agents that prevent clot formation from the adhesion and aggregation of platelets.

10.1 Blood Pressure

10.1a The Basics

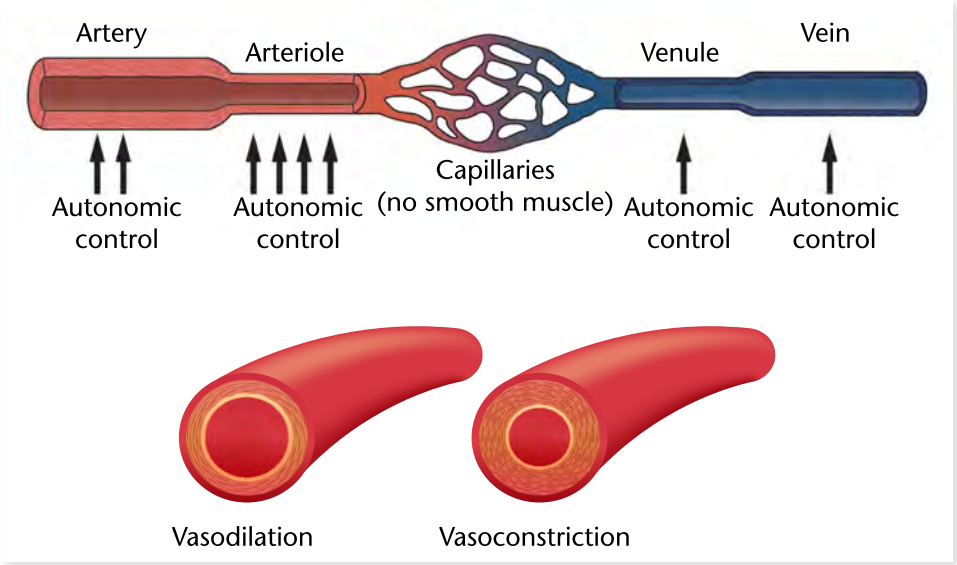
The cardiovascular system must be pressurized for blood to flow, providing vital gas exchange, nutrients, immunologic defense, and other functions. Too much pressure can be disruptive and have serious consequences, whereas too little pressure will not allow enough blood flow to vital areas such as the brain or kidneys and can again have dire consequences.

The heart, as discussed in Chapter 9, is the pump that is connected to a roadway of blood vessels traveling throughout the body. Circulatory flow results as pressure differences are created in the system by cardiac contraction. Vessels offer varying resistance to flow depending on their diameter or level of dilation or constriction. Just as the heart can be broken down into a right- and left-sided pump with different purposes, the circulatory system can be divided between the pulmonary and systemic vascular systems. The *pulmonary vascular system* represents the vessels that flow through the lungs for gas exchange. The *systemic vascular system* comprises all the other vessels that supply tissues and organs with blood flow (perfusion). Each system contains arteries, arterioles (small arteries), veins, venules (small veins), and capillaries.

10.1b Blood Vessels

A layer of endothelial cells lines each vessel in the vascular system. This layer is a passive barrier that keeps other cells and proteins from going into tissues; it also contains substances that control the contraction of underlying smooth muscle, such as prostacyclin (vasodilator), nitric oxide (vasodilator), and endothelin (vasoconstrictor) (see Figure 10–1). Some of the proposed pathophysiology of the cardiac system may be related to endothelial dysfunction. In Figure 10–1, notice that the walls of arteries, arterioles, veins, and venules all contain smooth muscle in different proportions. The capillaries contain no smooth muscle because this would act as a diffusion barrier to the vital gas exchange that occurs in capillaries. It is important to remember that arteries carry blood away from the heart to the organs and tissues, and veins carry blood back to the heart.

Figure 10–1 Schematic Diagram of Various Blood Vessels



Source: (bottom illustration) Shutterstock

The sympathetic nervous system, discussed in Chapter 3, controls the activity of smooth muscle. Both neural and humoral (circulating within the blood) mechanisms control blood vessel contraction. Because the arterioles contain more smooth muscle and are under more nervous system control, they are the main *resistance vessels* and regulate the force against which the heart must pump, or the **afterload**. If the arterioles are vasoconstricted, this will narrow the circulatory highway, thereby increasing afterload and systemic vascular resistance. This leads to an increase in blood pressure. Conversely, vasodilation relaxes the smooth muscle layers in the vessels and thereby reduces afterload and lowers blood pressure. Arterioles branch into capillaries at the tissues, where vital gas exchange takes place—the blood delivers its oxygen and picks up waste carbon dioxide.

The systemic venules and veins then collect the deoxygenated blood from the tissue sites and return it to the right side of the heart to be pumped through the pulmonary vascular system to gain vital oxygen (inhalation) and rid the body of waste carbon dioxide (exhalation). The systemic veins and venules have a large capacity to hold blood and relatively little musculature compared to arteries and arterioles; therefore, they can distend much more easily without major pressure changes. The veins are considered *capacitance vessels*—they regulate preload. **Preload** is the amount of blood returning to the heart, contained in the ventricles, before a contraction.

Learning Hint

A balloon is a good way to understand these relationships. A new balloon is very noncompliant, so it takes more pressure to inflate. If you stretch the balloon (vasodilate it), it becomes more compliant and takes less pressure to inflate. A good disease analogy is an aneurysm, which is like a weak patch in a balloon. This section is too compliant, and high pressures (hypertension) could cause it to burst. You can visualize this if you have ever seen a weak spot on a garden hose. The weakened part of the hose creates a bubble, and is the most likely place the hose will leak under continued pressure.

Compliance is the extent to which the pressure of the vascular system increases as volume increases. More work is needed to push blood through a constricted vessel, so compliance is decreased, resulting in a greater pressure. If the compliance increases and the vessels vasodilate, the pressure is reduced.

Thus far, we have focused on the systemic vascular system; however, it is important to note that pressure must also be regulated within the pulmonary vascular system, and this will be discussed in later chapters. Finally, the kidneys play a role in regulating blood pressure in addition to their other roles of ridding the body of waste products, excreting drugs or metabolites, and maintaining fluid, electrolyte, and acid–base balance. This role is discussed later in this chapter.

10.1c Regulation of Blood Pressure

Blood pressure is controlled by centers in the brain that respond to changes in the **baroreceptors** (pressure sensors) in the arterial system. Baroreceptor reflexes are the primary autonomic mechanism for blood pressure homeostasis. These reflexes react to input from the carotid sinus and output from parasympathetic and sympathetic nerves to maintain blood pressure control. If the baroreceptors are stretched too far, thus sensing high pressure, they send signals that decrease sympathetic tone and thus reduce blood pressure. If the receptors sense low pressure, they increase sympathetic tone to increase blood pressure and maintain perfusion.

A mathematical relationship describing blood pressure is helpful in understanding the various ways pharmacologic control of blood pressure can be exerted. The equation is:

Blood pressure (BP) = cardiac output (CO) × total peripheral resistance (TPR)

From this equation, it is easy to see that anything that increases CO or TPR will increase blood pressure and vice versa. Cardiac output, as established in Chapter 9, is related directly to heart rate and stroke volume. Therefore, anything that decreases heart rate, diminishes stroke volume, or decreases total peripheral resistance will lower blood pressure (see Figure 10–2).

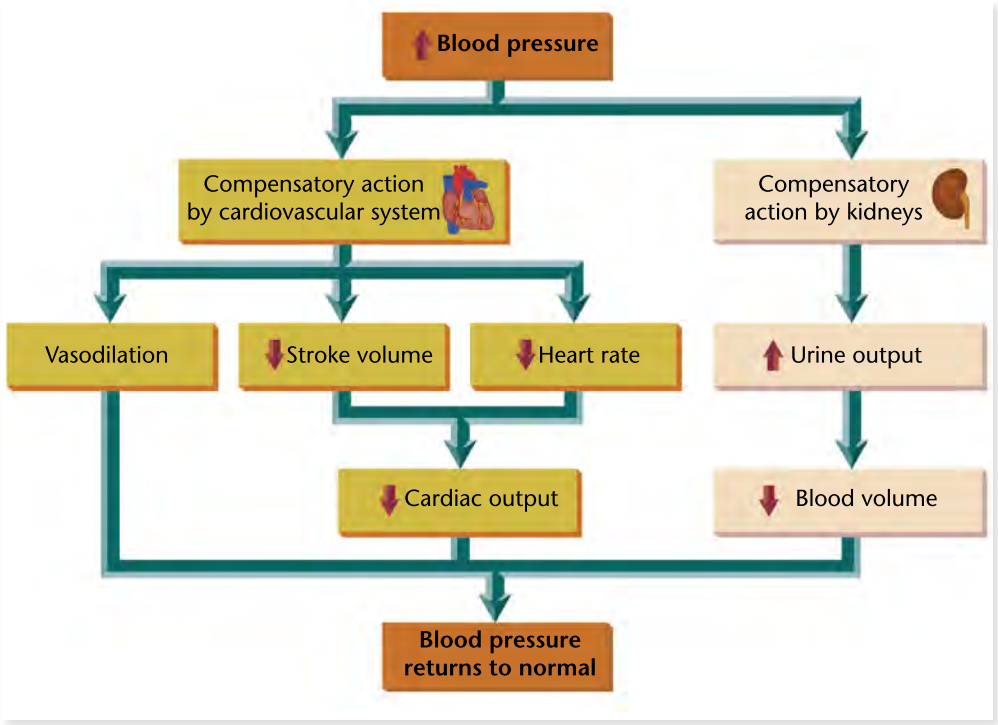
10.1d Hypertension

Hypertension can be characterized by an elevation in systolic blood pressure, diastolic blood pressure, or both. It is classified into stages as a guide to therapy. There are various causes of hypertension. If no specific cause can be found for the hypertension, it is termed **essential hypertension**; this is how we classify the majority of patients who have hypertension. This means that treatment of essential hypertension mainly focuses on lowering the blood pressure itself, rather than treating the underlying cause of the hypertension, which again, is unknown.

Controversy

Some of the etiologic factors that may contribute to the pathophysiology of hypertension are subject to debate, including the following: abnormal renin–angiotensin–aldosterone system, defective baroreceptors, insulin resistance, defective kidney response to fluid and electrolytes, deficient nitric oxide release from the endothelium, excess sodium, potassium depletion, and even too little calcium in the diet. Some of the drug classes discussed in this chapter involve one or more of these factors in terms of their mechanism of action.

Figure 10–2 Blood Pressure Homeostasis



Because the disease is usually asymptomatic, hypertension is frequently called the "silent killer." Hypertension, even without symptoms, is one of the leading causes of stroke, blindness, congestive heart failure, and renal disease. The Eighth Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-8) developed national clinical guidelines to aid clinicians in managing hypertension (please see Table 10–1). If hypertension is not treated, target organ disease (TOD) can result. Target organ disease may include, for example, left ventricular hypertrophy, transient ischemic attacks, peripheral vascular disease, retinopathy, or protein in the urine. If TOD is present at the time of diagnosis, it suggests that hypertension has been present long term but not treated adequately.

Clinical pearl

Many people with hypertension are asymptomatic, but others complain of a pounding in their heads. If pressure increases in your arms or legs, there is a certain "give" because the tissues are not rigid, allowing some of the pressure increase to dissipate. However, the skull does not allow this flexibility, and small increases in cerebral blood flow or pressure can increase the intracranial pressure (ICP) dramatically.

Table 10–1 Management of Hypertension (JNC-8)

Population	Systolic (mmHg) goal	Diastolic (mmHg) goal	Initial drug therapy
Patients with no cardiovascular disease	<140	<90	thiazide, ACEI, ARB, or CCB
Patients with or at high risk for cardiovascular disease (CVD)	<130	<80	thiazide, ACEI, ARB, or CCB
Any age with diabetes	<130	<80	thiazide, ACEI, ARB, or CCB
Any age with chronic kidney disease	<130	<80	ACEI or ARB

ACEI = angiotensin-converting enzyme inhibitor (ACEI)

CCB = calcium channel blocker

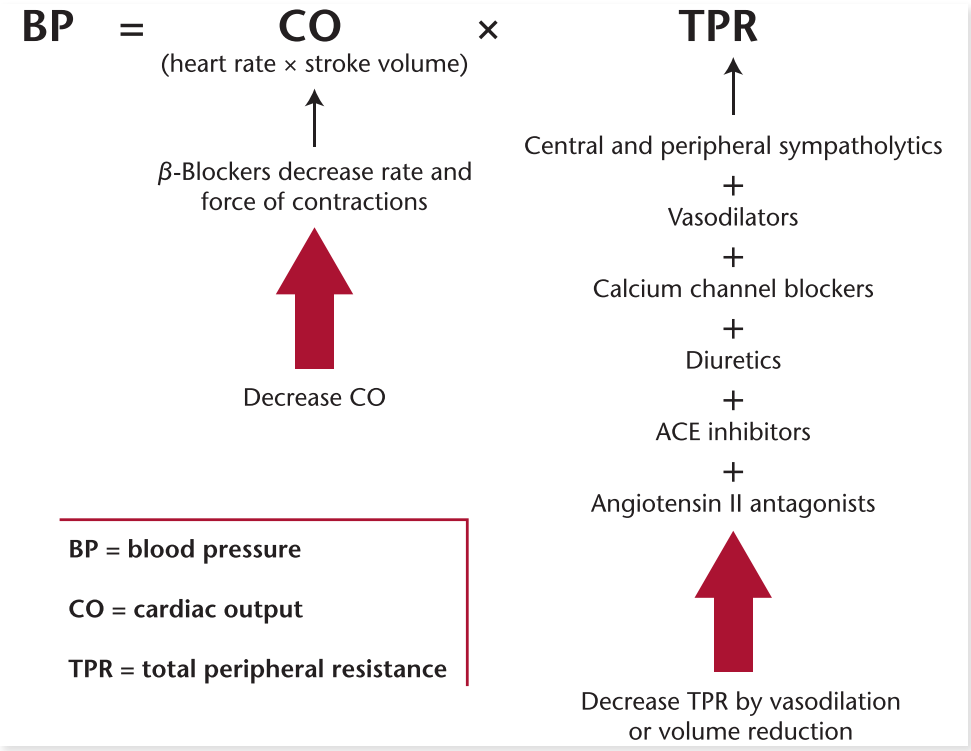
ARB = angiotensin II receptor blocker

CVD = cardiovascular disease

Data Source: Whelton PK, Carey RM, Aronow WS, Casey Jr DE, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith Jr SC, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams Sr KA, Williamson JD, Wright Jr JT, 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults, *Journal of the American College of Cardiology* (2017), doi: 10.1016/j.jacc.2017.11.006

Antihypertensives work on different parts of the blood pressure equation to either decrease cardiac output or decrease total peripheral resistance. See Figure 10–3, which shows the relationship between antihypertensive agents and the blood pressure equation. Looking at Figure 10–3, you can clearly see the potential role for combination antihypertensive therapy, which includes two drugs that work on different parts of the equation.

Figure 10–3 Relationship between Antihypertensive Agents and Blood Pressure Equation



Patient & Family Education

Benefits of Treating Hypertension

Because most patients with high blood pressure are not aware that their pressure is high, it is important to emphasize the long-term benefits of medicines they take for high blood pressure. This is especially important because blood pressure medicines may make them feel worse until their body gets used to them. Additionally, unlike other medications for pain or itching, the benefits of hypertension medications are not felt by the person taking them. For these reasons, hypertension medications show some of the highest nonadherence rates among chronic medications. Patients frequently feel that the medication is "not doing anything" and/or is "making them feel worse." Remind patients and their families that the benefits of lowering blood pressure to normal levels include reductions in strokes, heart attacks, and heart and kidney failures.

Before discussing the various pharmacologic agents to treat hypertension, it should be noted that nonpharmacologic lifestyle modification treatment is preferred if possible. By using lifestyle changes such as exercise, weight loss, alcohol restriction, smoking cessation, and salt restriction (aka, the DASH diet), patients may be able to control high blood pressure or decrease the amount of drug needed to control the disease. Some individuals are more sensitive than others to dietary salt intake, and they are referred to as salt sensitive. Salt-sensitive patients achieve greater degrees of blood pressure lowering by restricting dietary sodium intake. Numerous genes are probably responsible for salt excretion by the kidney. The different mechanisms for the pathophysiology of hypertension may explain why patients respond differently to nonpharmacologic treatment as well as different antihypertensives. If the hypertension cannot be treated effectively nonpharmacologically, then initial drug therapy is individualized according to concurrent compelling medical indications (see Table 10–2). In general, the goal blood pressure should be less than 130/80 mmHg if the patient has clinical cardiovascular disease (CVD). In patients without cardiovascular disease, goal blood pressure is less than 140/90 mmHg.

Table 10–2 Compelling Indications

Cause of Hypertension	Pharmacologic Treatment
Systolic heart failure	Diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist
Post–myocardial infarction	β-Blocker, ACE inhibitor, aldosterone antagonist
Diabetes mellitus	ACE inhibitor or ARB, diuretic, CCB
Chronic kidney disease	ACE inhibitor or ARB
Recurrent stroke	Diuretic or ACE inhibitor

An example of a treatment choice based on concurrent compelling medical conditions is a hypertensive patient with systolic heart failure. This patient will most likely be started on an angiotensin-converting enzyme inhibitor (ACEI) because these drugs can treat both medical conditions. If single-drug therapy is not successful, then additional drugs from a different class or a new drug from a different class are given until the right combination works. The various types of antihypertensive agents include (1) diuretics, (2) central- and (3) peripheral-acting sympatholytics, (4) β-blockers, (5) ACEIs, (6) angiotensin II receptor blockers (ARBs) or antagonists, (7) calcium channel blockers (CCBs), and (8) vasodilators. Again, please refer to Table 10–1 for the classification and management of blood pressure in adults and Table 10–2 for compelling indications for the various drug classes.

Controversy

There is no agreement as to which antihypertensive medicine should be used first. Unless there is an underlying condition that would benefit from a beta-blocker, this class of high blood pressure medicines is not used as a first-line treatment option. Another controversial area is the choice of a thiazide. Most of the research using a thiazide diuretic was done using chlorthalidone, which is approximately twice as potent and much longer acting than hydrochlorothiazide, the most frequently prescribed diuretic. Whether hydrochlorothiazide is interchangeable for chlorthalidone in not only reducing blood pressure but also preventing clinically important outcomes is questionable. Additionally, some hypertension medication classes have shown to have increased or decreased effectiveness in certain patient population. For example, calcium channel blockers like amlodipine, have shown increased effectiveness in African American patients and may be chosen as initial therapy over other first-line options.

10.2 Categories of Drugs to Treat Hypertension

In Chapter 3, you learned that any agent that inhibits or blocks (lytic) sympathetic nerve function results in decreased venous tone, decreased heart rate, decreased contractility of the heart, decreased cardiac output, and decreased total peripheral resistance. On this basis, it makes sense that sympatholytics are used as antihypertensives. Sympatholytic antihypertensives are classified by their central (brain) or peripheral (circulating vessels) site or mechanism of action. These antihypertensive agents affect the α- or β-receptors.

10.2a Direct-Acting α_2-Agonists or Central-Acting Sympatholytics

Central-acting agents work directly on the α_2-receptors in the central nervous system (CNS) to decrease sympathetic outflow of activity from the CNS. When they are stimulated, α_2-receptors block the release of norepinephrine. Remember that norepinephrine is an endogenous vasoconstrictor; thus, its blockage causes vasodilation and reduces blood pressure. α_2-Selective agonists such as clonidine therefore decrease centrally controlled sympathetic outflow from the brain, resulting in decreased cardiac output and decreased vascular resistance.

Clinical pearl

Clonidine can also be used to treat withdrawal symptoms in patients who are giving up smoking or going through opiate withdrawal. It is proposed that it works by decreasing the noradrenergic hyperactivity that is common in these situations. Guanfacine may also be used to treat attention-deficit/hyperactivity disorder.

Rebound hypertension may occur when a central α_2-agonist is discontinued. This means that the blood pressure can overshoot and become higher than it was before treatment. Another side effect to be aware of with this class, and all antihypertensives, is orthostatic hypotension. *Orthostatic hypotension* occurs when blood pressure drops as the patient moves from a sitting to a standing position. Patients should always rise slowly from a horizontal or sitting position to minimize dizziness that may accompany the orthostasis and lead to falls. The use of this class of drugs is limited due to a high incidence of common adverse effects such as sexual dysfunction, dry mouth, and sedation. Common types of central-acting or α_2-agonists are:

- clonidine (Catapres®)
- guanfacine (Intuniv®)

10.2b α_1-Blockers or Peripheral-Acting Sympatholytics

α_1-Receptors are found mainly in the blood vessels themselves, and their stimulation causes vasoconstriction. However, α_1-blockers or antagonists block receptors in both arterioles and veins, thus causing vasodilation. α_1-Blockers such as prazosin therefore decrease vascular resistance. α-Blockers are well known for their ability to cause orthostatic hypotension, especially with the first dose. Other common adverse effects include headache and weakness. Patients should always be counseled to take their first dose at bedtime as a way to lessen first-dose hypotension. These drugs are generally not used as first-line therapy except possibly for older men with symptomatic benign prostatic hyperplasia, for whom these medications help improve symptoms. Some common α_1-blockers or peripheral-acting sympatholytics are:

- prazosin (Minipress®)
- terazosin (Hytrin®)
- doxazosin (Cardura®)

Clinical pearl

α-Blockers that are prescribed for hypertension are also effective for benign prostatic hyperplasia. They work because the prostate has α-receptors whose blockade results in decreased smooth muscle tone and less obstruction. For many patients, not only is their blood pressure lowered but they also experience decreased frequency of urination (frequent urination is a symptom of benign prostatic hyperplasia). Treating two diseases with one drug is like killing two birds with one stone (but what a terrible saying)!

10.2c β-Blockers

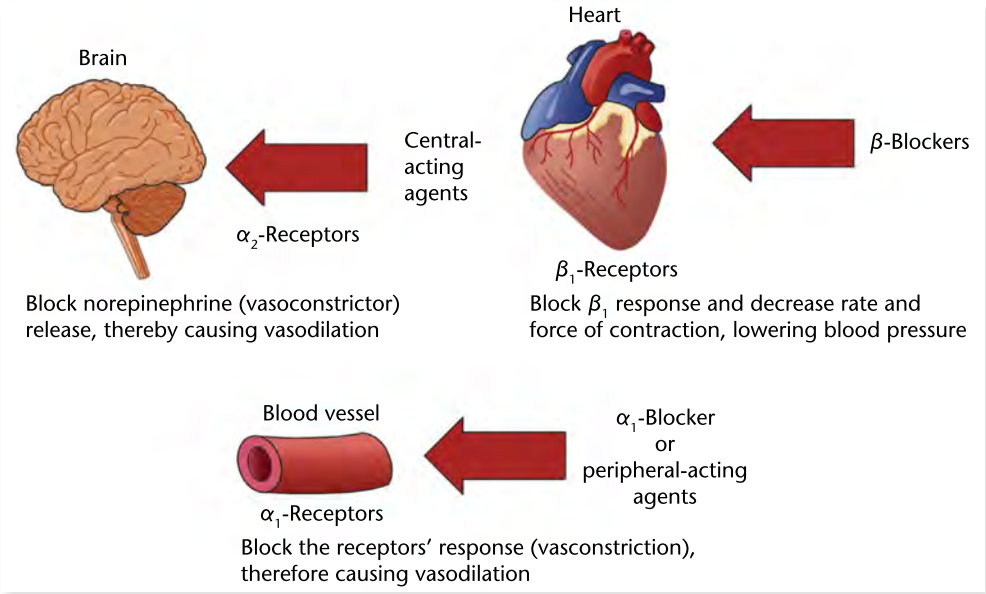
β_1-Receptors are found primarily in the heart, and their stimulation leads to an increase in the rate and force of contraction. β-Blockers inhibit sympathetic activity and decrease the rate and force of contraction, thus lowering blood pressure. As discussed in Chapter 9, β-blockers differ in their selectivity for β_1- and β_2-receptors.

β-Blockers need to be used cautiously in patients with severe peripheral vascular disease and insulin-dependent diabetics. This is because β-blockers can exacerbate symptoms of arterial insufficiency and mask warning signs of hypoglycemia. β-Blockers can also cause bradycardia or atrioventricular conduction abnormalities. β-Blockers that are *not* selective for β_1-receptors can exacerbate chronic obstructive pulmonary disease by blocking the β_2-receptors in the lung. The cardioselective beta$_1$-blockers include atenolol, betaxolol, bisoprolol, esmolol, acebutolol, metoprolol, and nebivolol. β-Blockers can decrease HDL cholesterol, raise triglycerides, and elevate plasma glucose. Some common β-blockers include:

- metoprolol (Lopressor®)
- propranolol (Inderal®)
- atenolol (Tenormin®)
- carvedilol (Coreg®)

See Figure 10–4, which illustrates the sites of action of sympatholytic antihypertensive agents.

Figure 10–4 Sites of Action of Sympatholytic Antihypertensive Agents



10.2d Diuretics

Learning Hint

To get a visual picture, imagine the tubular system as PVC piping—you know, the white plastic kind used for sink drains and such. Now wrap red yarn all around it to represent the peritubular capillary system. What stays in the pipe is excreted from the body via urination, or goes down the drain. What is "reabsorbed" (via capillary diffusion) goes into the red yarn to be recirculated in the bloodstream.

As discussed in Chapter 9, diuretics are used to treat edema associated with heart failure as well as to treat hypertension. To understand renal pharmacology, it is important to review the basics of renal physiology. Kidneys rid the body of waste products by filtering the blood. In addition, the kidneys maintain fluid, electrolyte, and acid–base balance. The kidney is thought of primarily as an excretory organ; it also plays an important role in drug elimination.

The functional unit of the kidney is the *nephron,* which is comprised of the glomerulus, proximal convoluted tubule, the loop of Henle, the distal convoluted tubule, and the collecting duct. As blood is filtered in the glomerulus, it drains into the tubular systems, where parts of the filtrate can be reabsorbed back into the blood via the peritubular capillary system. The filtrate remaining in the tubular system is excreted via the urine.

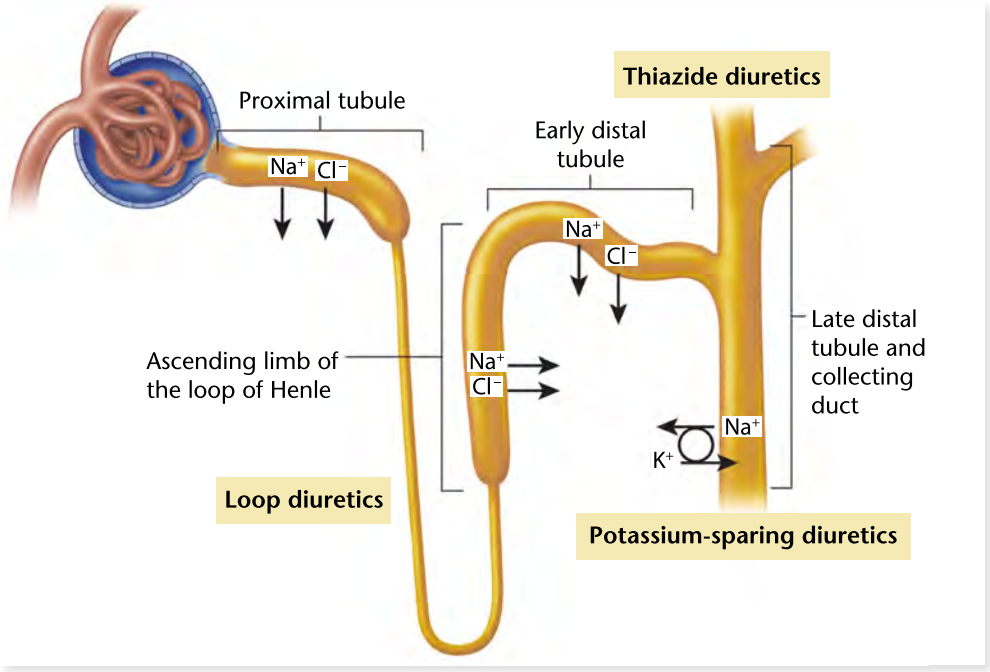
Electrolytes or salts that are filtered are usually reabsorbed at a certain site along the kidney. Electrolytes regulate acid–base balance and affect neuromuscular activity. Blood volume is regulated by sodium and water reabsorption, which are affected by osmosis and concentration gradients and are also influenced by antidiuretic hormone (ADH) and aldosterone. Renal secretion of electrolytes is important in helping to control the acid–base balance of the body.

Diuretics basically do not allow sodium to be reabsorbed back into the peritubular capillary system (bloodstream). If sodium stays in the tubular system, it draws water via osmosis into the tubular system, which is then excreted as increased urine output.

All diuretics increase salt and water excretion, but the effect that diuretics have on other ions depends on the diuretic. Different diuretics work on different sites in the kidney, and they are classified according to the site in the nephron where they work. Because the mechanisms of reabsorption of sodium and water and of chloride and potassium are different in each segment of the kidney, diuretics acting on different segments have different mechanisms. In general, thiazide diuretics are preferred as antihypertensives unless the patient has severe kidney disease. Initially, thiazide diuretics lower blood volume by increasing sodium and water excretion and therefore lower blood pressure. Over the longer term, blood volume returns to normal while systemic vascular resistance falls.

Three different classes of diuretics are used to treat hypertension: thiazide, loop, and potassium-sparing diuretics. Blood pressure–lowering effects are not necessarily dose related. There can be a *ceiling effect* for drugs, as with the thiazide class of diuretics, in which increased doses just cause more side effects and do not lower blood pressure. Side effects of diuretics differ depending on the class and may include hypokalemia, hypomagnesemia, hyperuricemia, and hyperglycemia. Loop diuretics cause less hyperglycemia and differ from thiazides in that they cause hypocalcemia, whereas thiazides can be calcium sparing. See Figure 10–5, which shows the mechanisms of action of diuretics.

Figure 10–5 Mechanisms of Action of Diuretics



Diruetic	Action
Thiazide	Act on the early distal tubule to block the reabsorption of sodium, chloride, and water. Excretion of potassium is increased.
Loop	Act on the ascending limb of the loop of Henle to block the reabsorption of sodium, chloride, and water. Excretion of potassium is increased.
Potassium-sparing	Act on the late distal tubule and collecting ducts to block the reabsorption of sodium and reduce the secretion of potassium (sodium-potassium exchange). Excretion of potassium is *not* affected.

Specific Diuretics

The thiazide diuretics block sodium and chloride reabsorption in the distal convoluted tubule, resulting in excretion of about 6% of the filtered sodium. Water follows this salt, but salt is excreted in excess of water. Examples of thiazide diuretics include:

- chlorthalidone (Thalitone®)
- hydrochlorothiazide (Microzide®)

Loop diuretics decrease sodium, chloride, and water absorption at the loop of Henle by blocking absorption of chloride into the bloodstream. Since sodium is

co-transported with chloride, it follows the chloride and water out of the kidney. Water is excreted in excess of salt. These are the most potent diuretics. Examples of loop diuretics include:

- bumetanide (Bumex®)
- furosemide (Lasix®)
- torsemide (Demadex®)

Loop diuretics such as furosemide (Lasix®) can be used for hypertension, but they have a shorter duration of action than thiazide diuretics; as mentioned previously, loop diuretics are generally reserved for patients with severe, chronic kidney failure. Loop diuretics are administered via IV drip or orally in multiple doses per day, compared to thiazide diuretics, which are taken daily. They are also useful in the treatment of edema and acute pulmonary edema. In that situation, in addition to diuresing, they act as venodilators via their effect on enhancing prostaglandin secretion. This is why patients report alleviation of their pulmonary edema symptoms before the medicine has caused an increase in urine production. Loop diuretics are also used in the treatment of hypercalcemia of malignancy to lower calcium levels.

Potassium-sparing diuretics avoid potassium being excreted along with sodium, as happens with thiazides or loop diuretics. Excessive loss of potassium leads to hypokalemia and can have serious cardiac effects. Potassium-sparing diuretics include:

- amiloride (Midamor®)
- spironolactone (Aldactone®)
- triamterene (Dyrenium®)
- eplerenone (Inspra®)

Potassium-sparing diuretics such as spironolactone (Aldactone®) may be administered in combination with other diuretics to prevent potassium depletion. If a potassium sparing diuretic cannot be used, potassium supplementation may be required with loop or thiazide diuretics. They have a weak antihypertensive effect when used alone but can be additive with thiazide or loop diuretics. If the hypertension is aldosterone mediated, an aldosterone-antagonist diuretic, such as spironolactone, is especially effective. Thiazide and loop diuretics both cause potassium loss and are not potassium sparing. Thiazides are frequently used in combination with a potassium-sparing diuretic such as triamterene (Dyrenium®). This is conveniently available as a combination product called Maxzide®.

Life Span Considerations

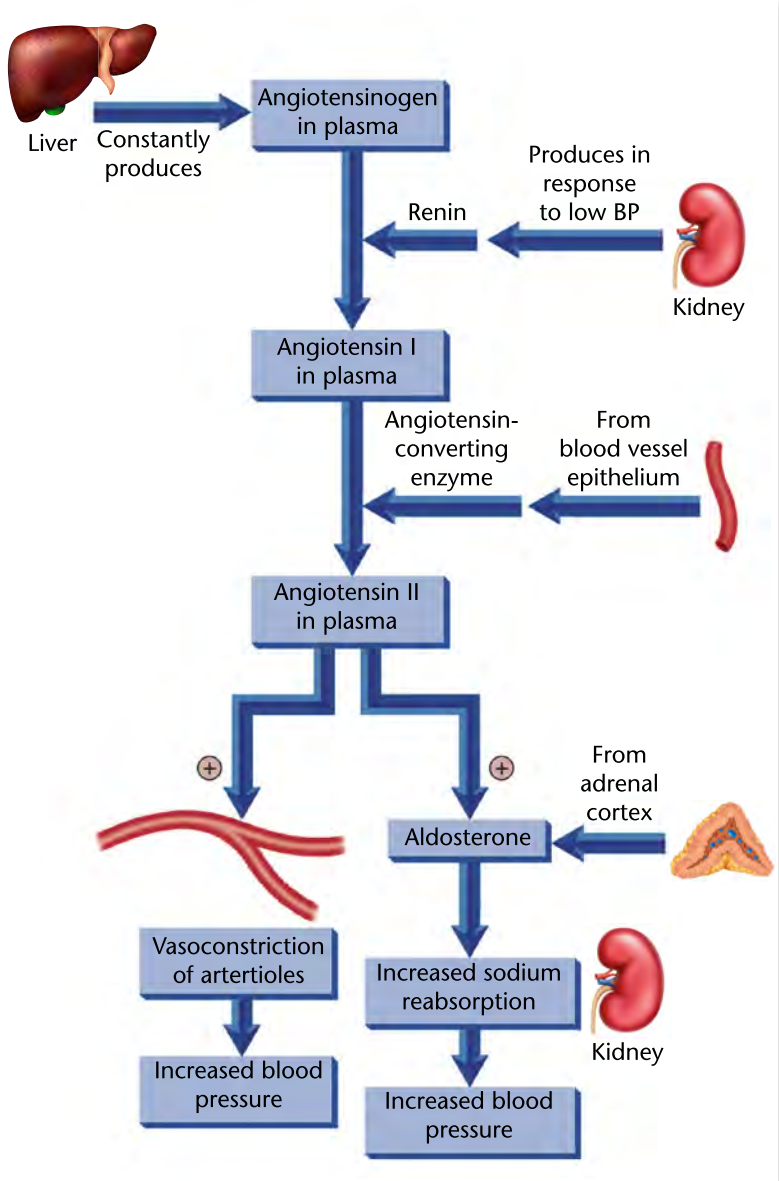
Limiting Dietary Salt

Whether a person with high blood pressure is young or old, restricting salt in the diet is extremely important. This is difficult to do because 80% of our salt intake comes from foods we buy at the grocery store and not from the salt shakers on our dinner tables. Helping patients learn how to read food labels and choose lower-sodium foods is one way of helping patients lower their dietary salt intake. As a good general rule of thumb, no more than 2,300 mg of sodium should be ingested per day from all sources.

10.2e Angiotensin-Converting Enzyme Inhibitors (ACEIs)

The kidneys are involved in blood pressure regulation through the renin–angiotensin system. They release renin into the bloodstream when renal blood flow decreases. Renin acts on angiotensinogen (also known as angiotensin precursor) in the bloodstream to form angiotensin I. It is then converted to angiotensin II as it circulates through the lungs; angiotensin II is a powerful vasoconstrictor. Angiotensin II also causes the release of the hormone aldosterone, which increases sodium and water reabsorption into the bloodstream. The increased blood volume, along with the vasoconstriction, increases blood pressure (see Figure 10–6). ACEIs decrease blood levels of angiotensin II and aldosterone by interrupting the renin–angiotensin–aldosterone system and thereby lower blood pressure. They reduce peripheral arterial resistance without affecting heart rate and cardiac output.

Figure 10–6 The Renin–Angiotensin–Aldosterone Pathway



Source: (organ illustrations) Shutterstock

These drugs have up to a 20% incidence of cough as a side effect. Cough can occur after anywhere from 1 week to 6 months of therapy and is more common in women than in men. Another side effect of ACEIs is hyperkalemia, especially in patients with decreased renal function. ACEIs may cause a decline in renal function that could be severe, even though they are also used to protect renal function (renal sparing), and they decrease protein loss via urine in patients with diabetes. Acute kidney failure or a decline in kidney function is unusual unless the patient has bilateral renal artery stenosis or is volume depleted. Hypertension and diabetes frequently coexist in patients, making ACEIs common drugs used. Common ACEIs include:

- benazepril (Lotensin®)
- captopril (Capoten®)
- enalapril (Vasotec®)
- lisinopril (Prinivil®)

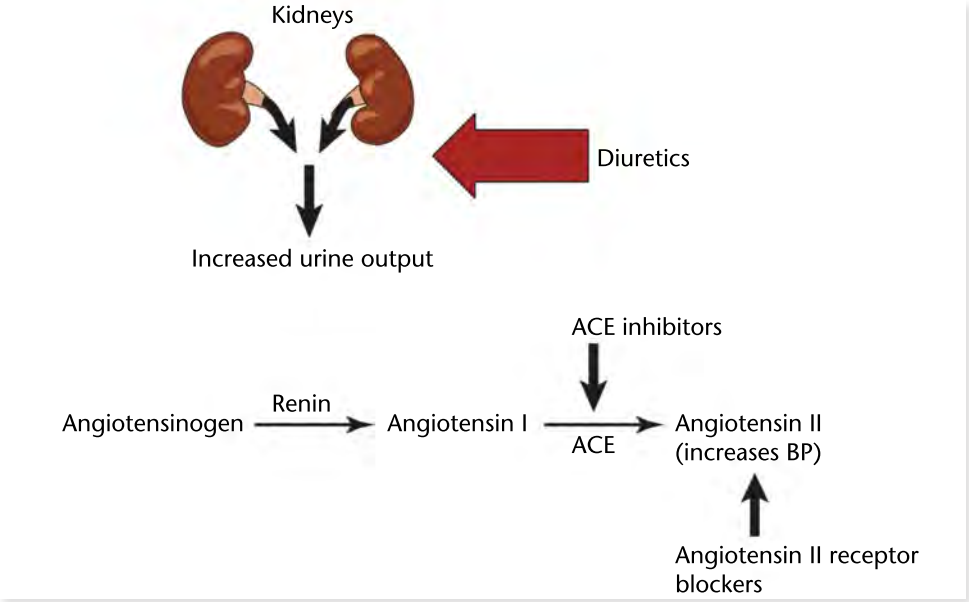
10.2f Angiotensin II Receptor Blockers (ARBs)

Angiotensin II antagonists inhibit angiotensin II at receptor sites on the blood vessels and therefore act differently than ACEIs. They are an alternative for patients with a cough side effect from an ACEI. They can also cause hyperkalemia and acute kidney failure, as discussed previously for ACEIs. They can be used as a first-line option for hypertension, but are also used as an alternative for those patients who cannot tolerate the aforementioned side effect of cough caused by ACEIs. Representative drugs in this category include:

- losartan (Cozaar®)
- valsartan (Diovan®)
- olmesartan (Benicar®)

See Figure 10–7, which shows the sites and mechanisms of action of diuretics, ACEIs, and angiotensin II receptor blockers.

Figure 10–7 Mechanisms of Action of Diuretics, ACEIs, and Angiotensin II Receptor Blockers



10.2g Calcium Channel Blockers

Learning Hint

Calcium channel blockers are also known as calcium entry blockers (CEBs).

Calcium channel blockers (CCBs) produce arteriole relaxation by the same mechanisms they use to relieve angina. By blocking calcium needed for vascular smooth muscle contraction, they relax vascular smooth muscle and vasodilation results. Any effects related to the drug's action on calcium in smooth muscle are unrelated to dietary calcium.

The most common side effects of CCBs are peripheral edema and dizziness. As explained in the section on arrhythmia in Chapter 9, CCBs have different effects on heart rate and atrioventricular nodal conduction. This may cause side effects when used for hypertension, therefore only amlodipine is used for primary hypertension when there are no comorbidities present. Diltiazem and verapamil are not used for primary hypertension treatment, but are used for hypertension when a heart rate/arrhythmia condition is also present. Common CCBs include:

- amlodipine (Norvasc®)
- diltiazem (Cardizem®)
- verapamil (Calan®)

10.2h Vasodilators

Vasodilators such as hydralazine are more effective at relaxing the smooth muscle in arteries than in veins. Vasodilators are usually considered last-line therapy for nonacute hypertension treatment. Vasodilators can cause a reflex tachycardia and peripheral edema. For those reasons, they are frequently used in combination with a β-blocker and a diuretic. One vasodilator you may recognize by name is minoxidil (Loniten®). One of the side effects of minoxidil is hypertrichosis, or increased hair growth. Drug manufacturers capitalize on this side effect and market minoxidil (Rogaine®) for male pattern baldness. The vasodilator action of Rogaine® reestablishes blood flow to the hair follicles of some individuals when it is applied topically. Common vasodilators include:

- hydralazine
- minoxidil

Understanding that the heart provides blood to two separate circulatory systems is extremely important. The right side of the heart is responsible for pumping blood to the pulmonary circuit, while the left side of the heart is responsible for pumping blood to the systemic circuit. Vessels in each system determine the afterload for the associated ventricles. Vasoconstriction of the pulmonary vessels increases afterload of the right ventricle, while vasoconstriction of the systemic vessels increases afterload of the left ventricle. If the underlying cause is not corrected, right heart failure eventually leads to left heart failure. The same can be said for the left side of the heart, eventually leading to right heart failure. Vasodilation is important in both the systemic and pulmonary circuit to ease the overall work of the ventricles.

Inability of the heart to move blood forward into one of the two different circulatory systems causes blood and other fluid to accumulate in the other circulatory system. If the right heart is unable to pump blood forward effectively into pulmonary circulation, then blood backs up into systemic circulation and manifests itself as peripheral edema, often showing up as swollen feet. When the left heart is unable to pump blood forward effectively into systemic circulation,

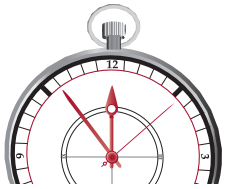
then blood backs up into pulmonary circulation and manifests itself as congestive heart failure. In both scenarios, the workload of the heart has increased. Vasodilators are advantageous for reducing afterload and making it easier for the heart to circulate blood volume.

Thus far, the vasodilators mentioned focus on reducing the workload of the left ventricle. The right side of the heart can benefit from vasodilation as well. Inhaled pulmonary vasodilators are very effective in reducing right ventricular afterload, which is extremely advantageous. Inhaled pulmonary vasodilators include:

- inhaled nitric oxide (iNO)
- inhaled Flolan (iFLO)
- inhaled Veletri (iVEL)
- inhaled epoprostenol (iEPO)

Obviously, the inhaled pulmonary vasodilators are administered as aerosolized solutions; however, Flolan, Veletri, and epoprostenol are also available as IV solutions.

Time for Review



After reading about all the side effects of blood pressure medications and reading about hypertension being a silent killer, how do you explain the importance of treatment compliance with antihypertensives? What are some reasons that noncompliance might occur?

10.2i Agents for Hypertensive Emergencies/Urgencies

Although hypertensive emergency and urgency may sound like the same condition, they are different medical conditions and are treated differently. The two conditions differ not so much by absolute blood pressure value as by the absence or presence of end organ damage (e.g., retinal hemorrhages or acute kidney failure) along with the elevated blood pressure. Physicians must do a physical exam and order lab work to detect end organ damage that may be present due to the elevated blood pressure. This can guide treatment aggressiveness and drug therapy selection.

Systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 120 mmHg can be immediately life-threatening, requiring fast-acting treatment; some patients can be relatively asymptomatic, presenting with just a headache. The optimal management in patients with minimal symptoms is unknown. In either case, too rapid a reduction in blood pressure can be dangerous. Both oral and parenteral antihypertensive drugs are options. Oral drugs are usually used for hypertensive urgencies, while intravenous medications are reserved for hypertensive emergencies. The oral antihypertensives clonidine (Catapres®) and captopril (Capoten®) have been given in loading doses in the past to achieve a fast response, but now they are generally given as a single dose for hypertensive urgencies along with allowing the patient to rest quietly in a dark room for 20 minutes.

Nitroprusside sodium (Nitropress®) is a potent agent that is used for minute-to-minute control of hypertensive emergencies. Nitroprusside is a potent vasodilator that dilates both venous and arterial vessels and has an immediate onset of action, within 30–60 seconds. Its most common side effect is too rapid a reduction in blood pressure, which, as previously mentioned, can be dangerous. Another problem with nitroprusside is the potential for cyanide toxicity. This problem is uncommon when nitroprusside is used at low doses or for brief periods. Cyanide toxicity can be fatal, so this medicine is usually only used in patients who are refractory to other antihypertensives and is stopped as soon as possible.

Clinical pearl

Excessive doses of nitroprusside can cause cyanide toxicity, since it is metabolized to cyanide.

Intravenous nitroglycerin dilates both arterioles and veins, reducing both preload and afterload. It is especially useful when hypertension occurs concurrently with myocardial ischemia.

Fenoldopam (Corlopam®) is a dopamine-1 antagonist with a quick onset of action. It is titrated by intravenous infusion and is commonly used for perioperative hypertension. Because it improves renal blood flow, it is useful for patients with renal insufficiency. Coronary, renal, mesenteric, and peripheral arteries are vasodilated and renal blood flow increases with this drug. Fenoldopam is more expensive than nitroprusside and is used primarily in patients at high risk for cyanide toxicity.

Nicardipine (Cardene®) and clevidipine (Cleviprex®) are intravenous calcium channel blockers useful in most hypertensive emergencies except acute heart failure. Adverse effects include tachycardia and flushing. Clevidipine is formulated within a 20% fat emulsion, which may result in hypertriglyceridemia, especially when used in high doses for extended periods of time.

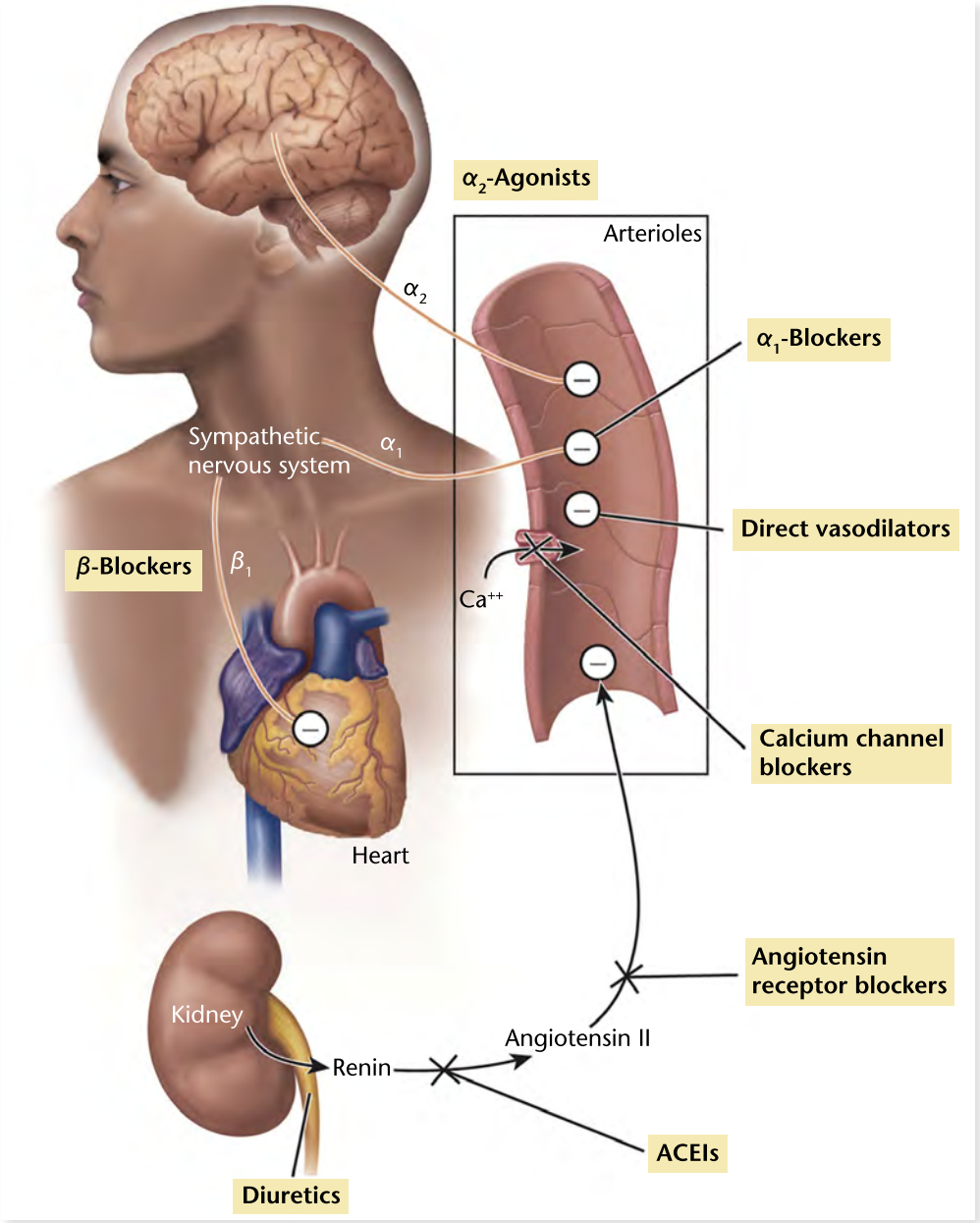
Labetalol (Trandate®) is a combination α- and β-blocker for intravenous infusion and is useful in most hypertensive emergencies except acute heart failure. Carvedilol is also a combination α- and β-blocker, but can be used in both hypertension and congestive heart failure. Adverse effects include bronchoconstriction and heart block.

See Table 10–3, which lists the various categories of antihypertensive agents along with representative drugs. See also Figure 10–8, which shows the mechanism of action of antihypertensive drugs.

Table 10–3 Categories of Antihypertensive Agents with Representative Drugs

Class	Action	Generic name	Brand name
Sympatholytics (central)	Decrease in sympathetic outflow from brain	guanfacine clonidine	Tenex® Catapres®
Sympatholytics (peripheral) α-blockers	Peripheral vasodilation	doxazosin prazosin terazosin	Cardura® Minipress® Hytrin®
β-Blockers	Decrease in CO	acebutolol atenolol metoprolol propranolol carvedilol	Sectral® Tenormin® Lopressor® Inderal® Coreg®
Diuretics	Decrease in blood volume	chlorthalidone furosemide spironolactone	Thalitone® Lasix® Aldactone®
ACEIs	Vasodilation	benazepril captopril enalapril lisinopril	Lotensin® Capoten® Vasotec® Prinivil®
Angiotensin II antagonists	Vasodilation	losartan valsartan olmesartan	Cozaar® Diovan® Benicar®
Calcium channel blockers	Vasodilation	amlodipine verapamil diltiazem	Norvasc® Calan® Cardizem®
Vasodilators	Direct relaxation of smooth muscle	hydralazine minoxidil	Apresoline® Loniten®
Emergency/urgency antihypertensives	Acute vasodilation	nitroprusside nicardipine IV clevidipine IV nitroglycerin IV	Nitropress® Cardene® Cleviprex® —

Figure 10–8 Mechanism of Action of Antihypertensive Drugs



Drug	Mechanism of Action
α_2-Agonists	Decrease sympathetic impulses from the CNS to the heart and arterioles, causing vasodilation
α_1-Blockers	Inhibit sympathetic activation in arterioles, causing vasodilation
Direct vasodilators	Act on the smooth muscle of arterioles, causing vasodilation
Calcium channel blockers	Block calcium ion channels in arterial smooth muscle, causing vasodilation
Angiotensin receptor blockers	Prevent angiotensin II from reaching its receptors, causing vasodilation
ACEIs	Block formation of angiotensin II, causing vasodilation and block aldosterone secretion, decreasing fluid volume
Diuretics	Increase urine output and decrease fluid volume
β-Blockers	Decrease the heart rate and myocardial contractility, reducing cardiac output

10.2j Treating Hypotension

The treatment of hypotension and shock will be covered in Chapter 15 as part of the discussion of advanced cardiac life support (ACLS). These drugs are primarily vasopressor and cardiotonic agents. Vasopressor drugs increase smooth muscle tone and thus cause vasoconstriction. Cardiotonic agents stimulate the heart to increase its rate and/or force of contraction to increase blood pressure and perfusion.

10.3 The Hemostatic System

10.3a The Clotting Process

An *embolism* is a general term for an obstruction of a blood vessel by a foreign substance. This may be fat or even a gas bubble. A *thromboembolism* refers specifically to a blood clot.

One of the amazing things about blood is its normal ability to flow freely through blood vessels and yet clot when the need arises, such as when you accidently cut yourself. The hemostatic system's job is to maintain fluidity of blood within the vasculature and minimize blood loss when blood leaks outside the vessels by clotting. Without the clotting mechanism, a minor cut would cause us to literally bleed to death. However, the clotting mechanism, like all physiologic mechanisms, can get out of balance, owing to disease states or other factors. If a clot forms within a blood vessel or an organ cavity such as the heart, it is termed a *thrombus*. This intravascular clot can partially or totally occlude the blood flow, which will diminish or stop the supply to the local tissue being fed by this vessel. Lack of blood flow leads to infarction and subsequent tissue necrosis.

The thrombus can dislodge and travel through the bloodstream. A traveling thrombus is called a **thromboembolism** (TE). The thromboembolism continues to move along the bloodstream until it reaches a vessel where its size matches the vessel's diameter, and it obstructs blood flow. This has very serious consequences—especially because emboli may reach the lungs (pulmonary emboli) or brain (cerebral emboli) and cause serious, irreversible tissue damage. The goal of anticoagulant therapy is to prevent clot formation in patients at risk and to prevent clot extension and embolization.

A thrombus can form because of local trauma to a blood vessel. This stimulates the specialized *thrombocytes*, or *platelets*, in the blood to bind together, or aggregate, forming a sticky gelatinous mass that begins to plug the leak. Platelet aggregation also causes the release of *thromboplastin*, which begins a cascade of steps that are simplified as follows:

1. Thromboplastin forms in the presence of vitamin K-dependent coagulation factors (released from aggregating platelets).
2. Prothrombin, in the presence of thromboplastin and calcium, forms thrombin.
3. Fibrinogen, in the presence of thrombin, forms fibrin, which causes the clot.

Vascular stasis or turbulent flow, such as occurs in atherosclerotic disease, and anything that damages the inner lining of the blood vessels can cause platelet aggregation and subsequent release of thromboplastin. Vascular clots can form in the venous or arterial system. Venous clots usually occur as a result of stasis because the venous system is a relatively low-pressure/low-flow system. Platelet aggregation usually occurs in the higher-flow/higher-pressure vessels of the arterial system.

Drugs are used to treat or prevent the formation of thrombi. **Anticoagulants** prevent the formation of the fibrin clot by interfering with one of the steps leading to fibrin formation. **Antiplatelet** drugs inhibit the aggregation of platelets and the release of thromboplastin that begins the clotting process. Finally, **fibrinolytics**

(thrombolytics) actually dissolve and liquefy the fibrin of existing clots. Thrombolytics enhance the conversion of plasminogen to plasmin, which degrades the fibrin.

10.3b Anticoagulants

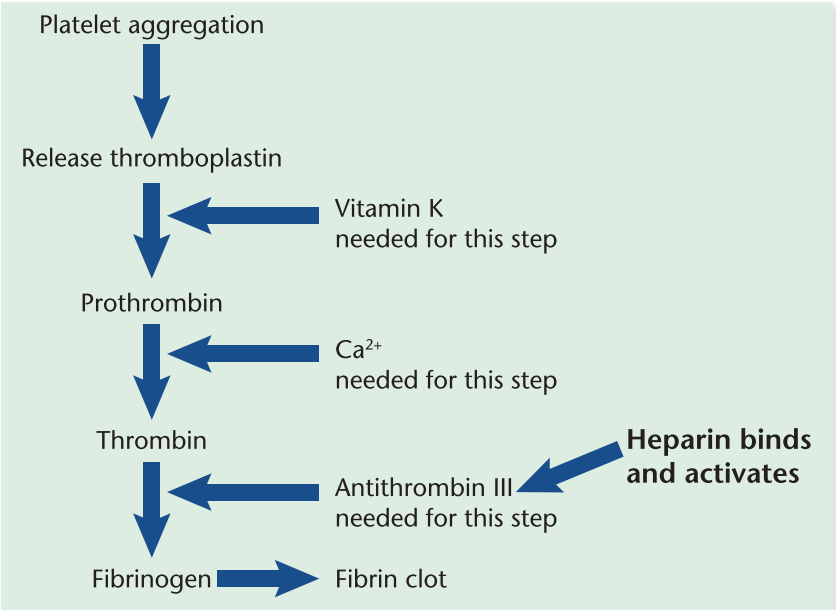
Anticoagulants are distinguished as either indirect or direct thrombin inhibitors. Indirect thrombin inhibitors include warfarin (Coumadin®), unfractionated heparin, and low-molecular-weight heparin (LMWH). Direct thrombin inhibitors include dabigatran (Pradaxa®), argatroban, bivalirudin (Angiomax®), apixaban (Eliquis®), rivaroxaban (Xarelto®), betrixaban (Bevyxxa®), and edoxaban (Savaysa®). Anticoagulants inhibit steps in the clotting cascade leading to fibrin formation and *do not* dissolve existing clots. They do prevent new clots from forming, as well as the extension of existing clots. They prevent mostly venous thrombosis formation. Anticoagulants are used primarily prophylactically to prevent deep vein thrombosis (DVT) after surgery and to decrease the risk of stroke in patients with atrial fibrillation or artificial heart valves. Candidates for anticoagulants may have any of the following:

- A history of embolus formation
- Prolonged bed rest
- Coronary artery disease
- Venous thrombosis
- Phlebitis
- Surgery with or without a previous history of thrombosis (especially orthopedic surgery)

Heparin

Standard (unfractionated) heparin (UFH) is a parenteral anticoagulant that binds with antithrombin to inhibit the conversion of fibrinogen to fibrin by thrombin. See Figure 10–9 for an illustration of its mechanism of action.

Figure 10–9 Mechanism of Action of Heparin



Heparin is a naturally occurring substance in mast cells and is broken down in the stomach, so it is effective only as an injectable medication. Low-dose subcutaneous heparin is used to prevent venous thromboembolism in immobile, bedridden patients postoperatively. Weight-based IV boluses and infusions of heparin are used to treat pulmonary emboli. Heparin is also used to prevent clots in cannulas or may be included in an IV or in procedures such as hemodialysis. In arterial blood sampling kits, needles and syringes are heparinized to prevent clotting from occurring and blocking the return of blood into the syringe.

The therapeutic goals, depending on the heparin indication, are aimed at increasing the activated partial thromboplastin time to a certain laboratory-defined range. *Activated partial thromboplastin time* (aPTT) and anti-Xa lab tests are used to make dosage adjustments for heparin. The aPTT time or anti-Xa level should be maintained within a specific therapeutic range depending on the indication. These ranges should be published by a hospital's laboratory and will vary depending on the type of thromboplastin used. The aPTT and anti-Xa lab tests are different from the prothrombin time (PT) lab test, which is used to make dosage adjustments for warfarin. The PT measures the activity of vitamin K-dependent factors. It has been replaced by the more reliable international normalized ratio (INR), which will be discussed later in connection with warfarin.

Side Effects of Heparin

Protamine, which is derived from salmon sperm, is an anticoagulant when given alone. But when given with heparin, it neutralizes heparin's effects. This reversal agent acts instantaneously and is long acting.

Standard heparin does not cross the placental barrier, has a rapid action, and is readily metabolized (because the body recognizes it). However, bleeding is the most important side effect of heparin. Watch for bleeding in the mucosa (petechiae) and gums and for hematuria and GI bleeding. An antidote for excess bleeding is protamine sulfate, which complexes with heparin to antagonize its action.

Heparin can cause thrombocytopenia and even osteoporosis with long-term use. Heparin is contraindicated with any serious active bleeding or thrombocytopenia. Use of heparin with brain, eye, or spinal cord surgery can be very risky because the slightest bleed could increase intracranial pressure (brain bleed) or cause paralysis (spinal cord bleed) or blindness.

Low-molecular-weight heparins (LMWHs) are the more modern version of heparin. They can be conveniently administered by the subcutaneous route, and since their absorption is more predictable than standard heparin, they are dosed based on body weight and rarely require monitoring with special coagulation tests. These agents differ in their antithrombotic properties, pharmacokinetics, side effects, and monitoring. As suggested by the name, LMWH is smaller in weight than standard heparin. This allows LMWH to have a different antithrombotic effect that is as effective as standard heparin but may have fewer side effects and less need for monitoring. A representative drug is the low-molecular-weight heparin enoxaparin (Lovenox®).

Indirect and Direct Factor Xa Inhibitors

Fondaparinux is a pentasaccharide that binds specifically but reversibly to antithrombin. It selectively inhibits factor Xa activity and prevents thrombus generation and clot formation by directly inhibiting factor Xa activity through its interaction with antithrombin. It is different from UFH and LMWH in that it has no direct effect on thrombin activity, but it is similar in that it is administered parenterally by subcutaneous injection. Apixaban (Eliquis®), rivaroxaban

(Xarelto®), betrixaban (Bevyxxa®), and edoxaban (Savaysa®) are oral direct factor Xa inhibitors. These medications, along with dabigatran (discussed previously), are replacing warfarin in a number of clinical situations because they do not require routine blood monitoring and they appear to be as good as, or better than, warfarin in preventing strokes in patients with atrial fibrillation. They also have no effect on platelet function and, as previously mentioned, routine coagulation testing is not needed other than a periodic blood count to detect occult bleeding. They are eliminated by the kidneys, and their use in patients with kidney disease is either contraindicated or they must be used at a reduced dose depending on the severity of the kidney disease.

Time for Review

What precautions would you take if you were obtaining an arterial blood gas from someone on heparin?

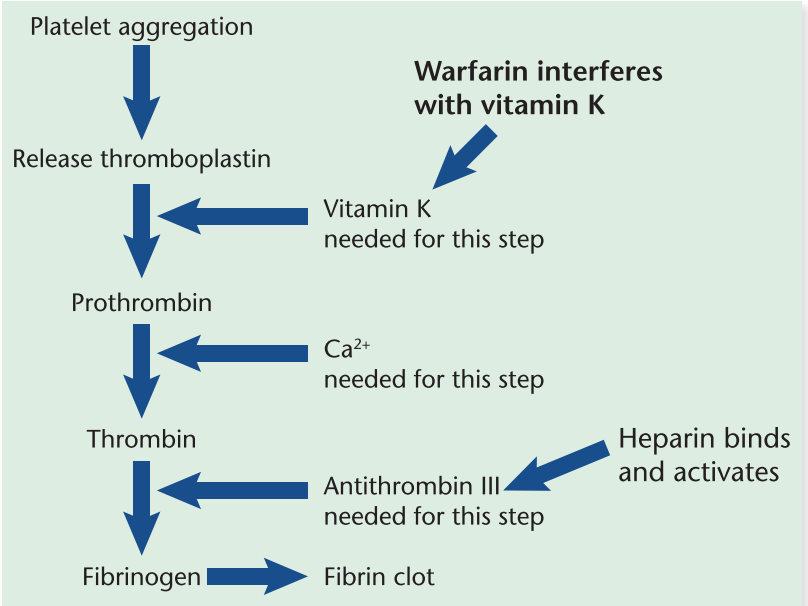
Clinical pearl

Warfarin is an oral anticoagulant that is sometimes referred to by patients as "rat poison" because the active components are similar. This drug was discovered when cattle died mysteriously after eating sweet clover. It turned out that the sweet clover was spoiled. This led to the isolation of the chemical components of the spoiled sweet clover and development of oral anticoagulants.

Warfarin

Warfarin is an orally administered anticoagulant that has been around for more than 50 years. Warfarin acts differently than heparin and works on vitamin K-dependent liver synthesis of certain clotting factors by inhibiting vitamin K, which is vital to the clotting process (see Figure 10–10 for this mechanism).

Figure 10–10 Mechanism of Action of Warfarin



Clinical pearl

Dabigatran, rivaroxaban, betrixaban, and apixaban cannot be used to prevent stroke in patients with mechanical heart valves. A study comparing warfarin to dabigatran was halted when the number of strokes in the dabigatran group far exceeded the number of strokes in the warfarin group.

Warfarin is used to prevent blood clots in patients with various medical conditions, such as atrial fibrillation, a prosthetic mechanical heart valve, or stroke. Depending on the indication, the goal international normalized ratio (INR) may be 2–3 or higher. Chronic warfarin therapy requires monthly lab monitoring and frequent dosage manipulations because the anticoagulant effect of warfarin is affected by many things, including dietary vitamin K intake, drug interactions, and other disease states. Although the lab monitoring for patients on warfarin can be a burden, warfarin remains one of the most easily reversible anticoagulants. This is important in the situation where an emergency surgery is needed or if excessive bleeding (sign of overdose) occurs. Other popular anticoagulants, such as apixaban (Eliquis®) and rivaroxaban (Xarelto®) require little to no lab monitoring, but have no reversal agents.

Controversy

A person's genetic makeup may influence how he or she responds to warfarin. Patients with variations in two genes may need lower doses of warfarin than people without these variations. The two genes are called VKORC1 and CYP2C9. The VKORC1 gene helps regulate warfarin's ability to prevent blood from clotting, and the CYP2C9 gene is involved with the metabolism of warfarin. Tests are commercially available to test for these gene variations, but testing is controversial until there is more information about how the results will inform patient care.

Interactions and Side Effects of Warfarin

Diet drug interactions with warfarin are important. Anything that increases vitamin K, such as yellow or green leafy vegetables, can also affect warfarin response. This can be used advantageously in cases of over-anticoagulation by administering pharmacologic doses of vitamin K. Patients on anticoagulants need to be monitored for bleeding gums, nose bleeds, petechiae, or blood in the urine or stool. Before surgery or certain dental procedures, warfarin patients may need to withhold doses. Any drug has the potential to interact with warfarin on the basis of the mechanistic principles described in Chapter 1. Most, but not all, patients on warfarin are instructed not to take aspirin concurrently because it may increase bleeding potential.

A representative drug is:

- warfarin (Coumadin®)

Clinical pearl

Hirudin is an anticoagulant protein found in leeches and was one of the first direct thrombin inhibitors identified. Leeches are dispensed from some hospital pharmacies to be used as an anticoagulant.

10.3c Direct Thrombin Inhibitors

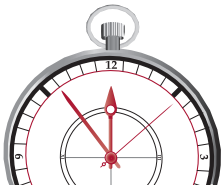
Direct thrombin inhibitors (DTIs) do not require antithrombin to have antithrombotic activity and are able to inhibit both circulating and clot-bound thrombin. The prototype of this class (hirudin) came from the medical leech. Other DTIs include desirudin, bivalirudin, and argatroban. Dabigatran (Pradaxa®) is an oral DTI that is used as an alternative to warfarin in a number of clinical situations.

Argatroban

The direct thrombin inhibitor argatroban has distinct pharmacologic properties relating to how it interacts with thrombin. This drug may be used in conjunction with aspirin in patients with unstable angina who are undergoing percutaneous coronary intervention (PCI) or as an alternative to heparin in patients with heparin-induced thrombocytopenia (HIT). Argatroban is monitored using the aPTT test, and bivalirudin by the activated clotting time (ACT). ACT is a point-of-care test done bedside, such as in the cardiac catheterization suite.

A representative drug is:

- bivalirudin (Angiomax®)



Time for Review

What is the difference between the PT, aPTT, ACT, and INR lab tests, and why are they important to pharmacotherapy?

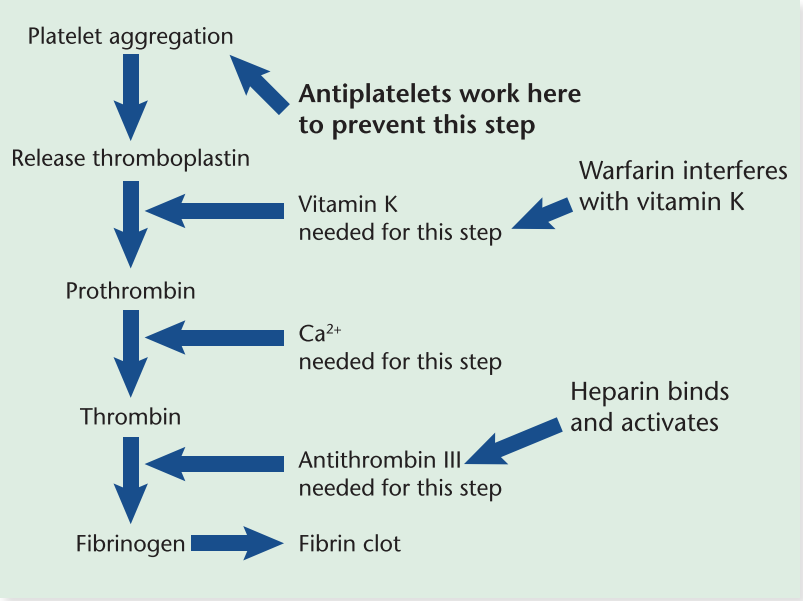
10.3d Antiplatelet Drugs

Antiplatelet agents inhibit the platelet phase of clotting (see Figure 10–11). Antiplatelet drugs are also called antithrombotic drugs and include aspirin. Aspirin irreversibly inhibits the enzyme prostaglandin synthetase, which is required for the formation of prostaglandin precursors. This means that once aspirin is taken, a platelet will be affected by aspirin's antiplatelet effects for the lifetime of that platelet.

For decades, low-dose aspirin has been widely administered for cardiovascular protection and is widely recommended for this indication, but recent studies have shown that aspirin should not be used in all patients. Most important is to avoid aspirin in patients with increased risk of bleeding or at increased age. The following recommendations are from the most recent guidelines of ACC/AHA:

- Low-dose aspirin may be considered for primary prevention of cardiovascular events in adults aged 40–70 years who are not at increased bleeding risk.
- Low-dose aspirin **should not** be administered on a routine for adults >70 years.
- Low-dose aspirin **should not** be administered for adults at any age who are at increased bleeding risk.

Figure 10–11 Mechanism of Action of Antiplatelet Drugs



Besides aspirin, representative antiplatelet drugs include:

- dipyridamole (Persantine®)
- clopidogrel (Plavix®)
- prasugrel (Effient®)
- ticagrelor (Brilinta®)

These drugs were initially used for patients who could not tolerate aspirin or who "failed," or still had symptoms, while on aspirin. More recently, with the new aspirin guidelines, their use is becoming more widespread as primary antiplatelet drugs. They are also used in combination with aspirin to prevent clot formation in bare-metal and drug-eluting stents. These stents are placed by interventional cardiologists in the coronary arteries of patients with coronary artery disease. Clopidogrel, prasugrel, and ticlopidine are thienopyridines that block adenosine diphosphate (ADP) receptors on platelets.

Controversy

Clopidogrel is a prodrug. This means it must be metabolized by the liver to its active metabolite before it can do its job of blocking platelets. The liver enzyme CYP2C9 is responsible for this metabolism. Depending on the genetic profile of the patient, some patients may not be able to convert clopidogrel to its active form as efficiently as others and therefore may have a reduced benefit from this medicine. A test is commercially available to see how well a patient is likely to metabolize clopidogrel. In patients found to be poor metabolizers, it isn't clear whether the dose of clopidogrel should be increased or whether the patient should switch to a different medicine. Additionally, some drugs can inhibit the metabolism of clopidogrel to its prodrug. Omeprazole and esomeprazole (used for GERD) can render clopidogrel ineffective.

10.3e Platelet Glycoprotein IIb/IIIa Receptor Inhibitors

Platelet glycoprotein (GP) IIb/IIIa receptor inhibitors are a class of drugs that are administered parenterally. They bind with and block GP IIb/IIIa receptors, which initiate platelet aggregation. They are used for unstable angina and myocardial infarction, and they have been used concurrently with heparin. Representative platelet GP IIb/IIIa receptor inhibitors include:

- tirofiban (Aggrastat®)
- eptifibatide (Integrilin®)
- abciximab (ReoPro®)

Clinical pearl

These drugs may also be used in patients undergoing primary PCI (percutaneous coronary intervention) who have not received fibrinolytics.

10.3f Fibrinolytics

Fibrinolytics stimulate fibrinolytic mechanisms to dissolve existing clots. Pharmacologic thrombolysis occurs when plasminogen is converted to plasmin, an enzyme that digests fibrin strands. In essence, thrombolytics promote the lysis of the fibrin to a gel or liquid, thereby dissolving the existing clot. Thrombolytics are used for patients with acute myocardial infarction (or, more commonly now, for acute ischemic stroke) because these drugs lyse the thrombus that caused the infarction and can reduce mortality and salvage heart tissue by reperfusion. These drugs dissolve existing clots but do not affect the underlying cause of the occlusion.

There are different generations of thrombolytics, each generation striving to be better than the previous. Improvements include things such as longer half-life, bolus IV administration, and fewer side effects. This is important because the goal is to treat myocardial infarction or stroke patients as early as possible after the onset of chest pain or within 4.5 hours of the onset of stroke symptoms.

tPAs (tissue plasminogen activators) are produced commercially by DNA technology. Clinical studies influence which thrombolytic is used most often. Because fibrinolytics can't differentiate between pathologic clots and hemostatic plugs, the biggest complication of fibrinolytics is bleeding. Representative thrombolytics include:

- alteplase (Activase®) (rtPA) (FDA approved to treat both heart attacks and strokes)
- reteplase (Retavase®) (rPA)
- tenecteplase (TNKase®) (TNK-tPA)

See Table 10–4 for a summary of the classes of antithrombotic agents.

Learning Hint

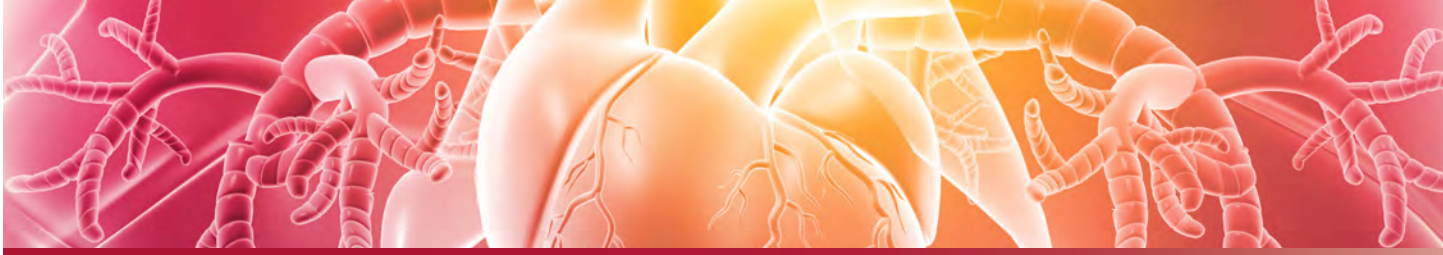
Notice that all the thrombolytic drugs end in "-ase," which is a formal suffix denoting an enzyme.

Table 10–4 Classes and Representative Drugs Used for Antithrombotic Therapy

Class	Generic name	Brand name
Unfractionated heparin	heparin sodium	Calciparine®
Low-molecular-weight heparin	enoxaparin	Lovenox®
Vitamin K antagonist	warfarin sodium	Coumadin®
Direct thrombin inhibitor	argatroban dabigatran	— Angiomax® Pradaxa®
Antiplatelet agents	aspirin dipyridamole clopidogrel prasugrel	— Persantine® Plavix® Effient®
Factor Xa inhibitors	fondaparinux rivaroxaban apixaban	Arixtra® Xarelto® Eliquis®
Fibrinolytic agents	alteplase tenecteplase reteplase	Activase® TNKase® Retavase®
Platelet glycoprotein IIb/IIIa receptor inhibitors	tirofiban eptifibatide abciximab	Aggrastat® Integrilin® ReoPro®

Controversy

In patients older than age 75, fibrinolytic therapy is controversial. A benefit-risk decision between risk of intracranial hemorrhage, risk of stroke, and the fact that 60% of all MI deaths occur in this age group makes the decision to use the drug differently in individual situations. Because of these bleeding risks and the possible failure of the drug to open the occluded coronary artery, most heart attack patients today are taken to a cardiac catheterization laboratory to have their artery opened by specially trained cardiologists. Unfortunately, not all parts of the United States have this type of health-care service available in the community.



Summary

This chapter concluded a 2-chapter sequence on cardiac pharmacotherapy. Antihypertensives, anticoagulants, antiplatelet agents, and thrombolytic agents have greatly influenced cardiac morbidity and mortality. The high prevalence of the conditions these drugs are used to treat indicates that you will encounter these drugs frequently in your professional practice and even in your personal life.

Review Questions

1. Nonpharmacologic approaches to hypertensive treatment include
   (a) fluid restriction
   (b) salt supplementation
   (c) exercise
   (d) folic acid
   (e) vitamin C

2. Which of the following is not an antihypertensive drug class?
   (a) β-agonist
   (b) β-blocker
   (c) α-agonist
   (d) α-blocker
   (e) diuretic

3. Sympatholytics
   (a) decrease venous tone
   (b) increase heart rate
   (c) increase cardiac contractility
   (d) increase total peripheral resistance
   (e) increase cerebral blood flow

4. Diuretics
   (a) can cause bleeding
   (b) have dose-related antihypertensive effects
   (c) are classified by where they work in the kidney
   (d) should not be used with other antihypertensives
   (e) (b) and (c)

5. ACE inhibitors
   (a) may cause a cough
   (b) may cause hypokalemia
   (c) increase aldosterone
   (d) work the same as angiotensin II receptor blockers
   (e) may cause heart failure

6. Explain the mathematical equation that describes blood pressure and how it relates to antihypertensive therapy.

7. Discuss the factors that influence which antihypertensive is used in an individual patient.

8. Explain the steps involved in platelet aggregation and clot formation.

9. Describe three categories of drugs used to treat or prevent thrombus formation.

10. A 47-year-old man presents with prehypertension (BP 136/86 mmHg) without target organ disease (TOD). Is pharmacotherapy indicated at this point? If not, what suggestions would you make?

11. A 53-year-old woman with a medical history of pulmonary emboli is admitted for pelvic surgery. What prophylactic pharmacotherapy may be indicated presurgery? What would be the therapeutic goal? What tests would help to confirm the effectiveness of the presurgical medications?

12. Explain what process is needed for a prodrug to become its active form in the body. What factors can influence this process?

13. Why is warfarin still used in practice, given the need for continuous lab monitoring, which can be difficult for patients?

14. Which class of medications can be used in place of ACEIs if the side effect of cough is intolerable?
    (a) angiotensin II receptor blockers
    (b) calcium channel blockers
    (c) potassium-sparing diuretics
    (d) vasodilators

15. Which class of medications should not be used as a first option when treating essential hypertension?
    (a) calcium channel blockers
    (b) diuretics
    (c) beta blockers
    (d) ACEIs

Case Study 10–1

Hypertensive emergency

An obese 75-year-old woman was admitted to the hospital for hypertensive emergency and chest pain 2 days ago. She now complains of shortness of breath, swelling, and soreness of her left calf. What potential medical problem might she have? What are her risk factors for this? What additional information do you need? What are some of the drug options available? What kind of adverse effects of drug therapy would you be concerned about? If this patient is discharged to home, what medications might be prescribed and what precautions emphasized?

Case Study 10–2

Antiplatelet therapy

An 85-year-old man has recently been identified to need antiplatelet therapy following a cardiac event. He has a history of diabetes, hyperlipidemia, and recurrent stomach and duodenal ulcers that caused bleeding complications last year. What would be the best antiplatelet choice for this patient? What information led to your decision? What other indications could these drugs be used for?