Cardiovascular Drugs Our Patients Take

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Introduction - Cardiovascular Drugs

Cardiac risk associated with dental treatment depends on procedure-specific and patient-specific factors. Important co-determinants of patient-specific risk factors include disease-related factors, including therapeutic variables. Cardiovascular Drugs Our Patients Take presents relevant information for oral healthcare providers, predicated on the mechanisms of action and indications for the use of cardiovascular drugs.

Course Contents

Overview

This course presents an overview of cardiovascular pharmacology predicated on the top 300 prescription drugs dispensed by U.S. community pharmacies, identifies the most common cardiovascular conditions encountered in ambulatory settings, and discusses their clinical relevance.

Learning Objectives

Upon completion of this course, the dental professional should be able to:

- Recognize cardiovascular drugs by name.
- Discuss the mechanisms of action of cardiovascular drugs.
- Identify prevalent cardiovascular diseases.
- Discuss key points for practice.

Introduction

A patient's overall health status determines the patient's ability to undergo and respond to dental care. Consequently, patient-specific problems that may interfere with the clinical process must be identified. In determining perioperative risk, clinicians must assess the patient's vital signs and functional capacity; and consider past and present illnesses, major hospitalizations, dietary supplements and special diets, history of drug allergies and other adverse drug reactions (ADRs), and medications taken by the patient.[1]

In the United States there are approximately 500 Food and Drug Administration (FDA)-approved active ingredients, i.e., therapeutic agents, available in several thousand different formulations.[2] **ClinCalc DrugStats** provides prescription drug utilization data estimates based on the annual Medical Expenditure Panel Survey (MEPS).[2] The Top 300 Prescription Drugs represent 60% of all available therapeutic agents and 97% of all prescription drugs dispensed by U.S. community pharmacies.[2]

Cardiovascular Drugs in the Top 300

Therapeutic agents in the Top 300 Prescription Drugs dispensed by U.S. community pharmacies indicated for the treatment of cardiovascular diseases fall into 6 major categories: (1) drugs that regulate cholesterol and lipoprotein metabolism, (2) drugs that regulate extracellular fluid volume, (3) drugs that regulate vascular tone, (4) drugs that regulate cardiac rhythm, (5) drugs that regulate cardiac contractility, and (6) drugs that affect hemostasis, i.e., platelet function and coagulation.[2-9]

In relation to cardiovascular drugs oral healthcare providers (OHCPs) must (1) recognize drugs by name (generic and/or brand name); (2) know their mechanisms of action and indications for use; (3) be aware of the spectrum of ADRs and be actively involved in monitoring for and reporting such drug effects; and (4) have access to reliable informational resources. **DailyMed** is the official repository for FDA-approved individual drug-related clinically relevant data and it is a useful online resource for clinicians.[10]

The Council of International Organizations of Medical Sciences in their publication "Reporting Adverse Drug Reactions: Definitions of Terms and Criteria for Their Use" codified ADRs under 21 major headings and defined 179 conditions considered reportable.[11] Since the top 200 drugs alone are associated with nearly 10,000 potential ADRs ranging from mild to severe illness and can lead to hospitalization, permanent disability, and even death, access to informational resources is imperative.[12]

Adverse drug effects may be explained by one of five mechanisms: (1) "on-target" adverse reactions, (2) "off-target" adverse reactions, (3) cytotoxic reactions, (4) immune-mediated reactions, and (5) idiosyncratic reactions, i.e., reactions of unknown mechanisms.[13] A discussion of mechanisms of ADRs, common ADRs associated with drugs dispensed by U.S. community pharmacies, and less common ADRs that may manifest in the head and neck area is presented elsewhere.[13-15]

Drugs that Regulate Lipoprotein Metabolism

Lipoproteins, differentiated on the basis of density, size, and protein content, are essential for the biogenesis of plasma membrane and maintenance of its integrity; they also serve as sources of energy, hormone precursors, and signaling molecules.[3] In blood, lipoproteins transport cholesterol and triglycerides. Abnormalities of lipoprotein metabolism appear to be the result of genetic factors, which modify the sensitivity of individuals to adverse dietary habits and to sedentary lifestyles.

Elevated cholesterol-rich low-density lipoproteins (LDLs) and lipoproteins that are rich in triglycerides (TGs), and decreased levels of high-density lipoproteins (HDLs) are strongly associated with **atherosclerosis**.[3] Diet and exercise can reduce total plasma cholesterol concentrations by as much as 25%. If this approach is insufficient to normalize lipid levels drug therapy is initiated. Drugs in the top 300 that regulate lipoprotein metabolism (Table 1) fall into six major classes.[2,3,10]

Drugs that Regulate Extracellular Fluid Volume

About ⅔ of total body water is intracellular and ⅓ is extracellular. Nearly ¾ of the extracellular fluid (ECF) resides in the interstitial space. The remaining ¼ of the ECF, a determinant of tissue perfusion, i.e., the distribution of O_2 and nutrients, is in plasma. Depletion of plasma volume (1) activates the renin-angiotensin-aldosterone system (RAAS), (2) promotes antidiuretic hormone release, and (3) increases renal sympathetic activity; volume overload promotes the release of natriuretic peptides.[4]

Excessive Na^+ and H_2O retention, primarily a result of renal abnormalities, is responsible for **volume-based hypertension**.[4] Pathological Na^+ and H_2O retention can also lead to **transudative edema associated with heart failure, cirrhosis of the liver, and nephrotic syndrome**.[4] Drugs in the top 300 that regulate extracellular fluid volume (Table 2) can be divided into two broad classes: (1) agents that act directly on the nephron to increase renal Na^+ excretion and (2) drugs that modulate the RAAS.[2,4,10]

Drugs that Regulate Vascular Tone

Vascular tone is another key determinant of tissue perfusion. Vascular smooth muscle cells are the functional regulatory units that integrate a variety of signals initiated by (1) local factors (e.g., H^+, CO_2, stretch), (2) endothelium-derived signaling molecules (e.g., nitric oxide, prostacyclin), (3) neurotransmitters (e.g., epinephrine), and (4) hormones (e.g., vasopressin) to optimize vascular tone.[5] Ultimately, vascular smooth muscle tone is determined by the intracellular Ca^{2+} ion concentration.

Drugs in the top 300 that regulate vascular tone (Tables 2 and 3) include (1) Ca^{2+} channel blockers, (2) β_1-adrenoceptor antagonists, (3) α_1-adrenoceptor antagonists, (4) α_2-adrenoceptor agonists, (5) K^+ channel openers, (6) nitric oxide donors, and (7) inhibitors of the RAAS.[2,5,6,10] These drug categories are intended for the management of **systemic and pulmonary hypertension, ischemic heart disease** (i.e., chronic coronary artery disease and acute coronary syndromes), and **congestive heart failure**.[5,6]

Drugs that Regulate Cardiac Rhythm

The heart is both a mechanical and an electrical organ. The electrical component controls the rhythm of the heart. Under the influence of the autonomic nervous system, the sinoatrial (SA) node initiates action potentials, i.e., paces the heart at normal resting rates between 60 and 100 beats per minute.[1] Other pacemaker cell are found in the atrioventricular (AV) node, and the ventricular conducting system. Abnormal impulse generation and/or impulse conduction lead to **cardiac arrhythmias**.[6,7]

The most common cause of cardiac arrhythmias is chronic coronary artery disease; less commonly, arrhythmias may be related to

Table 1. Drugs that Affect Cholesterol and Lipoprotein Metabolism.[2,3,10]

Drugs	Mechanisms of Action	Common Indications
Inhibitors of cholesterol synthesis • Atorvastatin • Simvastatin • Pravastatin • Rosuvastatin • Lovastatin	Inhibit HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis • Decrease LDL • Decrease TG • Increase HDL	• Hypercholesterolemia • Prophylaxis for coronary atherosclerosis
Inhibitors of bile acid absorption • Colestipol	Bind to bile acids and prevent enterohepatic circulation • Decrease LDL • Increase HDL	• Hypercholesterolemia
Inhibitors of cholesterol absorption • Ezetimibe • Ezetimibe w/simvastatin	Decrease cholesterol transport into enterocytes • Decrease LDL • Decrease TG • Increase HDL	• Hypercholesterolemia
Fibrates • Fenofibrate • Gemfibrozil	Agonists of peroxisome proliferator-activated receptor α (PPARα) in hepatocytes • Decrease TG • Decrease LDL • Increase HDL	• Hypertriglyceridemia
Niacin • Niacin • Niacin w/simvastatin	Reduces free fatty acid release from adipose tissue • Decreases TG • Decreases LDL • Increases HDL	• Hypertriglyceridemia • Hypercholesterolemia
Omega-3 fatty acids • Omega-3-acid ethyl ester	Regulate hepatic nuclear transcription factors to reduce TG synthesis and increase fatty acid oxidation • Reduces TG	• Hypertriglyceridemia

Table 2. Drugs that Regulate Volume.[2,4,10]

Drugs	Mechanisms of Action	Common Indications
Thiazide diuretics • Hydrochlorothiazide • Hydrochlorothiazide w/lisinopril • Hydrochlorothiazide w/losartan • Hydrochlorothiazide w/ triamterene • Hydrochlorothiazide w/valsartan • Chlorthalidone	Inhibit Na+ reabsorption by cells of the distal convoluted tubule	Hypertension Adjuncts in chronic edema states associated with • Congestive heart failure • Hepatic cirrhosis • Renal dysfunction • Pulmonary edema • Corticosteroid and estrogen therapy
Loop diuretics • Furosemide • Torsemide	Inhibit Na^+ reabsorption by cells of the Loop of Henle	
Collecting duct (potassium-sparing) diuretics • Spironolactone • Triamterene w/hydrochlorothiazide	Spironolactone inhibits Na^+ reabsorption by inhibiting aldosterone action Triamterene inhibits Na^+ reabsorption by principal cells of the collecting duct	
Angiotensin converting enzyme (ACE) inhibitors • Lisinopril • Enalapril • Benzapril • Ramipril • Quinapril	Inhibit the conversion of angiotensin (AT) I to AT II thereby decreasing • Arteriolar vasoconstriction • Aldosterone synthesis • Na^+ reabsorption by cells of renal proximal tubule • ADH release Inhibit the degradation of bradykinin and thereby increasing vasodilation	Hypertension Adjuncts in the prevention and treatment of • Myocardial infarction • Heart failure • Diabetic nephropathy
Angiotensin II receptor antagonists • Losartan • Valsartan • Irbesartan • Olmesartan	Antagonize the action of AT II at AT_1 receptors May indirectly increase AT_2-receptor-related vasodilation	

Table 3. Drugs that Regulate Vascular Tone.[2,5,6,10]

Drugs	Mechanisms of Action	Common Indications
Calcium channel blockers • Amlodipine • Amlodipine w/ benazepril • Amlodipine w/ olmesartan • Diltiazem • Nifedipine • Verapamil	Block voltage-gated L-type Ca2+ channels and thereby cause • Vasodilation • Depressed cardiac contractility • Depressed SA-node automaticity • Depressed AV-node conduction velocity	• Hypertension • Stable angina pectoris • Exertional angina pectoris • Unstable angina pectoris • Coronary spasm • Atrial flutter • Atrial fibrillation
β_1-adrenoceptor antagonists • Metoprolol • Atenolol • Atenolol w/chlorthalidone • Carvedilol • Propranolol • Nebivolol • Labetalol • Nadolol • Bisoprolol • Bisoprolol w/hydrochlorothiazide	Block β_1-adrenoceptors • Propranolol and nadolol also block β_2-adrenoceptors • Labetalol and carvedilol also block β_2- and α_1-adrenoceptors	• Hypertension • Angina pectoris • Post-MI syndrome • Heart failure • Cardiac arrhythmia
α_1-adrenoceptor antagonists • Doxazosin • Terazosin • Prazosin	Block the binding of catecholamines to α_1-adrenoceptors	• Hypertension
α_2-adrenoceptor agonists • Clonidine • Guanfacine	Selectively activate central α_2-adrenoceptors and thereby inhibit sympathetic outflow from the CNS	• Hypertension
K^+ channel openers • Hydralazine	Open K^+ channels in the plasma membrane of vascular smooth muscles thereby preventing the opening of C^{2+} channels causing arterial vasodilation	• Moderate to severe hypertension
Nitric oxide donors • Nitroglycerin • Isosorbide mononitrate • Ranolazine	Release NO, which activates guanylyl cyclase and increases dephosphorylation of myosin light chain in vascular smooth muscle causing vasodilation	• Acute angina pectoris (nitroglycerin) • Prophylaxis for ischemic heart disease

Table 4. Drugs that Affect Cardiac Rhythm and Cardiac Contractility.[2,6-8,10]

Drugs	Mechanisms of Action	Common Indications
Class IC antiarrhythmics • Flecainide	Block voltage-gated Na+ channels in ventricular myocytes	Sustained ventricular tachycardia Paroxysmal supraventricular tachycardia Paroxysmal atrial fibrillation
Class II antiarrhythmics • β_1-adrenoceptor antagonists (see Table 3)	Block β_1-adrenoceptors in SA and AV nodal cells	Supraventricular and ventricular arrhythmias precipitated by sympathetic stimulation
Class III antiarrhythmics • Sotalol • Amiodarone	Block K^+ channels and prolong repolarization	Recurrent and unstable ventricular arrhythmias Maintain normal sinus rhythm in patients with symptomatic atrial flutter or atrial fibrillation
Class IV antiarrhythmics • Ca^{2+} channel blocking agents (see Table 3)	Block Ca^{2+} channels • Decrease excitability of SA nodal cell • Prolong AV nodal conduction	Paroxysmal supraventricular tachycardias
Cardiac glycosides • Digoxin	Inhibit Na^+/K^+-ATPase leading to increased Ca^{2+} concentration in myocytes • Positive inotropic effect Prolong refractory period at AV node • Slow conduction velocity	Systolic heart failure Supraventricular arrhythmias • Atrial flutter • Atrial fibrillation • Paroxysmal atrial tachycardia

cardiomyopathies, valvular and congenital heart disease, primary electrophysiological disorders, and genetically determined ion-channel abnormalities.[1,7] Drugs in the top 300 that regulate cardiac rhythm (Table 4) include: (1) Na^+ channel blockers, (2) β_1-adrenoceptor antagonists, (3) K^+ channel blockers, (4) Ca^{2+} channel blockers, and (5) cardiac glycosides.[6,7,10]

Drugs that Regulate Cardiac Contractility

Cardiac muscles contract when action potentials depolarize plasma membranes. Decreased cardiac contractility is associated with dysregulation of calcium homeostasis, changes in cAMP-dependent regulation of contractile proteins, and alterations in β-adrenoceptor activity.[8] The most common

causes of contractile dysfunction include coronary artery disease resulting in myocardial infarction, systemic hypertension, and valvular disease. Progressive contractile dysfunction leads to **heart failure** (HF).[8]

The central role of intracellular Ca^{2+} and cAMP in cardiac muscle contraction provides a basis for the classification of agents with positive inotropic effects as (1) cardiac glycosides, (2) β_1-adrenoceptor agonists, and (3) phosphodiesterase inhibitors.[8] Currently, a cardiac glycoside, i.e., digoxin, is the only drug in the top 300 that regulates cardiac contractility (Table 4).[2,8,10] It inhibits Na^+/K^+-ATPase and thereby increases intracellular Ca^{2+} concentration in myocytes and exerts a positive inotropic effect.[8]

Drugs that Affect Hemostasis

A well-regulated hemodynamic system keeps blood fluid and clot-free in normal vessels and forms a localized clot rapidly in injured vessels.[9] The first step in the formation of a localized clot at the site of vessel injury is vasoconstriction. This is followed by platelet aggregation and the formation of a primary hemostatic plug. Secondary hemostasis, also known as the coagulation cascade, leads to the formation of a stable, permanent clot. An abnormal extension of hemostasis is thrombosis.[9]

Thrombosis is characterized by the uncontrolled enlargement of clots that occlude blood vessels as a result of (1) injury of the endothelium associated with hyperlipidemia and hypertension; (2) abnormal blood flow, i.e. turbulence or stasis associated with atherosclerosis, arrhythmias, valvular problems, and heart failure, and (3) genetic or acquired hypercoagulability.[9] Drugs in the top 300 that affect hemostasis (Table 5) fall into two major categories: antiplatelet agents and anticoagulants.[2,9,10]

Key Points for Practice

Cardiovascular agents represent the highest volume in the top 300 prescription drugs dispensed by U.S. community pharmacies.[2] Predicated on the mechanisms of action of these drugs, the most common cardiovascular conditions encountered in ambulatory settings include **hypertension** (HTN); **ischemic heart disease** (IHD), i.e., chronic coronary artery disease (CAD) and acute coronary syndromes (ACS); **cardiac arrhythmias**; **heart failure** (HF); and **thromboembolic complications**.[2-10,16]

Hypertension

Blood pressure (BP), the lateral pressure exerted by blood in a unit area of blood vessel wall, is a function of cardiac output and peripheral vascular resistance.[1] When the blood volume exceeds the limited volume capacity of the vascular compartment because of volume expansion or increased vascular resistance the patient develops **hypertension** (HTN). BP is classified as normal (<120/80 mmHg), elevated (120-129/<80 mmHg), stage 1 HTN (130-139/80-89 mmHg), or stage 2 HTN (≥140/90 mmHg).[17]

HTN is known as the "silent killer" because signs and symptoms, i.e., flushed face, restlessness, headache, dizziness, tinnitus, visual disturbances, dyspnea, and a hammering pulse are not observed until the systolic BP is ≥180 mmHg or the diastolic BP ≥110 mmHg; or until evidence of target organ damage manifests.[18] Target organ damage may include renal insufficiency and end-stage renal disease; CAD, left ventricular hypertrophy, and HF; stroke; peripheral vascular disease; and hypertensive retinopathy.[18]

The treatment of HTN may include (1) diuretics to reduce blood volume, (2) ACE inhibitors or AT II receptor antagonists to modulate the RAAS, (3) β_1-adrenoceptor antagonist, α_1-adrenoceptor antagonists, and central α_2-adrenoceptor agonists to reduce sympathetic tone, and (4) Ca^{2+} channel blockers and K^+ channel activators to reduce vascular tone.[4-6,16] It is of note that in many instances two or more agents from different drug classes may be required to reach target BP in a particular patient.

BP <179/109 mmHg is a minor, but not an independent risk factor for a major adverse cardiac event (MACE) in association with dental procedures performed under local dental anesthesia.[18] However, high BP is a useful marker for the presence of significant CAD and correlates well with obesity and sedentary lifestyle; significant use of tobacco, coffee, and alcohol; and a number of systemic diseases, e.g., dyslipidemia, diabetes mellitus,

Table 5. Drugs that Affect Hemostasis and Thrombosis.[2,9,10]

Drugs*	Mechanisms of Action	Common Indications
Class IC antiarrhythmics • Flecainide	Block voltage-gated Na+ channels in ventricular myocytes	Sustained ventricular tachycardia Paroxysmal supraventricular tachycardia Paroxysmal atrial fibrillation
Cyclooxygenase inhibitors • Aspirin	Inhibit platelet cyclooxygenase, thereby • Block thromboxane A_2-dependent platelet aggregation	Prophylaxis against • Transient ischemic attacks • Myocardial infarction • Thromboembolic disorders • Reocclusion in coronary revascularization procedures and stent implantation
ADP receptor pathway inhibitors • Clopidogrel	Block platelet ADP receptors thereby • Inhibit ADP-dependent platelet activation	Secondary prevention of atherosclerotic events in patients with recent MI, stroke, or peripheral vascular disease Acute coronary syndromes Prevention of stent thrombosis in combination with aspirin
Traditional anticoagulants • Warfarin	Inhibit hepatic peroxide reductase that catalyzes the regeneration of reduced vitamin K, which is required for the synthesis of biologically active coagulation factors II, VII, IX, and X	Prophylaxis and treatment • Pulmonary embolism • Deep vein thrombosis • Systemic embolism o Post-MI o Atrial fibrillation o Rheumatic HD with valve damage o Prosthetic heart valve
Selective Factor Xa inhibitors • Rivaroxaban • Apixaban	Competitively inhibit factor Xa by binding to the active side on the enzyme	Prevention • Thromboembolism with atrial fibrillation Prevention and treatment • Deep vein thrombosis • Pulmonary embolism
Direct thrombin inhibitors • Dabigatran	Bind directly to thrombin and thereby inhibit secondary hemostasis	Prevention • Thromboembolism with atrial fibrillation Treatment • Deep vein thrombosis • Pulmonary embolism

thyroid dysfunction, adrenal disease, and renal insufficiency.[17,18]

Hypertensive urgency is characterized by gradual elevation of BP in patients with chronic, slowly progressive end-organ damage.[16] Clinically it may manifest as stroke or myocardial infarction (MI).[16] Consider stroke when a patient smiles and one side of the face droops, or when raises both arms and one arm drifts downward; or when speaks and the speech is slurred. Perioperatively, when a conscious patient experiences chest pain and the BP drops from baseline consider the diagnosis of MI.

Hypertensive emergency is a rare life-threatening condition characterized by severe, acute BP elevation associated with acute vascular injury.[16] The vascular injury manifests clinically as retinal hemorrhage, papilledema, and altered mental state often accompanied by acute renal insufficiency and acute left ventricular (LV) failure. The treatment of patients with hypertensive emergency mandates rapid reduction of BP in a hospital setting to prevent irreversible end-organ damage.[16]

Signs and symptoms of **hypotension**, defined as BP <90/60 mmHg, include dizziness, and fainting (syncope); rapid, shallow breathing; fatigue, lack of concentration, and depression: cold, clammy, and pale skin; and thirst.[18] Causes range from impaired homeostatic mechanisms of BP regulation as in old age, dehydration, and antihypertensive therapy.[18] Perioperatively, when a conscious patient experiences chest pain and a rise in BP from baseline consider the diagnosis of acute angina pectoris.

Ischemic Heart Disease

I**schemic heart disease** (IHD) is characterized by an imbalance in myocardial oxygen supply and demand primarily as a result of atherosclerotic plaques in coronary arteries and endothelial dysfunction-associated vasoconstriction and thrombus formation.[16] It can be considered in two broad categories: **chronic coronary artery disease** (CAD), i.e., stable angina pectoris; and **acute coronary syndromes** (ACS), i.e., unstable angina pectoris and MI, each with a distinct pathogenesis.

Chronic CAD is associated with subintimal deposition of atheromas in coronary arteries.[16] Its principal clinical manifestation is **chronic stable angina pectoris**. Atherosclerotic plaques in patients with chronic stable angina are overlaid by a thick, fibrous cap that resists disruption, but that reduces vessel lumen diameter and causes inappropriate vasoconstriction resulting in acute myocardial ischemia and chest pain at reproducible workloads, e.g., walking up a flight of stairs.[16]

All patient with chronic CAD require aggressive lipid lowering therapy and BP control and focused therapy intended to reduce oxygen demand governed by heart rate, contractility, and ventricular wall stress: (1) β_1-adrenoceptor antagonists reduce heart rate and contractility, Ca^{2+} channel blocking agents decrease cardiac contractility and systemic vascular resistance, and (3) nitric oxide donors decrease preload and dilate peripheral capacity veins.[3,5,6,16] Nitroglycerin is used to treat acute symptoms.

Acute coronary syndromes are caused by the rupture of unstable atherosclerotic plaques that results in vasoconstriction, platelet aggregation, and thrombus formation, which lead to acute myocardial ischemia and, potentially, irreversible myocardial injury (myocyte necrosis).[16] The principal clinical manifestation of ACS is **unstable angina pectoris** (UA) characterized by increased frequency and severity of chest pain that may occur even at rest.[16] Patients with UA are at high risk for MI.

An unstable plaque that abruptly ruptures and partially occludes the lumen of a coronary artery causes **non-ST elevation MI** (NSTEMI).[16] Because there is a persistent prothrombotic surface at the site of plaque rupture, the patient is at high risk for recurrent ischemia. The goals of prevention and treatment of both UA and NSTEMI are (1) to relieve ischemic symptoms, i.e., β_1-adrenoceptor antagonists; and (2) to prevent additional thrombus formation, i.e., antiplatelet agents and/or an anticoagulant.[3,6,9,16]

Complete coronary artery occlusion, unless perfusion is reestablished, leads to **ST elevation MI** (STEMI).[16] The treatment of

STEMI is the same as that of UA and NSTEMI. When pharmacological strategies are sufficient to reestablish perfusion patients with STEMI require coronary artery bypass grafts or percutaneous coronary intervention, i.e., balloon angioplasty or stent implantation.[16] Ischemia-induced electrical instability of the myocardium can lead to **sudden cardiac death**.

The functional consequences of MI vary greatly among patients; consequently, post-MI therapeutic regimens are individualized and include (1) aspirin (clopidogrel if aspirin is contraindicated); (2) aspirin and another anti-platelet agent following percutaneous coronary intervention; (3) a β_1-adrenoceptor antagonist; (4) an ACE inhibitor for patients with HF, hypertension, and diabetes; (5) an aldosterone antagonist for patients with left ventricular dysfunction; and (6) lipid-lowering agents.[16]

Cardiac Arrhythmias

The primary pacemaker of the heart is the sinoatrial (SA) node.[1] Electrical impulses generated by the SA node at a normal frequency of 60 to 100 beats per minute spread rapidly through the atria and enter the atrioventricular (AV) node. After a brief delay at the AV node, the impulses continue to propagate over the Bundle of His and converge on the Purkinje system as depolarization progresses over the ventricles in an anatomically synchronous and hemodynamically effective fashion.[1] When impulse generation and/or impulse conduction malfunctions, the patient develops cardiac arrhythmias.[7]

Sinus bradycardia - Impulses originate from the sinoatrial node (SA) at a rate <60 beats per minute under the influence of increased parasympathetic (vagal) tone.[1] The rhythm is regular. Sinus bradycardia is common in athletes, in patients with hypothyroidism, in patients with increased intracranial pressure, and during treatment with drugs with negative chronotropic action (e.g., β_1-adrenergic receptor antagonists, calcium channel blocking agents, and digoxin). The patient may be asymptomatic or experience weakness, palpitation, chest discomfort, dyspnea, and syncope.

Sinus tachycardia - Impulses originate from the SA node at a rate of 100 to 180 beats per minute under the influence of increased sympathetic tone or vagal blockade.[1] The rhythm is regular. Sinus tachycardia is found in patients after exercise or smoking; in patients with hyperthyroidism, anxiety, toxic states, fever, anemia, and acute or chronic heart diseases; and in patients consuming stimulants such as tea, coffee, and medications with positive chronotropic effects (e.g., epinephrine). The patient may be asymptomatic or experience weakness, palpitation, chest discomfort, dyspnea, and syncope.

Atrial flutter - Impulses originate from a single abnormal atrial focus at a rate of 250 to 300 beats per minute.[1] The rhythm is regular. Because the pace of atrial firing is rapid, some of the impulses reach the AV node during its refractory period. These impulses are not transmitted to the ventricles, and the ventricular rate is slower than the atrial rate. The ratio of atrial to ventricular firing rate is typically 2:1, i.e., the ventricular rate is between 125-150 beats per minute. The patient may be asymptomatic or experience weakness, palpitation, chest discomfort, dyspnea, and syncope.

Atrial fibrillation - Impulses originate from multiple abnormal atrial foci at a rate of 350 to 450 beats per minute.[1] Impulses in the atria travel in a random manner and the rhythm is irregular. The AV node is unable to transmit all of the impulses and the ventricular rate is between 120 to 180 beats per minute. Turbulence and/or stasis of blood in the fibrillating atrium can lead to clot formation. Systemic embolization may present clinically as a stroke-like illness characterized by sudden confusion: acute, painful, pulseless limbs: and an acute abdomen.

Premature ventricular contractions (PVCs) are characterized by a pronounced pause in an otherwise normal rhythm.[1] Impulses originate from an ectopic ventricular focus. PVCs may be an occasional finding in otherwise healthy adults and the incidence increases with age, fatigue, emotional stress, and the use of coffee and tobacco. PVCs are considered benign

if fewer than six such pauses are noted per minute. PVCs are significant in a patient with a history of cardiovascular diseases, i.e., ischemic heart disease, valvular disease, hypertension, and congestive heart failure.

Ventricular tachycardia (VT) usually evolves from an ectopic focus in a ventricle, which generates ventricular extrasystoles at a rate of 120 to 220 beats per minute.[1] VT occurs in patients with organic heart disease and may be precipitated by drugs such as digoxin and tricyclic antidepressants. A patient with sustained VT is almost always symptomatic experiencing fatigue, palpitation, light-headedness, and syncope. VT is a serious arrhythmia, if left untreated, it may lead to ventricular fibrillation manifested as loss of consciousness and sudden cardiac death.

Ventricular fibrillation (VF) - The heart rate is 350-450 beats per minute and the rhythm is irregular.[1] The myocardium depolarizes in a chaotic manner. Coordinated ventricular activity ceases. The heart ceases to pump, the blood pressure falls, and unconsciousness occurs. If left untreated, death will follow in about three to five minutes. CAD-associated ischemia-induced electrical instability of the myocardium is the most common cause of VF and it is the main cause of **sudden cardiac death**, which occurs most frequently in the first few hours after a MI.

Atrioventricular (AV) blocks are characterized by a delay or failure in impulse conduction from the atria to the ventricles.[1] It occurs at three levels: first degree, with a delay in impulse conduction; second degree, with an intermittent failure in conduction; and third degree, with permanent failure in conduction. First degree AV block is usually asymptomatic. Second degree AV block may be asymptomatic or manifest as light-headedness and syncope. Third degree or high-grade AV block is characterized by fatigue, light-headedness, syncope and, if left untreated, leads to HF.

Generally, to restore synchronous myocardial contraction, Class I and Class III antiarrhythmic agents are used to treat both supraventricular tachycardias (SVTs) and ventricular tachycardias (VTs), Class II and Class IV antiarrhythmic agents are used to treat SVTs, and cardiac glycosides such as digoxin are used to treat atrial flutter and atrial fibrillation.[7] In addition, antiplatelet drugs and/or anticoagulants are prescribed to prevent thromboembolic complications.[9] If pharmacological strategies fail, a patient with cardiac arrhythmias requires a pacemaker or an implanted cardiac defibrillator.

Heart Failure

Heart failure (HF) is a chronic contractile dysfunction characterized by myocyte loss and increased interstitial collagen deposits associated with structural cardiac diseases.[8,16,19] Cardiac output is decreased resulting in reduced renal perfusion. Reduced renal perfusion leads to increased renin-angiotensin-aldosterone synthesis. Decreased hepatic perfusion leads to decreased aldosterone clearance. Increased aldosterone concentrations lead to coronary artery and renovascular fibrosis, endothelial cell and baroreceptor dysfunction, and decreased myocardial norepinephrine uptake.

The most common cause of HF is **left ventricular (LV) dysfunction**.[16,19] LV dysfunction develops as a complication of HTN, CAD, cardiomyopathy, and most forms of congenital heart defects. It may manifest as tachycardia, fatigue on exertion, dyspnea on mild exercise, and intolerance to cold. Paroxysmal nocturnal dyspnea and nocturnal cough reflect the redistribution of excess fluid into the lungs with the recumbent position. Occasionally, bronchospasm, wheezing and hemoptysis are present.

Right-ventricular (RV) dysfunction is usually a consequence of LV dysfunction; or tricuspid regurgitation, mitral or pulmonary valve stenosis, or pulmonary hypertension or pulmonary emboli.[16,19] Cardinal symptoms include fatigue; an awareness of fullness in the neck, i.e., jugular vein distension; fullness in the abdomen with an enlarged liver with tenderness in the right upper quadrant; and, in advanced cases, abdominal swelling secondary to ascites and pitting edema of the lower extremities.

A clinical classification of HF, i.e., Class I, II, III, and IV, is based on a patient's functional capacity (FC).[19] FC is expressed in metabolic equivalents (METs).[19] One MET equals the resting

or basal oxygen requirement (i.e., 3.5 ml of O_2 per kg per minute) of a 40–year-old, 70-kg man. FC can be classified as excellent (>10 METs), good (7-10 METs), moderate (4-7 METs), and poor (<4 METs).[20-22] A functional capacity <4 METs is predictive of increased cardiac risks in association with noncardiac procedures.[23]

Patients with **Class I heart failure** are typically asymptomatic at rest and ordinary physical activities do not cause fatigue, dyspnea, palpitation, or acute angina pectoris. These patients can complete physical activities requiring a FC of ≤7 METs, e.g., run a short distance; do heavy work around the house such as scrubbing floors or moving furniture; and participate in recreational activities such as golfing, bowling, dancing, or playing basketball.

Patients with **Class II heart failure** are typically asymptomatic at rest; however, ordinary physical activities can cause fatigue, dyspnea, palpitation, or acute angina pectoris. These patients can only complete physical activities requiring a FC ≤5 METs, e.g., do light work around the house such as dusting and washing dishes; garden; climb a flight of stairs or walk up a hill; walk on level ground at 4 mph (6.4 km per h): and run a short distance.

Patients with **Class III heart failure** are typically asymptomatic at rest; however, ordinary physical activities can cause fatigue, dyspnea, palpitation, or acute angina pectoris. These patients can only complete physical activities requiring a FC ≤2 METs, e.g., walk indoors around the house, dress, eat, and use the toilet. Patients with **Class IV heart failure** are typically symptomatic at rest and either cannot complete or cannot perform physical activities requiring a FC ≤2 METs.

The treatment of HF includes (1) cardiac glycosides to increase contractility and (2) antiplatelet agents or anticoagulants to prevent thromboembolic events; in addition, (3) diuretics and/or nitric oxide donors to reduce preload (i.e., the end diastolic volume or filling pressure of the heart when it is relaxing during diastole) and (4) ACE inhibitors, β_1-adrenoceptor antagonists or direct-acting vasodilators to reduce afterload (the pressure of the contracting heart or the left ventricular wall tension during systole).[8,16] When pharmacological strategies fail, a patient with HF becomes a candidate for heart transplantation.

Thromboembolic Complications

A blood clot, or thrombus, that forms in a blood vessel or heart chamber may be either venous or arterial in origin. **Venous thrombi** develop in areas of slow blood flow, e.g., in a lower extremity. The clot forms rapidly and lacks organization. Although venous occlusion does occur, a far greater concern is the tendency of small emboli to detach from venous thrombi.[9] These emboli tend to travel to and wedge into pulmonary arteries, preventing deoxygenated blood from entering the lungs.[9]

An **arterial thrombus** forms when platelets aggregate and become surrounded by fibrin and erythrocytes.[9] Arterial thrombi cause coronary artery thrombosis, coronary artery rethrombosis after thrombolysis, occlusion of coronary artery grafts and lead to unstable angina pectoris, MI, recurrent MI, and sudden cardiac death. Arterial thrombi also contribute to systemic embolization in patients with atrial fibrillation or prosthetic heart valves and cause transient ischemic attacks and stroke.[9]

To prevent and/or treat thromboembolic complications patients are prescribed antiplatelet agents and/or anticoagulants.[9] It is of note that antithrombotic therapy should not be interrupted for most dental procedures.[24,25] The risk of perioperative and postoperative bleeding complications in patients in whom antiplatelet and anticoagulation therapy is continued is exceedingly small and is outweighed by the small risk of serious and sometimes fatal embolic events when antithrombotic therapy is interrupted.

Summary

Familiarity with the top 300 prescription drugs dispensed by U.S. community pharmacies provides an insight into prevailing disease trends in the U.S. population. Predicated on the mechanisms of action of cardiovascular drugs in the top 300, the most common cardiovascular diseases include HTN, IHC (i.e., chronic CAD and ACS), cardiac arrhythmias, heart failure, and thromboembolic complications.

The risk of a major adverse cardiac event (MACE), i.e., myocardial infarction, heart failure, and sudden cardiac death, with advanced age, atrial fibrillation, stroke, uncontrolled HTN, chronic stable angina pectoris, previous MI (>60 days), Class I HF, diabetes mellitus, and renal insufficiency in association with low surgical stress, e.g., dental procedures under local dental anesthesia, is very low to low.

The risk of MACE with acute coronary syndromes, i.e., unstable angina pectoris and recent MI (<60 days), Class II, III, and IV HF, sever valvular disease, and significant arrhythmia, i.e., supraventricular arrhythmias with uncontrolled ventricular rate, high-grade AV bloc, and symptomatic ventricular arrhythmias in the presence of underlying heart disease is elevated independent of surgical stress.

Before elective dental care, estimate the patient's perioperative risk for MACE. If the combined procedure- and patient-specific variables predict low-risk for MACE and the patient's FC is ≥4 METs no further preoperative evaluation may be needed. If the FC is <4 METs and/or the risk for MACE is elevated, before initiating any elective dental care, the patient should undergo medical evaluation.

Course Test Preview

To receive Continuing Education credit for this course, you must complete the online test. Please go to: *www.dentalcare.com/en-us/professional-education/ce-courses/ce581/start-test*

1. Which of the following statements related to cardiovascular drugs apply to oral healthcare providers (OHCPs)? OHCPs must _____.

A. recognize them by name (generic and/or brand name)
B. know their mechanisms of action and indications for use
C. be aware of the spectrum of ADRs and be actively involved in monitoring for and reporting such drug effects
D. All of the above.

2. Drugs taken by our patients are associated with at least 10,000 potential ADRs ranging from mild to severe illness and can lead to hospitalization, permanent disability, and even death; consequently, OHCPs are expected to have access to reliable informational resources.

A. True
B. False

3. All of the following statements related to lipoproteins are correct EXCEPT which one?

A. In blood, lipoproteins transport cholesterol and triglycerides.
B. Abnormalities of lipoprotein metabolism appear to be the result of genetic factors, which modify the sensitivity of individuals to adverse dietary habits and to sedentary lifestyles.
C. Low levels of low-density lipoproteins (LDLs) and low levels of triglycerides (TGs) and high levels of high-density lipoproteins (HDLs) are strongly associated with atherosclerosis.
D. Diet and exercise can reduce total plasma cholesterol concentrations by as much as 25%, if this approach is insufficient to normalize lipid levels drug therapy is initiated.

4. Which of the following classes of drugs are prescribed for the treatment of hypercholesterolemia and/or as prophylaxis for coronary atherosclerosis?

A. Inhibitors of cholesterol synthesis, i.e., the "statins, which inhibit HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis.
B. Inhibitors of bile acid absorption, e.g., colestipol, which bind to bile acid and prevent enterohepatic circulation.
C. Inhibitors of cholesterol absorption, e.g., ezetimibe, which decreases cholesterol transport into enterocytes.
D. Omeda-3 fatty acids, which regulate nuclear transcription factors to reduce TG synthesis and increase fatty acid oxidation.

5. All of the following statement related to plasma volume depletion are correct EXCEPT which one? Plasma volume depletion _____.

A. activates the renin-angiotensin-aldosterone system (RAAS)
B. promotes the release of natriuretic peptides
C. promotes antidiuretic hormone release
D. increases renal sympathetic activity

6. Excessive Na^+ and H_2O retention, primarily a result of renal abnormalities, is responsible for volume-based hypertension and can also lead to transudative edema associated with heart failure, cirrhosis of the liver, and nephrotic syndrome.

A. True
B. False

7. All of the following statement related to drugs indicated for the treatment of hypertension and/or as adjuncts in chronic edema states, and/or as adjuncts in the prevention and treatment of MI, HF, or diabetic nephropathy are correct EXCEPT which one?

A. Thiazide diuretics, e.g., hydrochlorothiazide, inhibit Na+ reabsorption by cells of the distal convoluted tubule.
B. Loop diuretics, e.g., furosemide, inhibit Na+ reabsorption by cells of the Loop of Henle.
C. Spironolactone, a collecting duct (potassium sparing) diuretic, inhibits Na+ reabsorption by inhibiting aldosterone action.
D. Angiotensin II receptor antagonists, i.e., the "artans", inhibit the conversion of angiotensin (AT) I to AT II and the degradation of bradykinin.

8. Vascular smooth muscle cells are the functional regulatory units responsible for maintaining vascular tone, which is ultimately is determined by the intracellular Ca^{2+} ion concentration.

A. True
B. False

9. All of the following statement related to drugs that regulate vascular tone are correct EXCEPT which one?

A. Calcium channel blockers, e.g., amlodipine, block voltage-gated L-type Ca^{2+} channels and are indicated for the treatment of hypertension, anginal pectoris, and cardiac arrhythmias.
B. Beta-adrenoceptor blocking agents such as metoprolol selectively block β_1-adrenoceptors, propranolol and nadolol also block β_2-adrenoceptors, and labetalol and carvedilol also block β_2- and α_1- adrenoceptors.
C. Alpha$_2$-adrenoceptor agonists, e.g., clonidine, selectively activate central α_2-adrenoceptors, thereby increasing sympathetic outflow from the CNS.
D. Nitric oxide donors, e.g., nitroglycerin, are indicated for the treatment of acute angina pectoris and or prophylaxis for ischemic heart disease.

10. All of the following statement related to cardiac arrhythmias are correct EXCEPT which one?

A. Under the influence of the autonomic nervous system, the sinoatrial (SA) node paces the heart at normal resting rates between 60 and 100 beats per minute.
B. The atrioventricular (AV) node and the ventricular conducting system contain pacemaker cells.
C. Abnormal impulse generation and/or impulse conduction lead to cardiac arrhythmias.
D. The most common cause of cardiac arrhythmias is primary electrophysiological disorders and genetically determined ion-channel abnormalities.

11. All of the following statement related to drugs that affect cardiac rhythm are correct EXCEPT which one?

A. Class IC antiarrhythmics such as flecainide block voltage-gated Na^+ channels in ventricular myocytes.
B. Class II antiarrhythmics, i.e., β_1-adrenoceptor antagonists, block β_1-adrenoceptors in SA and AV nodal cells.
C. Class IV antiarrhythmics, i.e., Ca^{2+} channel blocking agents, decrease excitability of SA nodal cell and prolong AV nodal conduction.
D. Cardiac glycosides, e.g., digoxin reduce the refractory period at AV nodal cell and thereby increase conduction velocity.

12. Cardiac glycosides, e.g., digoxin, inhibit Na^+/K^+-ATPase and thereby increase intracellular Ca^{2+} concentration in myocytes exerting a positive inotropic effect and are indicated for the treatment of heart failure.

A. True
B. False

13. Thrombosis is characterized by the uncontrolled enlargement of clots that occlude blood vessels as a result of _____.

A. injury of the endothelium associated with hyperlipidemia and hypertension
B. abnormal blood flow, i.e. turbulence or stasis associated with atherosclerosis, arrhythmias, valvular problems, and heart failure
C. genetic or acquired hypercoagulability
D. All of the above.

14. All of the following statements related to drugs that affect hemostasis and thrombosis are correct EXCEPT which one?

A. When a patient is taking both aspirin and clopidogrel it is most likely to prevent systemic embolism in association with prosthetic heart valves.
B. Traditional anticoagulants such as warfarin inhibit hepatic peroxide reductase that catalyzes the regeneration of reduced vitamin K, which is required for the synthesis of biologically active coagulation factors II, VII, IX, and X
C. Rivaroxaban and apixaban competitively inhibit factor Xa by binding to the active side on the enzyme.
D. Dabigatran directly binds to thrombin and thereby inhibit secondary hemostasis.

15. HTN is known as the "silent killer" because signs and symptoms, are not observed until the systolic BP is ≥180 mmHg or the diastolic BP ≥110 mmHg or until evidence of target organ damage manifests.

A. True
B. False

16. All of the following statements related to the prescription of two or more agents from different drug classes to reach target BP in a particular patient are correct EXCEPT which one?

A. Diuretics to reduce blood volume.
B. ACE inhibitors or AT II receptor antagonists to modulate the RAAS.
C. β_1-adrenoceptor antagonist, α_1-adrenoceptor antagonists, and central α_2-adrenoceptor agonists to increase sympathetic tone.
D. Ca^{2+} channel blockers and K^+ channel activators to reduce vascular tone.

17. Which of the following statements related to hypertension is correct?

A. BP <179/109 mmHg is a minor, but not an independent risk factor for a major adverse cardiac event (MACE) in association with dental procedures performed under local dental anesthesia.
B. Hypertensive urgency is characterized by gradual elevation of BP in patients with chronic, slowly progressive end-organ damage that perioperatively may manifest as stroke or myocardial infarction.
C. Hypertensive emergency is a rare life-threatening condition characterized by severe, acute BP elevation associated with acute vascular injury that perioperatively may manifests as retinal hemorrhage, papilledema, and altered mental state.
D. All of the above.

18. In addition to aggressive lipid lowering therapy and BP control, focused therapy in patients with chronic coronary artery disease, i.e., chronic stable angina pectoris may include _____.

A. β_1-adrenoceptor antagonists reduce heart rate and contractility
B. Ca^{2+} channel blocking agents decrease cardiac contractility and systemic vascular resistance
C. nitric oxide donors to decrease preload and dilate peripheral capacity veins
D. All of the above.

19. All of the following statements related to acute coronary syndromes (ACS), i.e., unstable angina pectoris (UA) and MI are correct EXCEPT which one?

A. Acute coronary syndromes are caused by the rupture of unstable atherosclerotic plaques that results in vasoconstriction, platelet aggregation, and thrombus formation.
B. The principal clinical manifestation of UA is chest pain at reproducible workloads, e.g., walking up a flight of stairs.
C. The goals of prevention and treatment of ACS are to relieve ischemic symptoms, i.e., β_1-adrenoceptor antagonists; and to prevent additional thrombus formation, i.e., antiplatelet agents and/or an anticoagulant.
D. If pharmacological strategies are not sufficient to reestablish perfusion patients with STEMI require coronary artery bypass grafts or percutaneous coronary intervention.

20. Which of the following statements related to cardiac arrhythmias is correct?

A. In patients with atrial fibrillation systemic embolization may present clinically as a stroke-like illness characterized by sudden confusion.
B. A patient with sustained VT is almost always symptomatic, if left untreated it may lead to ventricular fibrillation.
C. Ventricular fibrillation, if left untreated, leads to death within about three to five minutes.
D. All of the above.

21. The goals in treating cardiac arrhythmias is to restore synchronous myocardial contraction and to prevent thromboembolic complications, when pharmacological strategies fail, a patient with cardiac arrhythmias requires a pacemaker or implanted cardiac defibrillator.

A. True
B. False

22. All of the following statements related to HF are correct EXCEPT which one?

A. Heart failure (HF) is a chronic contractile dysfunction characterized by myocyte loss and increased interstitial collagen deposits associated with structural cardiac diseases.
B. Patients with Class I heart failure are typically asymptomatic at rest and ordinary physical activities do not cause fatigue, dyspnea, palpitation, or acute angina pectoris; these patients can complete physical activities requiring a FC of ≤7 METs.
C. Patients with Class II heart failure are typically asymptomatic at rest; however, ordinary physical activities can cause fatigue, dyspnea, palpitation, or acute angina pectoris; these patients can only complete physical activities requiring a FC ≤5 METs.
D. Patients with Class IV heart failure are typically asymptomatic; however, ordinary physical activities can cause fatigue, dyspnea, palpitation, or acute angina pectoris; these patients can only complete physical activities requiring a FC ≤2 METs.

23. The treatment of HF includes _____.

A. Cardiac glycosides and antiplatelet agents or anticoagulants
B. Diuretics and/or nitric oxide donors
C. ACE inhibitors, β_1-adrenoceptor antagonists or direct-acting vasodilators
D. All of the above.

24. All of the following statements related to thromboembolic complications are correct EXCEPT which one?

A. Venous thrombi develop in areas of slow blood flow, e.g., in a lower extremity, small emboli tend to detach and travel to and wedge into pulmonary arteries preventing deoxygenated blood from entering the lung.
B. Arterial thrombi cause coronary artery thrombosis, coronary artery rethrombosis after thrombolysis, occlusion of coronary artery grafts and lead to unstable angina pectoris, MI, recurrent MI, and sudden cardiac death.
C. Arterial thrombi contribute to systemic embolization in patients with atrial fibrillation or prosthetic heart valves and cause transient ischemic attacks and stroke.
D. The risk of perioperative and postoperative bleeding complications in patients in whom antiplatelet and anticoagulation therapy is continued is predictably high and far outweighs the small risk of serious and sometimes fatal embolic events when antithrombotic therapy is interrupted.

25. Before elective dental care _____.

A. estimate the patient's perioperative risk for MACE
B. if the combined procedure- and patient-specific variables predict low-risk for MACE and the patient's FC is ≥4 METs no further preoperative evaluation may be needed
C. if the FC is <4 METs and/or the risk for MACE is elevated, before initiating any elective dental care, the patient should undergo medical evaluation
D. All of the above.

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Additional Resources

- No Additional Resources Available

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