# Pharmacotherapy for Cardiac Diseases

# 26

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**Abstract**

Clinical trial design inclusion criteria typically require that patients be on optimal medical therapy prior to their enrollment or randomization, i.e., they are currently being managed by medical regimens proven to be safe and effective and considered standard in clinical practice for the particular disease state being studied. Only if this is the case can any trial's clinical or statistical significance be determined between study groups. This chapter outlines the current optimal medical management/therapy for patients eliciting: (1) hypertension, (2) acute coronary syndromes and myocardial infarction, (3) heart failure, and/or (4) arrhythmias.

**Keywords**

Diuretics • Beta-blockers • Angiotensin-converting enzyme inhibitors • Angiotensin receptor blockers • Calcium channel blockers • Antiplatelets • Anticoagulants • Aldosterone antagonists

## 26.1 Abbreviations

| | |
|---|---|
| ACE | Angiotensin-converting enzyme |
| AF | Atrial fibrillation |
| ARB | Angiotensin receptor blocker |
| CHD | Coronary heart disease |
| CRT | Cardiac resynchronization therapy |
| CVD | Cardiovascular disease |
| HF | Heart failure |
| ICD | Implantable cardioverter defibrillator |
| NSTEMI | Non-ST segment elevation myocardial infarction |
| PCI | Percutaneous coronary intervention |
| STEMI | ST segment elevation myocardial infarction |

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## 26.2 Introduction

Chronic disorders such as heart disease, diabetes, stroke, obesity, and cancer remain today as the leading causes of death and disability in the United States. Nearly half of all Americans have at least one chronic condition, and seven out of the top ten causes of death are due to chronic diseases [1]. Importantly, heart disease, or cardiovascular disease (CVD), is the chronic disorder that is the leading cause of death in the United States, accounting for 600,000 deaths annually or roughly 25 % of all deaths [2]. Yet this represents a 2 % rate of decline for deaths attributed to heart disease over the past few years. In addition, between 1999 and 2010, the prevalence of adults with at least one of the three following CVD risk factors: uncontrolled high blood pressure, uncontrolled high levels of low-density lipoproteins cholesterol, or current smoking, decreased from 58 to 47 % [3]. For a complete list of CVD risk factors, see (Table 26.1). While these morbidity and mortality improvements represent important successes, the medical management of patients living with CVD



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**Table 26.1** Cardiovascular disease risk factors

| |
|---|
| • Tobacco use |
| • Dyslipidemia |
| • Overweight (body mass index ≥ 25 kg/m$^2$) |
| • Diabetes mellitus |
| • Age (>45 years for men; >55 years for women) |
| • Physical inactivity |
| • Family history of early cardiovascular disease or hypertension (men <55 years; women <65 years) |

**Table 26.2** American College of Cardiology Foundation/American Heart Association level of evidence designations

| | |
|---|---|
| Level A | Data derived from multiple *randomized* clinical trials involving a large number of individuals |
| Level B | Data derived from a limited number of trials involving comparatively small numbers of patients or from well-designed data analysis of *nonrandomized* studies or *observational* data registries |
| Level C | Consensus of expert opinion is the primary source of recommendation |

continues to require significant utilization of healthcare dollars and resources.

Cardiovascular disease is comprised of multiple disease states, the pathogeneses of which are often interrelated. Today, the most common form of CVD is coronary heart disease (CHD), which occurs in 17.6 million Americans [4]. This chapter will provide general pharmacotherapy treatment guidelines for the management of the following CVDs: hypertension, acute coronary syndrome and myocardial infarction, heart failure, and arrhythmias.

## 26.3 Evidence-Based Medicine

In order to describe the drug therapy regimens for the disease states listed above, first there needs to be a brief explanation of how general clinical guidelines are developed and implemented. As such, evidence-based medicine is the process of conscientious, explicit, and judicious use of current best evidence in making decisions about the care of an individual patient [5]. Several expert working groups and agencies have developed systems for grading recommendations and classifying evidence according to the scientific rigor of the study results available. The system used most often in medicine is GRADE, the Grading of Recommendations Assessment, Development, and Evaluation system. For the purposes of this chapter, which focuses on pharmacotherapy for the treatment of cardiac diseases, strength of recommendation and evidence levels developed by the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) clinical data standards will be utilized for the discussion that follows (Tables 26.2 and 26.3) [6]. Treatment recommendations will focus primarily on those that have a class I or IIa strength of recommendation.

## 26.4 Hypertension

Nearly one-third of people in the United States have high blood pressure [7, 8], defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg [8, 9], yet less than half (47 %) of these individuals have their blood pressure controlled. Unfortunately, this not only increases morbidity and mortality but ultimately impacts healthcare consumption and cost.

### 26.4.1 Goals of Therapy for Hypertension

Left untreated, hypertension can lead to target organ disease in the cardiovascular system and also within the cerebrovascular system, peripheral vascular system, kidneys, and/or eyes; it can eventually lead to consequences such as stroke, transient ischemic attacks, peripheral artery disease, chronic kidney disease, and retinopathy. Figure 26.1 illustrates the generally accepted continuum of hypertensive disease and, specifically, its effects on the myocardium. The primary goal of treatment for hypertension is to reduce the blood pressure to a level below that which was used to diagnose the condition; however, these thresholds have been recently debated in the literature. In addition, the role that an individual's race plays in the development of hypertension is rightfully gaining more research and clinical attention, e.g., African Americans develop hypertension earlier in life and have higher average blood pressures than Caucasians [10]. Recent guidelines account for this difference and contain specific recommendations for black and non-black patients [11].

The highly anticipated and debated Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC8) outlines nine recommendations for the management of

**Table 26.3** American College of Cardiology Foundation/American Heart Association classification of recommendations

| | |
|---|---|
| Class I | Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective |
| Class II | Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness or effectiveness of a procedure or treatment<br>• Class IIa: Weight of evidence/opinion favor usefulness/efficacy<br>• Class IIb: Usefulness/efficacy is less well established by evidence/opinion |
| Class III | Conditions for which there is evidence and/or general agreement that a procedure or treatment is not useful or effective and, in some cases, may be harmful |

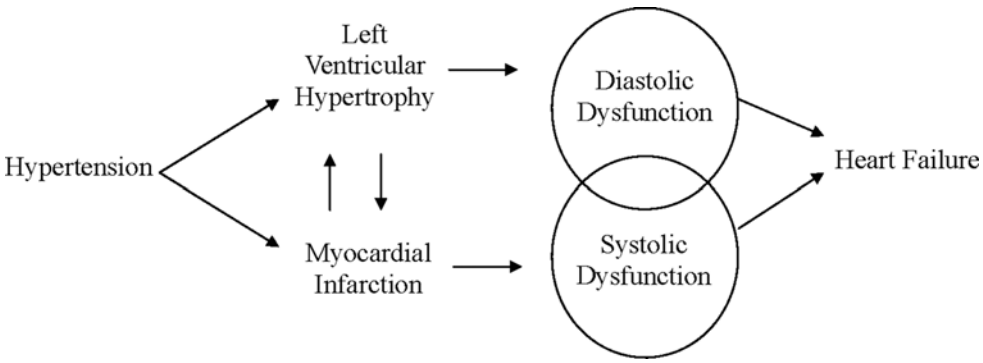


**Fig. 26.1** Continuum of hypertensive disease and its effects on the myocardium

hypertension based on evidence published exclusively from randomized controlled trials [11]. While continuing to endorse a hypertension goal of <140/90 mmHg for patients less than 60 years old, the new recommendations relax to some extent the previously published goals if patients are ≥60 years old (new goal: <150/90 mmHg), have diabetes, or have chronic kidney disease (new goal: <140/90 mmHg for both) [9]. Since the release of these JNC8 guidelines, a number of other groups such as the American Society of Hypertension (ASH), European Society of Hypertension, and the National Institute for Health and Clinical Excellence have reaffirmed recommendations of a blood pressure goal of <140/90 mmHg for all patients, providing an exception that it may be appropriate to target a blood pressure of <150/90 in patients over 80 years old [12–14]. For example, ASH delineates staging of hypertension (e.g., prehypertension versus hypertension) and blood pressure goals based on age and comorbid conditions. They recommend that the general population and patients with diabetes, kidney disease, and coronary artery disease should attempt to achieve a blood pressure of <140/90 mmHg but recommend <150/90 mmHg for patients over 80 years old and a diastolic goal of <90 mmHg for patients less than 50 years old [12]. Despite this controversy and uncertainty in optimal blood pressure targets, the ultimate goal of hypertension prevention and management is to prevent disease progression and reduce overall morbidity and mortality.

### 26.4.2 Treatment Guidelines for Hypertension

Lifestyle modifications are considered as a key component in the treatment regimen for patients with hypertension. Modifications such as smoking cessation, weight loss, increased physical activity, and decreased sodium intake have all been shown to have profound effects on lowering blood pressure and improving overall health [9, 11–14]. Medications of choice for managing hypertension have also changed with the release of recent guidelines. The JNC8 guidelines indicate that an angiotensin-converting enzyme (ACE) inhibitor (or angiotensin receptor blocker [ARB]), a dihydropyridine calcium channel blocker, and thiazide-type diuretics are considered "first-line" therapy options for such patients [11]. Selection of an antihypertensive will also be determined by patient race (black or non-black) and/or whether the patient has a concomitant condition. In following JNC8 recommendations, additional considerations should be determined relative to patients with various races, diabetes mellitus, and/or chronic kidney disease; however, other organizations such as ASH consider the presence of other compelling indications for selection of medication or combination of medications (Table 26.4). Indeed, beta-blockers are no longer a preferred agent unless the patient has a compelling indication. For example, for those patients with hypertension and coronary artery disease, a beta-blocker plus an ACE inhibitor may be warranted. Lastly, if blood pressure therapeutic goals are not

**Table 26.4** Agents with compelling indications for treatment of hypertension [12]

| Compelling indication | Diuretic | Beta-blocker | ACE inhibitor | Angiotensin receptor blocker | Calcium channel blocker | Aldosterone antagonist |
|---|---|---|---|---|---|---|
| Heart failure | X | X | X | X | X[a] | X |
| Post-myocardial infarction | | X | X | | | X |
| High coronary heart disease risk | X | X | X | X | X | |
| Diabetes | X | X | X | X | X | |
| Chronic kidney disease | | | X | X | X | |
| Recurrent stroke prevention | X | | X | X | X | |

[a]A dihydropyridine calcium channel blocker may be added if needed for blood pressure control

achieved with a single agent, a second or third antihypertensive may need to be added.

## 26.5 Acute Coronary Syndrome and Myocardial Infarction

Acute coronary syndrome is a condition used to describe any clinical symptoms associated with acute myocardial ischemia, including: unstable angina, ST segment elevation myocardial infarction (STEMI), or non-ST segment elevation myocardial infarction (NSTEMI). It is estimated that nearly 1.7 million hospital admissions associated with acute coronary syndrome occur annually in the United States; 500,000 of these are classified as STEMI [4, 15]. Typically, an imbalance between myocardial oxygen supply and demand occurs when a thrombus develops where an atherosclerotic plaque was disrupted, thereby blocking the arterial blood flow. Subsequently, the detection of biochemical cardiac markers such as troponin or the MB isoenzyme of creatine phosphokinase (CK-MB) indicates that myocardial cell death has occurred in STEMI or NSTEMI; however, these markers are not released in the setting of unstable angina [16]. Further, typically an electrocardiogram can be utilized to differentiate between STEMI and NSTEMI.

### 26.5.1 Goals of Therapy for Treating Acute Coronary Syndromes

The proper and immediate management for acute coronary syndrome is pivotal in preventing the progression of myocardial tissue damage. Aside from early recognition and response, goals of therapy are to remove the precipitating factor(s) causing the ischemia and to minimize irreversible damage from occurring to the myocardial tissue. Importantly, patients are at a higher risk of death or worsening myocardial infarction if they have prolonged ischemic symptoms, clinical and ECG findings, and/or elevated biochemical cardiac markers [17, 18].

### 26.5.2 Treatment Guidelines for Acute Coronary Syndromes

After an initial stratification of risks for the determination of the planned intervention (i.e., percutaneous coronary intervention, or PCI), patients with unstable angina/NSTEMI should undergo a medical therapy regimen that includes: (1) rapid vasodilation with nitroglycerin; (2) supplemental oxygen to achieve a goal arterial oxygen saturation >90 %; (3) morphine sulfate for pain and agitation control; (4) beta-blockade in patients without contraindications (e.g., bradycardia, lung disease, or hemodynamic decompensation); (5) correction of serum potassium and magnesium levels as indicated; (6) antihyperlipidemia treatment, (e.g., with a statin either initially or upon discharge for lipid management); (7) arrhythmia management, both atrial and ventricular; and (8) an ACE inhibitor for blood pressure control and prevention of myocardial injury progression [16]. In addition to this regimen, antiplatelet and anticoagulation therapy should be initiated immediately. Antiplatelets include aspirin and adenosine diphosphate $P2Y_{12}$ protein receptor blocker such as clopidogrel, prasugrel, or ticagrelor; these are drugs of choice, and a glycoprotein IIb/IIIa receptor antagonist can be considered if ischemia persists or if a patient is deemed at high risk for immediate death or severe complications. If revascularization with PCI is performed, dual antiplatelet therapy (e.g., aspirin and clopidogrel) is typically indicated for at least one year post-procedure. In some settings dual antiplatelet therapy may also be indicated for medical management in the absence of PCI. In other words, the decision to use an anticoagulant agent in the setting of unstable angina/NSTEMI depends on whether the patient undergoes reperfusion therapy with PCI. Currently, the common anticoagulation options include: heparin, unfractionated or low molecular weight (e.g., enoxaparin), direct thrombin inhibitors (e.g., bivalirudin), or factor Xa inhibitors (e.g., fondaparinux) [16, 18].

It is imperative to achieve myocardial reperfusion of STEMI patients in a timely manner, to salvage as much viable myocardium as possible. The preferred method of

myocardial reperfusion is PCI [19]. Fibrinolytic pharmacologic therapy (tissue plasminogen activator, streptokinase, or urokinase) is an alternative option for patients being first treated in a non-PCI-capable hospital, with expected transport delays exceeding 120 min [16, 17]. The timing of reperfusion therapy is essential in achieving the highest survival benefit; it has the most impact on infarct size and preservation of left ventricular function. For example, the goal of first medical contact (FMC) to PCI time is 90 min with initial presentation to a PCI-capable center and 120 min with initial presentation to a non-PCI-capable center necessitating transport to a PCI-capable center. In cases where PCI is not feasible, a goal time to initiation of fibrinolytic therapy is within 30 min after a diagnosis of STEMI. After reperfusion efforts, continued management is achieved through routine measures listed above, including oxygen, nitroglycerin, aspirin, analgesia, statin, beta-blocker, and an ACE inhibitor [17]. Aldosterone antagonists are also recommended after STEMI in patients who develop heart failure.

## 26.6 Heart Failure

Heart failure (HF) is considered a major public health problem; over five million people in the United States [4] have been diagnosed with HF, and data indicate that it affects both men and women in equal proportions. It is defined as a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject adequate blood volumes [20–22]. In general, the incidence of HF will increase to 10 in 1,000 after the age of 65, and nearly 75 % of all HF cases have hypertension as a previously diagnosed medical condition [4]. Other common risk factors for HF patients are CHD, hyperlipidemia, and/or diabetes. Heart failure has several types of classifications such as ischemic or non-ischemic, diastolic or systolic, acute or chronic, and preserved or reduced ejection fraction. Efforts have been made to designate the severity of HF by New York Heart Association (NYHA) classification and ACCF/AHA staging systems (Table 26.5). One ranking is based primarily on physical assessment of symptoms (NYHA), and the other (ACCF/AHA) is based on the origins of the underlying cardiac disease. Unfortunately, mortality remains between 50 and 70 % at 5 years for all classes of HF, and the cause of death is typically either sudden cardiac arrest or pump failure [23, 24].

### 26.6.1 Goals of Therapy for Heart Failure

Heart failure is a progressive disease in which initial compensatory mechanisms will eventually become themselves detrimental to the patient (Fig. 26.2). Therefore, pharmacologic treatment is aimed at those neurohormonal mechanisms, such as the renin-angiotensin-aldosterone system and sympathetic nervous system, which mediate the progression of the disease. Goals of therapy include: (1) improving quality of life, (2) reducing HF symptoms and hospitalizations, and (3) prolonging overall survival.

**Table 26.5** New York Heart Association (NYHA) functional classification and American College of Cardiology Foundation/American Heart Association stages of heart failure

| Functional classification | Definition | Stage | Definition |
|---|---|---|---|
| **None** | | **A** | Patients with normal heart structure and function, no signs or symptoms of heart failure, and at increased risk for developing heart failure due to comorbid conditions (hypertension, coronary artery disease, diabetes) (**asymptomatic risk**) |
| **I** | Patients with cardiac disease but *without limitations* of physical activity | **B** | Asymptomatic patients with abnormal heart structure or function (left ventricular hypertrophy, enlarged, dilated ventricles, asymptomatic valve disease, previous myocardial infarction) (**asymptomatic damage**) |
| **II** | Patients with cardiac disease resulting in *slight limitations* of physical activity | C | Patients with abnormal structure or function and symptomatic heart failure (symptomatic damage) |
| **III** | Patients with cardiac disease resulting in *marked limitations* of physical activity | C | Patients with abnormal structure or function and symptomatic heart failure (symptomatic damage) |
| **IV** | Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. *Symptoms present at rest* | **D** | Patients with extremely abnormal and symptomatic heart failure despite optimal medical therapy and specialized interventions (**extreme symptomatic damage**) |

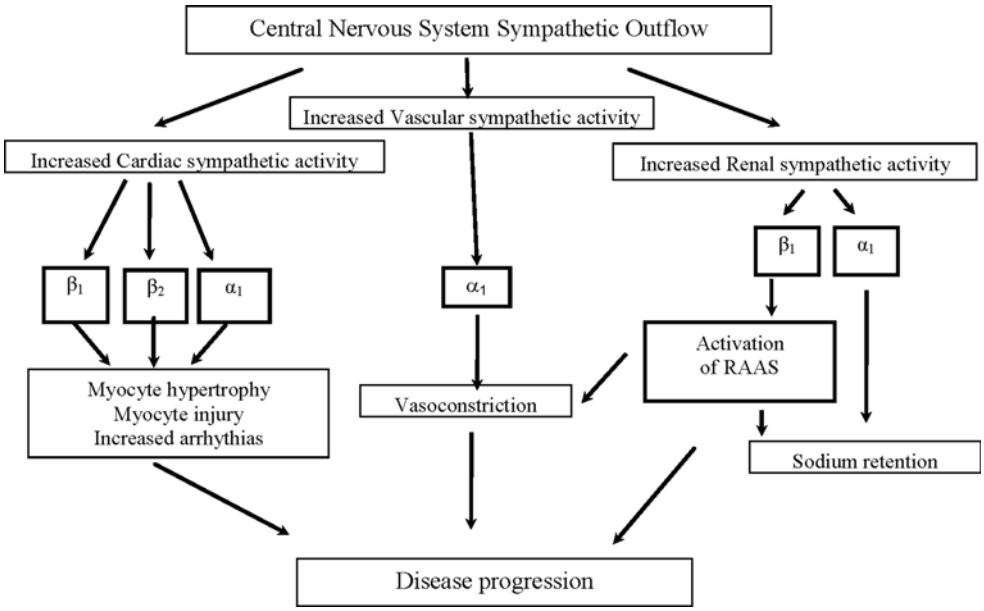


**Fig. 26.2** Neurohormonal activation in heart failure. *RAAS* renin-angiotensin-aldosterone system

**Table 26.6** Heart failure medication selection based on American College of Cardiology Foundation/American Heart Association staging

| At risk for heart failure | | Heart failure | |
|---|---|---|---|
| Stage A | Stage B | Stage C | Stage D |
| ACE inhibitor or ARB | ACE inhibitor or ARB; beta-blocker as indicated | Diuretics for fluid management; ACE inhibitor or ARB; beta-blocker as indicated; aldosterone antagonist<br>In selected patients, consider hydralazine/isosorbide dinitrate or digoxin | Presser support; chronic inotropes; symptom management with diuretics and/or digoxin as indicated |

*ACE* angiotensin-converting enzyme, *ARB* angiotensin receptor blocker

### 26.6.2 Treatment Guidelines for Heart Failure

In the past, treatment decisions were largely guided by NYHA classification; however, in recent years they are increasingly determined by ACCF/AHA disease staging (Table 26.6) [22]. Management of HF begins with correcting any factors (e.g., infection or nonsteroidal anti-inflammatory drugs) and addressing comorbid conditions (e.g., sleep-disordered breathing) that may be contributing to the progression of the disease. After underlying conditions have been improved or corrected, efforts are made to follow guideline-directed medical therapy (GDMT) in order to realize the mortality and morbidity benefits demonstrated in reported clinical trials. To date, ACE inhibitors and beta-blockers remain the cornerstones of GDMT and are proven to provide significant morbidity and mortality benefits [25–29]. Initial doses for each agent are very low and titrated as tolerated over 3–6 months, until goal doses are reached (Tables 26.7). In circumstances where a patient has a contraindication or experiences an adverse event with an ACE inhibitor, an ARB may be substituted as a means to retain mortality benefits [30]. Aldosterone antagonists have a role in decreasing mortality and hospitalization rates in patients with class III and IV heart failure [31]. The vasodilators hydralazine and isosorbide dinitrate, given in combination, are recommended for the management of black patients with NYHA III and IV on GDMT and for patients with contraindications to ACE inhibitors or ARBs [32]. Other agents such as diuretics and digoxin can also be given for symptom relief and to reduce subsequent hospitalizations. Currently, loop diuretics are the most potent class of clinically used diuretics and are the mainstay in volume control for HF pharmacotherapy. In all such patients, fluid status is an important monitoring parameter; for example, fluid retention can blunt the response of ACE inhibitors and increase beta-blocker adverse events, whereas fluid depletion can increase the risk of renal insufficiency. Importantly, both electrolyte levels and kidney function need to be monitored regularly when these agents are used in combination. Recently, cardiac resynchronization therapy (CRT) is a nonpharmacologic strategy that has been shown to reduce mortality and hospitalization rates in patients with class III or IV heart failure, who are already receiving optimal medical management [23]. Implantable cardioverter defibrillators (ICDs) may be used in selected

**Table 26.7** Medications with indications for heart failure

| Drug | Starting dose | Target dose or maximum dose |
|---|---|---|
| Angiotensin-converting enzyme inhibitors | | |
| Captopril | 6.25 mg three times daily | 50 mg three times daily |
| Enalapril | 2.5 mg twice daily | 10–20 mg twice daily |
| Fosinopril | 5–10 mg daily | 40 mg daily |
| Lisinopril | 2.5–5 mg daily | 20–40 mg daily |
| Perindopril | 2 mg daily | 8–16 mg daily |
| Quinapril | 5 mg twice daily | 20 mg twice daily |
| Ramipril | 1.25–2.5 mg daily | 10 mg daily |
| Trandolapril | 1 mg daily | 4 mg daily |
| Angiotensin receptor blockers | | |
| Candesartan | 4–8 mg daily | 32 mg daily |
| Losartan | 25–50 mg daily | 50–150 mg daily |
| Valsartan | 20–40 mg twice daily | 160 mg twice daily |
| Aldosterone antagonists | | |
| Spironolactone | 12.5–25 mg daily | 25 mg once-twice daily |
| Eplerenone | 25 mg daily | 50 mg daily |
| Beta-blockers | | |
| Bisoprolol | 1.25 mg daily | 10 mg daily |
| Carvedilol | 3.125 mg twice daily | 50 mg twice daily |
| Carvedilol controlled release | 10 mg daily | 80 mg daily |
| Metoprolol succinate extended release | 12.5–25 mg daily | 200 mg daily |

**Table 26.8** Definitions of atrial fibrillation and goals of therapy

| Type of atrial fibrillation | Definition | Goals of therapy |
|---|---|---|
| Paroxysmal | Rhythm restores to normal sinus rhythm spontaneously or with interventions within 7 days of onset | 1. Anticoagulation<br>2. Rate control<br>3. Rhythm control as indicated |
| Persistent | Rhythm is continuous and sustained for longer than 7 days | 1. Anticoagulation<br>2. Rate control<br>3. Rhythm control as indicated |
| Permanent | Attempts to restore and/or maintain normal sinus rhythm are unsuccessful | 1. Anticoagulation<br>2. Rate control |

individuals for the primary prevention of sudden cardiac death [33]. For more information on these technologies, the reader is referred to Chap. 30.

## 26.7 Arrhythmias

Atrial fibrillation (AF) is defined as a supraventricular arrhythmia characterized by chaotic electrical activity in the atria. AF affects nearly two and a half million people in the United States alone [34], and its prevalence increases rapidly after the sixth decade of life [35]. Patients with AF often experience a lower quality of life and frustration with currently available pharmacotherapy options for treatment; to date, prescribed agents offer marginal safety and efficacy. Risk factors for AF include hypertension, CHD, valvular disease, cardiomyopathy, chronic obstructive pulmonary disease, thyroid disease, electrolyte disturbances, alcohol abuse, and/or vagal stimulation. Clinically, AF is classified as paroxysmal, persistent, or permanent (Table 26.8).

Types of ventricular arrhythmias include: (1) premature ventricular complexes, (2) nonsustained ventricular tachycardia, (3) sustained ventricular tachycardia, and (4) ventricular fibrillation. Each rhythm is complex and has a unique electrocardiography classification (see Chap. 28 for more details). Of late, *sudden cardiac arrest* and *sudden cardiac death* have gained more attention as they claim nearly 450,000 lives annually in the United States [35, 36]. Ventricular fibrillation is the primary mechanism of sudden cardiac arrest, but evidence also attributes the elicitation of bradyarrhythmia, ventricular tachycardia, and torsades de pointes as additional mechanisms [32, 36].

**Table 26.9** $CHADS_2$ scoring for stroke risk assessment in atrial fibrillation

| | Risk factor | Point(s) |
|---|---|---|
| **C** | Recent cardiac failure | 1 |
| **H** | Hypertension | 1 |
| **A** | Age ≥75 years | 1 |
| **D** | Diabetes | 1 |
| **S** | Stroke | 2 |
| Add points for total $CHADS_2$ score | | Total |

**Table 26.10** $CHA_2DS_2$-VASc scoring for ischemic stroke risk in patients with atrial fibrillation

| | Risk factor | Point(s) |
|---|---|---|
| **C** | Congestive heart failure | 1 |
| **H** | Hypertension | 1 |
| **A** | Age ≥75 years | 2 |
| **D** | Diabetes mellitus | 1 |
| **S** | Stroke, TIA, or TE | 2 |
| **V** | Vascular disease | 1 |
| **A** | Age 65–74 years | 1 |
| **SC** | Sex category[a] | 1 |
| Add points for total $CHA_2DS_2$-VASc score | | Total |

*TIA* transient ischemic attack, *TE* thromboembolism
[a]Female sex indicates higher risk

### 26.7.1 Goals of Therapy for Treating Arrhythmias

Atrial fibrillation has been linked with an increased risk of ischemic stroke; therefore, the primary goal of pharmacotherapy in such patients is to prevent embolic events through the use of oral anticoagulants [37]. The risk of ischemic stroke increases with age and risk factors such as heart failure, hypertension, diabetes, history of stroke or transient ischemic attack, gender, and/or vascular disease. The $CHADS_2$ and $CHA_2DS_2VASc$ stroke risk assessment scores have been developed to determine the annual stroke risk and determine the need for anticoagulant therapy (Tables 26.9 and 26.10) [38, 39]. Significant advancements have been made in recent years for the treatment and prevention of thromboembolic diseases, beyond that of the traditionally used heparin and warfarin. Newer oral agents known as factor Xa inhibitors (e.g., rivaroxaban and apixaban) and direct thrombin inhibitors (e.g., dabigatran) act later and in a more targeted fashion in the clotting cascade than heparin or warfarin [40]. All of these agents, however, target thrombin, the final enzyme of the clotting cascade. It should be noted that several studies have evaluated the newer agents for safety and efficacy, using non-inferiority trial designs versus warfarin. While they have all proven non-inferior, careful consideration in patient selection is essential in determining which agent is best to use. Table 26.11 compares the differences between warfarin and the new agents, dabigatran, rivaroxaban, and apixaban.

Additional goals of therapy in such patients are to prevent tachycardia-induced cardiomyopathy, reduce symptoms of AF, and minimize adverse consequences of therapy [41]. Risk factor awareness and minimization are the main goals in the prevention of sudden cardiac arrest; risk factors are CHD, heart failure, or decreased left ventricular ejection fraction (≤30 %), previous sudden cardiac arrest event, prior episode of ventricular tachycardia, hypertrophic cardiomyopathy, and/or long QT syndrome [30]. To date, beta-blockers are the only antiarrhythmic drugs to have shown benefits in the primary prevention of sudden cardiac death; all other agents should be considered as adjuvant therapies to implantable cardioverter defibrillators [42–44].

### 26.7.2 Treatment Guidelines for Arrhythmias

All currently available antiarrhythmic drugs exert inhibitory activity on different phases of the cardiac action potential. In nodal tissue, type II and IV antiarrhythmic drugs control rate by decreasing calcium entry and therefore decreasing automaticity and associated conduction velocities in the depolarization phase. Type I and III antiarrhythmic drugs inhibit either sodium entry or potassium outflow, thereby decreasing automaticity and/or conduction velocities or increasing the refractory periods of the nodal action potential. For a summary of these primary mechanisms, see Table 26.12. In general, antiarrhythmic agents are used to either control ventricular rates or maintain normal sinus rhythm. Each strategy has

**Table 26.11** Comparison of oral anticoagulants

| | Vitamin K antagonists (e.g., warfarin) | Direct thrombin inhibitors (e.g., dabigatran) | Factor Xa inhibitors (e.g., rivaroxaban, apixaban) |
|---|---|---|---|
| Mechanism of action | Vitamin K inhibition prevents the hepatic synthesis of coagulation factors II, VII, IX, X, and protein C and protein S | Thrombin inhibition prevents thrombin-mediated effects such as factor activation and platelet aggregation | Inhibition of factor Xa prevents the conversion of prothrombin to thrombin; prevent clot formation and platelet aggregation |
| Indications | – Treatment and prevention of DVT and PE<br>– Embolic risk from AF or cardiac valve replacement<br>– Systemic embolic risk after myocardial infarction | – Treatment and prevention of DVT and PE<br>– Prevention of stroke and embolism for nonvalvular AF | – Prevention of DVT in hip or knee replacement<br>– Treatment of DVT (rivaroxaban only)<br>– Prevention of stroke and embolism for nonvalvular AF |
| Dosing | Once daily | Twice daily | Once or twice daily |
| Monitoring requirements | International normalized ratio/ prothrombin time | None | None |
| Drug interactions | Multiple | Multiple | Multiple |
| Reversal agent | Vitamin K, fresh frozen plasma, prothrombin complex concentrates, or factor products | Not identified, prothrombin complex concentrates may be used or hemodialysis | Not identified, prothrombin complex concentrates may be used or hemodialysis |
| Dosing considerations/ alterations | Based on INR | Requires consideration in renal dysfunction | Requires consideration in renal dysfunction, elderly, obesity, or administration with food |

*DVT* deep vein thrombosis, *PE* pulmonary embolism, *AF* atrial fibrillation

**Table 26.12** Antiarrhythmic drug mechanism of action

| Type | Drug | Channel activity | Automaticity | Conduction velocity | Refractory period |
|---|---|---|---|---|---|
| **Ia** | Quinidine | – Na + blocker<br>– K+ blocker | ↓ | ↓ | ↓ |
| | Procainamide[a] | | ↓ | ↓ | ↓ |
| | Disopyramide | | ↓ | ↓ | ↓ |
| **Ib** | Lidocaine | –Na + blocker | ↓ | ↓ | __ |
| | Mexiletine | | ↓ | ↓ | __ |
| **Ic** | Flecainide | – Na + blocker | ↓ | ↓↓ | __ |
| | Propafenone | | ↓ | ↓↓ | __ |
| **II** | Beta-blockers | – Decreases Ca++ (nodal cells) | ↓ | ↓ | __ |
| **III** | Amiodarone | – K+ blocker<br>– Na + blocker<br>– Ca ++ and beta-blocker (nodal cells) | ↓ | __ | ↑↑ |
| | Dronedarone (Multaq) | – K+ blocker<br>– Na + blocker<br>– Ca ++ and beta-blocker (nodal cells) | ↓ | __ | ↑↑ |
| | Dofetilide (Tikosyn) | – K+ blocker | __ | __ | ↑↑ |
| | Ibutilide (Corvert) | – K+ blocker | __ | __ | ↑↑ |
| | Sotalol (Betapace) | – K+ blocker<br>– Beta-blocker (nodal cells) | ↓ | __ | ↑↑ |
| **IV** | Diltiazem | – Ca++ blocker (nodal cells) | ↓ | ↓ | __ |
| | Verapamil | | | | |

[a]Metabolized to *N*-acetylprocainamide (NAPA) which has class III activity

important considerations for minimizing consequences of AF and thus burdensome symptoms. Figure 26.3a, b outline commonly employed treatment algorithms for maintaining normal sinus rhythm in both paroxysmal and persistent AF in patients, with and without associated structural heart disease [41].

Type III antiarrhythmic agents are used more frequently than type I agents in the setting of ventricular tachycardia/ventricular fibrillation. Note that amiodarone, a type III agent, is often used to decrease the frequency of supraventricular or ventricular arrhythmias in patients with an implantable cardioverter defibrillator to minimize defibrillation shock delivery [44, 45].

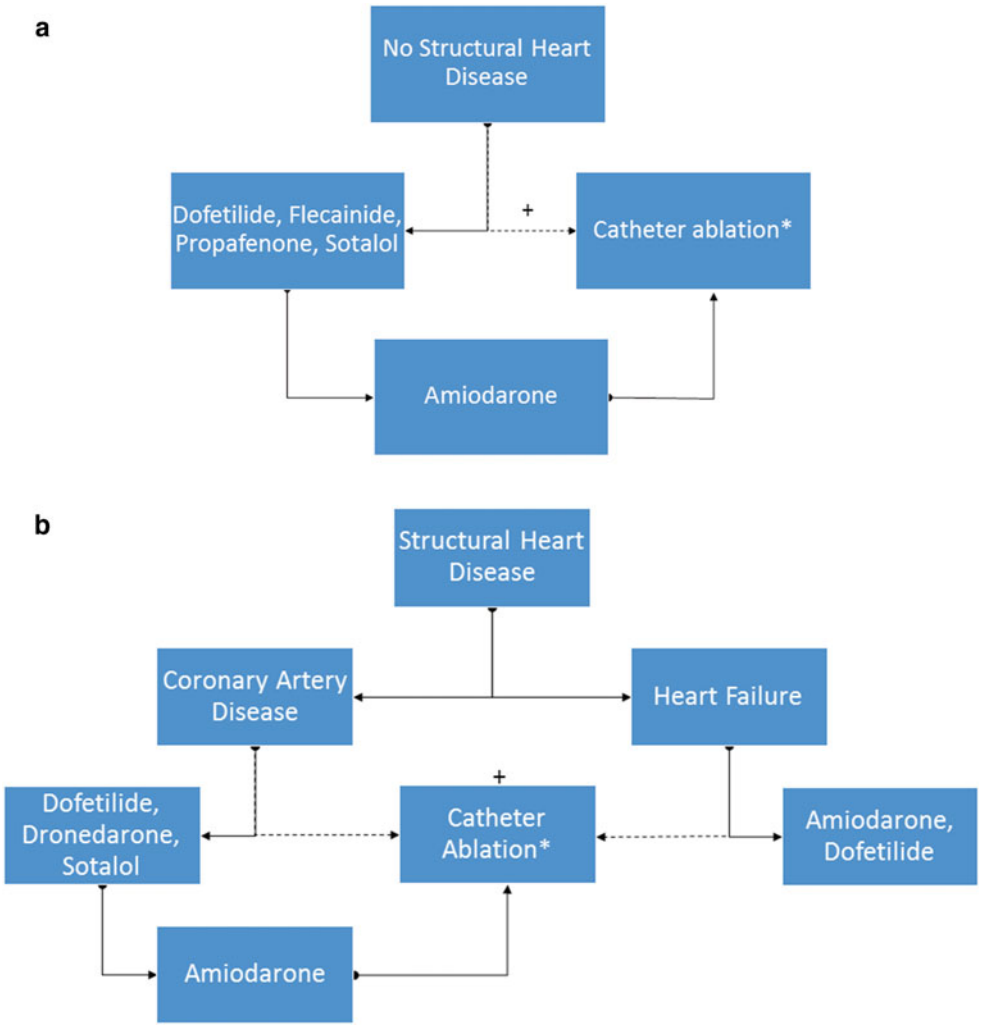


**Fig. 26.3** (**a**, **b**) Commonly employed treatment algorithms maintaining normal sinus rhythm in patients with paroxysmal and persistent atrial fibrillation [41]. +Depends on patient preference; *Considered first-line for paroxysmal atrial fibrillation only

## 26.8 Local Drug Delivery

Local drug delivery allows for therapeutic concentration of a drug to be administered to a designated target without exposing the rest of the body to potential adverse effects or toxic concentrations. Several methods for local drug delivery are already used in clinical practice. Transdermal delivery systems allow for localized penetration of a drug into the skin through a patch. Intrathecal drug pumps, through intraspinal catheters, deliver drugs to treat chronic pain and spasticity disorders with smaller doses of agents that traditionally would have been less effective and more sedating [46, 47]. Further, drug-eluting stents release drugs with anti-inflammatory properties from a polymer to prevent restenosis after a PCI and need for target lesion revascularization [48]. For that reason, they are generally preferred over bare metal stents. Researchers have evaluated drug delivery into the pericardial space with antiarrhythmic agents and vasodilators and have found benefits such as enhanced efficacy, increased duration of action, lower doses, and less toxicity [49–51]. See Chap. 9 for an additional discussion of this topic.

### 26.8.1 Future Potential for Targeted Drug Delivery

Polymers being designed to allow for controlled, targeted release of drugs (i.e., technology used with drug-eluting stents) are successful in preventing vessel restenosis relative to that seen with bare metal stents. Similarly, drug-containing hydrogels placed next to a therapeutic target allow for controlled delivery [52]. As such, drug-eluting implants using these materials are intended to deliver a drug over a period of hours to months. In contrast, recent catheter technology has the potential for delivering a precise amount of drug to a very specific target while maintaining the efficiency of intravascular delivery but without obstructing blood flow [53]. It is predicted that these local drug delivery methodologies, and those being developed, will become more prevalent as biologics and personalized medicine, such as gene therapy, begin to play a larger role in the treatment of cardiovascular diseases.

## 26.9 Summary

This chapter has provided a very brief overview of the pharmacotherapy decisions that have shown to be most beneficial for the current treatments of hypertension, acute coronary syndrome, heart failure, and arrhythmias. Such guidelines and subsequent updates, developed by experts in each of these respective areas of specialty, should be routinely consulted to maintain one's awareness of the optimal medical therapies, including pharmacotherapy, for the treatment of cardiovascular disorders.

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