PSAP

Arrhythmia Management: An Evidence-Based Update

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Learning Objectives

1. Demonstrate knowledge of the most recent evidence regarding the pathophysiology and prognosis of atrial fibrillation (AF).
2. Using evidence-based guidelines, develop an appropriate treatment regimen for patients with postoperative AF.
3. Distinguish the major changes in the most recent treatment guidelines for preventing thromboembolic events in patients with AF.
4. Given patient-specific information, design an individualized drug treatment plan for the chronic management of patients with paroxysmal, persistent, or permanent AF that includes monitoring parameters, and recommendations for managing adverse events or drug interactions.
5. Evaluate the clinical and economic impact of implantable cardioverter defibrillators and adjunctive therapy for patients with primary and secondary prevention indications.
6. Given patient-specific information, design an individualized drug treatment plan for the acute management of pulseless ventricular tachycardia/ventricular fibrillation (VF), asystole, or pulseless electrical activity (PEA).

Introduction

Over the past decade, prescribing patterns for the use of antiarrhythmic drugs has dramatically changed, with overall outpatient prescription rates for these drugs markedly declining. When examining the prescribing patterns by individual drug class, the outpatient use of class I antiarrhythmic drugs has significantly declined, whereas the prescription rate of class III antiarrhythmic drugs, particularly amiodarone, has nearly doubled. Several factors may have played a role in the decline in the use of antiarrhythmic drugs. Negative results of the Cardiac Arrhythmia Suppression Trial likely had a significant influence on the downward prescribing patterns of class I antiarrhythmic drugs. In addition, increasing clinical evidence to support the use of nonpharmacological strategies for the treatment of both supraventricular and ventricular arrhythmias has likely contributed to the decline in use. The results of recent trials that evaluated the safety and efficacy of rate-control and rhythm-control strategies in atrial fibrillation (AF) may also contribute to this continuing downward trend in the future.

Although the overall use of antiarrhythmic drugs has declined for the chronic treatment of supraventricular and ventricular arrhythmias, these drugs continue to have a significant role in the acute management of these arrhythmias. Because pharmacists are vital members of the cardiac arrest team in most institutions, they should familiarize themselves with the most recent guidelines for managing life-threatening arrhythmias. In addition, because the use of antiarrhythmic drugs for the chronic management of arrhythmias is unlikely to completely disappear any time soon, monitoring toxicities associated with these drugs remains vital need to provide patient care. Pharmacists have an important role in managing cardiac arrhythmias by understanding the adverse effects, potential drug interactions, and monitoring guidelines of all antiarrhythmic drugs.

This chapter focuses on the most recent data in the past few years (since the publication of the Cardiology Book in the Fifth Edition of the Pharmacotherapy Self-Assessment Program) regarding acute and chronic management of AF, ventricular arrhythmias, asystole, and pulseless electrical activity (PEA). The data encompass both pharmacological and nonpharmacological treatment strategies.

Atrial Fibrillation

Pathophysiology

Over the past several years, there has been evolving evidence that describes the potential pathophysiological role of the renin-angiotensin-aldosterone system (RAAS) in the

Abbreviations in this Chapter

ACC	American College of Cardiology
ACCP	American College of Chest Physicians
ACE	Angiotensin-converting enzyme
AF	Atrial fibrillation
AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management
AHA	American Heart Association
ARB	Angiotensin receptor blocker
AV	Atrioventricular
CABG	Coronary artery bypass graft
CCB	Calcium channel blocker
CMS	Centers for Medicare and Medicaid Services
CPR	Cardiopulmonary resuscitation
DINAMIT	Defibrillator in Acute Myocardial Infarction Trial
ECC	Emergency cardiovascular care
ESC	European Society of Cardiology
FDA	Food and Drug Administration
HF	Heart failure
HOT CAFE	How to Treat Chronic Atrial Fibrillation
HTN	Hypertension
ICD	Implantable cardioverter defibrillator
INR	International normalized ratio
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MADIT	Multicenter Automatic Defibrillator Implantation Trial
MI	Myocardial infarction
NYHA	New York Heart Association
PAPABEAR	Prophylactic Amiodarone for the Prevention of Arrhythmias that Begin Early After Revascularization, Valve Replacement, or Repair
PEA	Pulseless electrical activity
PIAF	Pharmacological Intervention in Atrial Fibrillation
RAAS	Renin-angiotensin-aldosterone system
RACE	Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation
SAFE-T	Sotalol Amiodarone Atrial Fibrillation Efficacy Trial
SCD	Sudden cardiac death
SCD-HeFT	Sudden Cardiac Death in Heart Failure Trial
STAF	Strategies of Treatment of Atrial Fibrillation
TEE	Transesophageal echocardiogram
TIPS	Tikosyn in Pharmacy System
VF	Ventricular fibrillation
VT	Ventricular tachycardia

development and perpetuation of AF. The RAAS appears to be activated in AF, and may induce and sustain this arrhythmia by promoting structural and electrical remodeling in the atria. Structural remodeling induced by RAAS occurs by several mechanisms. Angiotensin II promotes cardiac fibroblast proliferation, which leads to the development of atrial fibrosis. The presence of atrial fibrosis creates a favorable structural environment for developing and maintaining AF by causing electrophysiological abnormalities. Angiotensin II also significantly increases left atrial pressure and wall stress, which subsequently leads to left atrial distention. Angiotensin II potentially contributes to electrical remodeling by shortening the atrial effective refractory period and blunting the rate-adaptive shortening of the atrial effective refractory period, both of which promote the inducibility and maintenance of AF. Given the potential mechanisms by which RAAS promotes the genesis and recurrence of AF, there has been interest in evaluating the role of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in treating this arrhythmia.

Etiology

Although the presence of structural heart disease (e.g., hypertension [HTN], coronary heart disease, valvular heart disease, and left ventricular [LV] systolic dysfunction) continues to be the most common cause of AF, there has been increasing evidence that obesity and inflammation may be emerging risk factors for the development of this arrhythmia. Several mechanisms may explain the potential association between obesity and AF. Body mass index appears to be a strong determinant of left atrial size; therefore, the higher the body mass index, the larger the diameter of the left atria, which consequently increases a patient's risk for developing AF. In addition, patients who are obese tend to have elevated plasma volumes, ventricular diastolic dysfunction, and increased neurohormonal activation, all of which can lead to left atrial distention and increased arrhythmogenicity. The presence of obstructive sleep apnea in these patients can also contribute to the development of AF by causing hypoxemia and hypercapnia, both of which can result in electrical instability. In addition, obstructive sleep apnea can cause systemic and pulmonary vasoconstriction, both of which can lead to left atrial enlargement.

Evidence suggesting that AF may be an inflammatory disorder has also continued to emerge in the literature. Concentrations of both high-sensitivity C-reactive protein and interleukin-6 have been significantly higher in patients with AF compared with patients in sinus rhythm. Several potential mechanisms may explain the role of inflammation in the pathophysiology of AF. The development of AF can promote the accumulation of calcium within the atrial myocytes, which can lead to atrial cell death or apoptosis. This apoptosis is often followed by the development of atrial fibrosis, which can be a component of the remodeling

process that fosters the persistence of AF. The C-reactive protein may directly mediate the inflammatory process by activating the complement pathway in the atria, which can promote the development of AF. The presence of inflammation may also confer an increased risk of hypercoagulability in patients with AF, as elevated concentrations of both C-reactive protein and interleukin-6 have been associated with an increased risk of thromboembolic events in this patient population.

Epidemiology

Atrial fibrillation is the most common sustained arrhythmia encountered in clinical practice, affecting more than 2.2 million people in the United States. With the aging population, improved survival rates associated with coronary heart disease, heart failure (HF), and HTN, as well as the increased frequency of surgical procedures being performed, it is expected that the prevalence of AF will increase considerably in the near future, thereby potentially transforming this disease into a major public health concern. In fact, between the years 2000 and 2050, a 2-fold increase in the prevalence of this arrhythmia is expected. In a recent analysis of 8725 participants in the Framingham Heart Study, the overall lifetime risk of developing AF was 1 in 4 in men and women who were at least 40 years old. Even when those patients with a prior or current history of HF or myocardial infarction (MI) were excluded from the analysis, the lifetime risk of developing AF remained relatively high (1 in 6). Given that the overall lifetime risk of developing AF exceeds those associated with development of important conditions, such as breast cancer (1 in 8 at age 40), hip fractures (1 in 6 for white women at age 50, 1 in 20 for white men at age 50), and HF (1 in 5 at age 40), strategies aimed at appropriately identifying and treating any predisposing conditions (e.g., coronary heart disease, HF, HTN, and diabetes) may reduce the prevalence of this arrhythmia in the future.

Prognosis

Atrial fibrillation continues to be an independent risk factor for increased morbidity and mortality. Most of the morbidity associated with AF can be attributed to the 5-fold increased risk of stroke that is observed in this population compared with patients in sinus rhythm. The presence of AF also confers a mortality risk that is about 2-fold higher compared with patients who are in sinus rhythm.

Recently, risk scoring systems for predicting stroke alone and stroke or death in patients with AF were developed. These risk stratification schemes were based on data derived from a cohort of 868 patients with new-onset AF from the Framingham Heart Study. Overall, these risk scoring systems are similar to the Framingham risk score that was incorporated into the Adult Treatment Panel III guidelines for managing dyslipidemia. Although the risk assessment tool in the Adult Treatment Panel III guidelines estimates a patient's 10-year risk of developing MI or death from coronary heart disease, the AF risk scores predict a patient's 5-year risk of either stroke alone or the composite of stroke or death.

Figure 3-1 depicts the point-based scoring system for estimating a patient's 5-year risk of stroke alone or stroke or death. As with the Framingham risk score in the Adult Treatment Panel III guidelines, the number of points is determined for each risk factor and then totaled to determine a patient's overall 5-year risk. If practitioners do not have access to this point-based scoring system, a more precise tool for determining a patient's risk for these end points can be found on the Web site of the National Heart, Lung, and Blood Institute in the form of an Excel spreadsheet (*www.nhlbi.nih.gov/about/framingham/stroke.htm*).

Patients with AF are at low risk if their 5-year risk of stroke is 10% or less. Using this risk scoring system to determine the 5-year risk of stroke in patients with AF can help in terms of making decisions regarding initiating and/or discontinuing anticoagulant therapy. However, until these risk stratification schemes are validated in an independent cohort and compared with other available risk scoring systems for AF, these tools should be used with caution in clinical practice.

Therapeutic Goals/Outcomes

The disease-specific goals of therapy for AF include controlling the ventricular rate, preventing thromboembolic events, restoring sinus rhythm, and maintaining sinus rhythm. Although ventricular rate control and prevention of thromboembolic events should be addressed in nearly all patients with AF, the goals of restoring and maintaining sinus rhythm need to be addressed only in a select group of patients with AF. In addition, because of the significant morbidity and mortality and the future projected increase in the prevalence of AF, strategies should be implemented to appropriately identify and manage risk factors of this arrhythmia. In patients undergoing cardiac surgery (i.e., coronary artery bypass graft [CABG] surgery or valvular surgery), an additional goal is to prevent the development of postoperative AF.

Global goals for treating AF include decreasing overall and cardiovascular mortality, reducing symptoms, improving quality of life, and reducing hospitalizations. Five major clinical trials, Pharmacological Intervention in Atrial Fibrillation (PIAF), Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE), Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM), Strategies of Treatment of Atrial Fibrillation (STAF), and How to Treat Chronic Atrial Fibrillation (HOT CAFE), provide valuable insight on the effects of various pharmacological regimens on these global goals. Because the primary results of the PIAF, RACE, and AFFIRM trials have been previously reviewed, only the primary results of the most recently published trials, STAF and HOT CAFE, as well as the results of a meta-analysis of all five of these trials are discussed below.

Quality Patient Care

Pharmacological Therapy

Management of Postoperative Atrial Fibrillation

Postoperative AF occurs in up to 65% of patients undergoing cardiac surgery. Because of the increased morbidity, hospital costs, and length of stay associated with postoperative AF, considerable research has been performed to find safe and effective treatment strategies to not only treat this arrhythmia once it occurs, but also to prevent its

Risk Score for Stroke Alone

Age (years)	Points
55-59	0
60-62	1
63-66	2
67-71	3
72-74	4
75-77	5
78-81	6
82-85	7
86-90	8
91-93	9
> 93	10

Gender	Points
Male	0
Female	6

SBP (mm Hg)	Points
< 120	0
120-139	1
140-159	2
160-179	3
> 179	4

Diabetes	Points
No	0
Yes	5

Prior Stroke or TIA	Points
No	0
Yes	6

Total Points	5-Year Risk of Stroke (%)
0-1	5
2-3	6
4	7
5	8
6-7	9
8	11
9	12
10	13
11	14
12	16
13	18
14	19
15	21
16	24
17	26
18	28
19	31
20	34
21	37
22	41
23	44
24	48
25	51
26	55
27	59
28	63
29	67
30	71
31	75

Risk Score for Stroke or Death

Age (years)	Points
55	0
56	1
57	2
58-59	3
60	4
61	5
62	6
63	7
64-65	8
66	9
67	10
68	11
69	12
70-71	13
72	14
73	15
74	16
75	17
76-77	18
78	19
79	20
80	21
81	22
82-83	23
84	24
85	25
86	26
87	27
88	28
89	29
90-91	30
92	31
93	32
94	33

SBP (mm Hg)	Points
<120	0
120-139	1
140-159	2
160-179	3
>179	5

Diabetes	Points
No	0
Yes	4

Smoker	Points
No	0
Yes	5

Prior MI or CHF	Points
No	0
Yes	6

Murmur	Points
No	0
Yes	4

ECG LVH	Points
No	0
Yes	2

Total Points	5-Year Risk of Stroke or Death (%)
0	8
1	9
2-3	10
4	11
5	12
6	13
7	15
8	16
9	17
10	19
11	20
12	22
13	24
14	26
15	28
16	30
17	32
18	35
19	37
20	40
21	43
25	55
26	58
27	61
28	65
29	68
30	71
31	75
32	78
≥ 33	≥ 80

Figure 3-1. Scoring systems for assessing the 5-year risk of stroke alone and stroke or death in patients with new-onset atrial fibrillation.
CHF = congestive heart failure; ECG LVH = electrocardiographic left ventricular hypertrophy; MI = myocardial infarction; SBP = systolic blood pressure; TIA = transient ischemic attack.
Adapted with permission from the American Medical Association. Wang TJ, Massaro JM, Levy D, Vasan RS, D'Agostino RB, Larson MG, et al. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: The Framingham Heart Study. JAMA 2003;290:1049–56.

initial development. In recent years, much of the data that have emerged regarding the pharmacological treatment of this particular arrhythmia focused on the use of prophylactic therapy. One of the most clinically relevant trials to focus on this issue was the Prophylactic Amiodarone for the Prevention of Arrhythmias that Begin Early After Revascularization, Valve Replacement, or Repair (PAPABEAR) trial.

Several randomized trials have evaluated the efficacy of amiodarone for prophylaxis of AF after cardiac surgery. However, those trials were limited by their relatively small sample sizes, which may have contributed to their inability to detect significant differences with regard to the efficacy of amiodarone in specific patient subgroups and the safety of this antiarrhythmic drug in the postoperative setting. The PAPABEAR trial was appropriately designed and adequately powered to evaluate the efficacy of preoperative amiodarone in specific patient subgroups. A total of 601 patients undergoing nonemergent CABG and/or valve replacement/repair surgery were randomized to receive either oral amiodarone 10 mg/kg/day (in two divided dosages) for 6 days before and after surgery (total of 13 perioperative days) or placebo. Overall, significantly fewer patients in the amiodarone group developed postoperative atrial tachyarrhythmias compared with the placebo group (16.1% vs. 29.5%, respectively). In the subgroup analysis, the significant benefit of amiodarone persisted in patients older and younger than age 65, in those who underwent CABG and/or valve replacement/repair surgery, and in those who did or did not receive preoperative β-blocker therapy. No significant difference was observed between the treatment groups with regard to length of hospital stay. Overall, results of this trial demonstrated that a 13-day perioperative course of oral amiodarone was effective in reducing the incidence of postoperative atrial tachyarrhythmias in a broad range of patients undergoing cardiac surgery. However, because this treatment regimen must be initiated several days before surgery, routine use of this prophylactic therapy is usually reserved for patients who are specifically undergoing elective cardiac surgery.

Chronic Management of Atrial Fibrillation

Update on Recent Clinical Trials. ***Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers.*** There has been a growing body of evidence in recent years that suggests that ACE inhibitors and ARBs may be effective in preventing the development of AF in certain patient populations. However, most data have been derived from post hoc analyses of trials that enrolled patients with HF, HTN, or MI. A meta-analysis was recently conducted on 11 randomized, clinical trials in patients with HF (four trials), HTN (three trials), after MI (two trials), or after cardioversion for AF (two trials) to evaluate the effects of ACE inhibitors and ARBs in preventing AF. Overall, the results suggest that these drugs appeared to significantly reduce the risk of AF by 28%. The reduction in the risk of developing AF was similar between ACE inhibitors and ARBs. The greatest reduction in AF occurred in patients with HF, with a significant 44% relative risk reduction being observed. Although there was no significant reduction in AF in patients with HTN or in those after MI, results of the individual trials within each of these patient populations were heterogeneous. In post-MI trials, the reduction in AF was only significant in one trial, which exclusively included patients with concomitant LV systolic dysfunction; however, in the other trial, where no significant reduction in AF was observed, only 16% of patients had evidence of HF. Similarly, in the HTN trials, a significant reduction in AF was only demonstrated in one of the trials, which was the only one to include patients with LV hypertrophy. The incidence of recurrent AF was significantly reduced by 48% in the trials that enrolled patients who had undergone electrical cardioversion; however, these results, in particular, should be interpreted with caution as both of these trials were limited by their relatively small sample sizes, short follow-up periods (about 6 months), and open-label designs.

Although these results appear to suggest that ACE inhibitors and ARBs possess direct antiarrhythmic properties, because the significant reduction in AF was primarily observed in patients with LV systolic dysfunction or LV hypertrophy, their benefit may be more related to an attenuation of the structural remodeling process in the atria. However, larger, prospective, randomized trials need to be performed to conclusively determine whether ACE inhibitors and ARBs are effective in preventing recurrence of AF, as well as the mechanisms responsible for these potential benefits. One such trial, the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events, has been initiated and is expected to randomize about 9000 patients with a history of AF to receive either irbesartan or placebo. Although the primary end point is the composite of stroke, MI, and vascular death, the effects of irbesartan on the frequency of recurrent AF and on the structural remodeling process in the heart will also be evaluated in prespecified subgroup analyses. Until this additional data become available, routine use of ACE inhibitors or ARBs to solely prevent the recurrence of AF is not recommended.

Omega-3 Fatty Acids. Another intriguing therapy being investigated for preventing and treating AF are omega-3 fatty acids. Several mechanisms have been postulated to explain the antiarrhythmic effect of omega-3 fatty acids, including inhibition of the fast, voltage-dependent sodium and L-type calcium channels and reduction in the omega-6 fatty acid/omega-3 fatty acid ratio, which may shift the myocardium from a proarrhythmic to an antiarrhythmic state. The majority of studies that investigated the potential antiarrhythmic effects of omega-3 fatty acids examined the incidence of ventricular arrhythmias. In fact, several clinical trials have shown that an increased intake of omega-3 fatty acids is associated with a reduction in the risk of sudden cardiac death (SCD), perhaps by the suppression of life-threatening ventricular arrhythmias.

Given their potential antiarrhythmic effects in the ventricular myocardium, omega-3 fatty acids are now being evaluated for managing supraventricular arrhythmias to determine if these antiarrhythmic properties might also extend to the atria. Most recently, two trials, that specifically evaluated the risk of developing AF with the use of omega-3 fatty acids administered either through the ingestion of fish or as a commercial product, were published. The first was a population-based prospective cohort study that

enrolled 4815 patients at least 65 years of age who did not have AF at baseline. Each patient's usual dietary intake was assessed at baseline, including his or her frequency of consuming tuna fish, other broiled or baked fish, and fried fish or fish sandwiches. After a follow-up period of 12 months, consumption of tuna or other broiled or baked fish, but not fried fish or fish sandwiches, was associated with a significant reduction in the incidence of AF, even after adjustment for many factors. In fact, the magnitude of the risk reduction was directly correlated with the frequency at which the tuna or broiled/baked fish was consumed. Study results suggest, but do not prove, an association between the ingestion of fatty types of fish and the incidence of AF.

The other study randomized 160 patients undergoing CABG surgery to receive either commercially available omega-3 fatty acids 2 g/day or placebo for at least 5 days before surgery and until the day of discharge. Patients undergoing valvular surgery and those with a previous history of AF were excluded from this study. Overall, the incidence of postoperative AF was significantly reduced in the omega-3 fatty acid group compared with placebo. Although study results are limited by the relatively short follow-up period and can only be applied to a low-risk cardiac surgery population, they provide some initial insight into the potential antiarrhythmic effects that omega-3 fatty acids may have in the atrium. However, larger studies need to be performed in both surgical and nonsurgical populations to assess the potential benefits of such supplementation on the prevention and treatment of AF.

Results of Sotalol Amiodarone Atrial Fibrillation Efficacy Trial. With regard to the use of conventional antiarrhythmic therapy to restore and maintain sinus rhythm in patients with AF, one of the most important trials in the past several years is the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T). In this double-blind study, patients with persistent AF who were receiving anticoagulant therapy were randomized to receive amiodarone (n=267), sotalol (n=261), or placebo (n=137) on an outpatient basis. Amiodarone was administered at 800 mg/day for 14 days, then 600 mg/day for 14 days, then 300 mg/day for the first year, and then 200 mg/day thereafter. Sotalol was administered at 80 mg twice daily for 1 week, then 160 mg twice daily thereafter. Direct current cardioversion was performed if patients did not spontaneously convert to sinus rhythm by day 28 after enrollment.

Before day 28, rates of spontaneous conversion to sinus rhythm were comparable between the amiodarone and sotalol groups. However, amiodarone was significantly more effective than sotalol at maintaining patients in sinus rhythm. Amiodarone was more effective than sotalol at maintaining sinus rhythm in all subgroups except in patients with ischemic heart disease, where both antiarrhythmic drugs had similar efficacy. Both quality of life and exercise tolerance were significantly improved in patients who were in sinus rhythm compared with those who remained in persistent AF. Overall, trial results suggest that rhythm control should remain a viable option in managing AF.

Update on Rate Versus Rhythm Control Controversy.

Recent Clinical Trials. Although results of the PIAF, RACE, and AFFIRM trials have been previously discussed, two additional trials, STAF and HOT CAFE, add to the body of literature that has evaluated the safety and efficacy of rate-control and rhythm-control strategies in patients with AF. In the STAF trial, 200 patients with persistent AF, who were at moderate to high risk for recurrence, were randomized to either a rate-control or a rhythm-control group. To demonstrate that they were at significant risk for arrhythmia recurrence, patients needed to have at least one of the following: AF duration longer than 4 weeks, left atrial size greater than 45 mm, congestive HF, New York Heart Association (NYHA) class II–IV HF, left ventricular ejection fraction (LVEF) less than 45% (LVEF less than 20% was an exclusion criteria), or at least one prior episode of cardioversion with arrhythmia recurrence. In the rate-control group, β-blockers, diltiazem, verapamil, digoxin, or atrioventricular (AV) node ablation/modification with or without pacemaker implantation were used. In the rhythm-control group, all patients initially underwent electrical cardioversion and then received an antiarrhythmic to prevent recurrence of AF. More specifically, patients with LV dysfunction or coronary heart disease received amiodarone and/or a β-blocker while other patients in this treatment group received either a class I antiarrhythmic drug or sotalol. Overall, in the rhythm-control group, 42% of the patients received amiodarone. All patients in this study received oral anticoagulation to achieve an international normalized ratio (INR) between 2 and 3. The primary end point was the composite of death, cardiopulmonary resuscitation (CPR), cerebrovascular event, and systemic embolism.

After a mean follow-up period of 19.6 months, the incidence of the primary end point was similar between the rhythm-control and rate-control groups. At the end of the follow-up period, 38% of patients in the rhythm-control group were in sinus rhythm despite performance of up to four cardioversions. Although there were no significant differences between the treatment groups with regard to the individual components of the primary end point, almost 95% of all the end points occurred while the patients were in AF. Although the findings of this trial suggest that that a rate-control strategy is an acceptable alternative to rhythm control in patients with persistent AF, this study was limited by its small sample size, short follow-up period, and nonrandomized approach to the use of antiarrhythmic drugs in the rhythm-control group.

The most recent study to compare the efficacy of a rate-control and rhythm-control strategy is the HOT-CAFE trial. This trial enrolled 205 patients between the ages of 50 and 75 who had their first episode of clinically overt persistent AF. In the rate-control group, digoxin, diltiazem, verapamil, or a β-blocker could be used alone or in combination. In the rhythm-control group, patients initially underwent electrical cardioversion and then received disopyramide, propafenone, or sotalol if sinus rhythm had been restored. Selection of an antiarrhythmic drug was primarily based on the presence of structural heart disease. If there was a recurrence of AF, electrical cardioversion was repeated and, if successful, another antiarrhythmic drug from the list above was initiated. If there was another recurrence of AF, loading doses of amiodarone were given (600 mg/day for 3 weeks, then 400 mg/day until patient received total

loading dose of 12-16 g) and electrical cardioversion was repeated. Amiodarone was then lowered to a maintenance dose of 100–200 mg/day. In patients who did not convert to sinus rhythm with either the first or second attempt of electrical cardioversion, loading doses of amiodarone were given and electrical cardioversion was repeated. If successful, the amiodarone was continued at maintenance doses. Antithrombotic therapy in both treatment groups was based on the guidelines from the American College of Chest Physicians (ACCP) available when the study was conducted. The primary end point of this study was the composite of death, thromboembolic complications, and intracranial or other major hemorrhage.

In the rate-control group, β-blockers alone or in combination with digoxin were primarily used. Although 56% of patients in the rhythm-control group received amiodarone after restoration of sinus rhythm, the remaining breakdown of antiarrhythmic drugs used in this group was not specified. After a mean follow-up of 1.7 years, sinus rhythm was present in 63.5% of patients in the rhythm-control group. No significant difference was observed with regard to the primary end point between the rate-control and rhythm-control groups, which may be attributed to the small number of events that occurred in each group. Significantly more hospitalizations, primarily for repeated cardioversions, occurred in the rhythm-control group compared with the rate-control group. Even though this trial was limited by its relatively small sample size, short follow-up period, and low number of events, its results are consistent with those of the PIAF, RACE, AFFIRM, and STAF trials, and further demonstrate that a rate-control strategy is a viable alternative to a rhythm-control strategy in patients with persistent AF.

Given the publication of five trials that have compared the efficacy of a rate-control and rhythm-control strategy for treating AF, a meta-analysis was recently performed that analyzed the pooled results of these trials. This analysis included data from 5239 patients enrolled in the PIAF, RACE, AFFIRM, STAF, and HOT CAFE trials. The primary end point of this meta-analysis was all-cause mortality while the secondary end point was ischemic stroke. Data on all-cause mortality were available from all five trials, whereas only the AFFIRM, STAF, and HOT-CAFE trials reported data about ischemic strokes. Results of this analysis demonstrated no significant difference in all-cause mortality between the rate-control and rhythm-control groups, which persisted even when the results from the AFFIRM trial were excluded from this analysis. In addition, there was no significant difference in the risk of ischemic stroke between these treatment groups. Although there was no evidence of significant heterogeneity between the trials, a potential limitation was that the data from the AFFIRM trial may have skewed the analysis because more than 75% of the patients included in the meta-analysis were enrolled in this trial. Nevertheless, until additional large-scale trials are performed, results of all five trials are relatively consistent and suggest that a rhythm-control strategy does not confer any advantage over a rate-control strategy in managing patients with persistent AF.

Nonpharmacological Therapy

In view of the limited efficacy and the risk of proarrhythmia and other long-term adverse effects of antiarrhythmic drugs, various nonpharmacological therapies are being evaluated for managing AF, including surgical ablation, catheter ablation, atrial pacing, and implantable atrial defibrillators. Most emerging data in the literature have primarily focused on the safety and efficacy of catheter ablation techniques. Overall, in these trials, the use of catheter ablation in patients with AF has been associated with a significant reduction in recurrence of AF and improvement in quality of life compared with antiarrhythmic drugs. Although there are limited data to suggest that catheter ablation may be superior to antiarrhythmic drugs as first-line therapy for symptomatic AF, until larger trials are performed, this procedure is usually reserved for patients who have failed multiple antiarrhythmic drug regimens because of its potential risks (e.g., pulmonary vein stenosis and tamponade).

Treatment Plan

Management of Postoperative Atrial Fibrillation

The ACCP recently developed evidence-based clinical practice guidelines for preventing and treating postoperative AF after cardiac surgery. According to these guidelines, β-blockers are recommended as first-line therapy for patients in whom prophylaxis is indicated. If β-blocker therapy is contraindicated, then amiodarone or sotalol can be considered as prophylactic drugs. However, the results of a study that was not completed at the time these guidelines were developed suggest that although amiodarone and sotalol provide comparable efficacy in preventing AF in patients undergoing CABG, amiodarone may be more effective than sotalol in patients undergoing valvular surgery who may be at higher risk for developing this postoperative arrhythmia. Therefore, to minimize drug-induced toxicities in patients requiring prophylactic therapy, sotalol may be preferred in patients undergoing CABG who have normal renal and LV systolic function while amiodarone can be used in patients undergoing more complex valvular surgery, or those with renal or LV systolic dysfunction (i.e., LVEF of 40% or less). According to the guidelines, non-dihydropyridine calcium channel blockers (CCBs), magnesium, or digoxin are not recommended as prophylactic therapy against postoperative AF.

If AF develops after cardiac surgery, β-blockers are considered first-line therapy to achieve acute ventricular rate control because of the heightened adrenergic tone that is present in the postoperative state. Non-dihydropyridine CCBs can be used as second-line therapy provided that the LVEF is greater than 40%. Although the evidence regarding the efficacy of amiodarone for controlling ventricular rate in the postoperative setting is relatively weak, its use may be considered in patients who cannot tolerate or have a contraindication to both β-blockers and CCBs. Because the efficacy of digoxin is significantly reduced in the presence of increased adrenergic tone, its use for ventricular rate control in patients with postoperative AF is not encouraged. Cardioversion is recommended for patients who are highly symptomatic or hemodynamically unstable. In addition, patients who have a contraindication to anticoagulation

should be cardioverted within 48 hours after the onset of AF. In the absence of these indications, a rate-control strategy may be equivalent to a rhythm-control strategy. In patients in whom cardioversion is indicated, the selection of antiarrhythmic therapy should primarily be based on the patients' LV function. If LV dysfunction is present (LVEF of 40% or less), amiodarone is considered the antiarrhythmic drug of first choice. In patients with normal LV function, amiodarone, sotalol, or ibutilide can be initially considered for cardioversion of AF; however, sotalol is less effective than other antiarrhythmic drugs for cardioversion of AF. In this particular patient population, the class Ia antiarrhythmic drugs, disopyramide, quinidine, or procainamide, can be considered as alternative therapies. Because of the increased risk of mortality associated with their use in patients with coronary heart disease, the class Ic antiarrhythmic drugs, flecainide and propafenone, should not be used for cardioversion of AF following cardiac surgery. In addition, dofetilide is not recommended because its efficacy has not been demonstrated in this setting. Regardless of antiarrhythmic drug selected, it is usually recommended that therapy be continued for a total of 4–6 weeks after surgery.

Management of Atrial Fibrillation

Overview of Updated Treatment Guidelines. In 2006, the American College of Cardiology, American Heart Association, and the European Society of Cardiology (ACC/AHA/ESC) updated treatment guidelines for AF. When comparing these updated guidelines to those previously published in 2001, there are several important changes regarding the management of AF. Perhaps the most significant change is the incorporation of catheter ablation as a viable treatment alternative for patients with either recurrent paroxysmal or recurrent persistent AF who fail or do not tolerate at least one antiarrhythmic drug. In previous guidelines, ablation was usually considered last-line therapy once patients failed all antiarrhythmic therapies, including amiodarone. However, based on the updated guidelines, in patient populations where amiodarone is considered second-line antiarrhythmic drug therapy (e.g., without structural heart disease, no significant LV hypertrophy, or coronary artery disease), ablation may be considered an alternative to amiodarone if the recommended first-line antiarrhythmic drug therapy has failed. In addition, by incorporating the results of the most recently published rate-control versus rhythm-control trials (STAF and HOT-CAFE), the updated guidelines continue to emphasize that both of these treatment strategies are reasonable options in patients with AF. However, when considering long-term treatment goals, a rhythm-control strategy is preferred for patients who have intolerable symptoms attributable to the AF despite having reasonable heart rate control. Based on the results of the rate-control versus rhythm-control trials, the updated guidelines also recommend that antithrombotic therapy should be considered for all patients with AF regardless of whether a rate-control or rhythm-control strategy is initiated. Although an overall approach to managing newly discovered, recurrent paroxysmal, recurrent persistent, and permanent AF is presented in Figure 3-2, specific drug therapy recommendations for controlling ventricular rate, restoring/maintaining sinus rhythm, and preventing thromboembolic events in these patients is reviewed in the sections below.

Ventricular Rate Control. Achieving adequate ventricular rate control should be a treatment goal for all patients with AF. When initiating therapy to control ventricular rate in either the acute or chronic setting, drug selection is primarily based on the patient's LV function. In the acute setting, intravenous β-blockers, diltiazem, or verapamil are first-line therapy to control ventricular rate in patients with normal LV function (LVEF greater than 40%). In patients with LV dysfunction (LVEF of 40% or less), intravenous non-dihydropyridine CCBs should be avoided because of their potent negative inotropic effects. Intravenous β-blockers should be used with caution in this patient population and should be avoided if patients have decompensated HF. If patients have an exacerbation of HF symptoms, intravenous administration of either digoxin or amiodarone should be used as first-line therapy to achieve ventricular rate control. Intravenous amiodarone can also be used when the ventricular rate cannot be adequately controlled with or if patients have contraindications to the other negative chronotropic drugs. However, because of amiodarone's ability to convert AF to sinus rhythm, the potential thromboembolic risks associated with cardioversion should be considered when using this antiarrhythmic drug for ventricular rate control in patients with AF that is at least 48 hours or of unknown duration.

In the chronic setting, therapy with oral β-blockers, diltiazem, or verapamil is preferred over digoxin in patients with normal LV function because of their relatively quick onset and maintained efficacy during exercise. In patients with LV dysfunction, non-dihydropyridine CCBs should be avoided. β-Blockers and digoxin are preferred in this patient population because these drugs are also concomitantly used to treat chronic HF. In general, if the patient is not having an episode of decompensated HF, β-blockers (i.e., metoprolol, carvedilol, or bisoprolol) are preferred over digoxin because of their survival benefits in chronic HF. If patients are having an exacerbation of HF symptoms, digoxin is preferred as first-line therapy to achieve ventricular rate control. Digoxin can also be added if additional ventricular rate control is needed despite monotherapy with β-blockers or non-dihydropyridine CCBs. If adequate ventricular rate control during rest and exercise cannot be achieved with β-blockers, non-dihydropyridine CCBs, and/or digoxin, oral amiodarone can be used as alternative therapy to control the heart rate.

Restoring/Maintaining Sinus Rhythm. Restoration of sinus rhythm is usually not considered first-line therapy for most patients with AF. However, if patients with AF present with hemodynamic instability (i.e., severe hypotension, HF, or angina), direct-current cardioversion is indicated as initial therapy. If patients are hemodynamically stable, restoration of sinus rhythm can be performed by either direct-current cardioversion or with the use of antiarrhythmic drugs. Despite the relatively high success rate associated with direct-current cardioversion (95%), antiarrhythmic drugs are often used for this purpose in the clinical setting. Pharmacological cardioversion is most effective when initiated within 7 days after the onset of AF. According to the ACC/AHA/ESC guidelines, antiarrhythmic drugs that

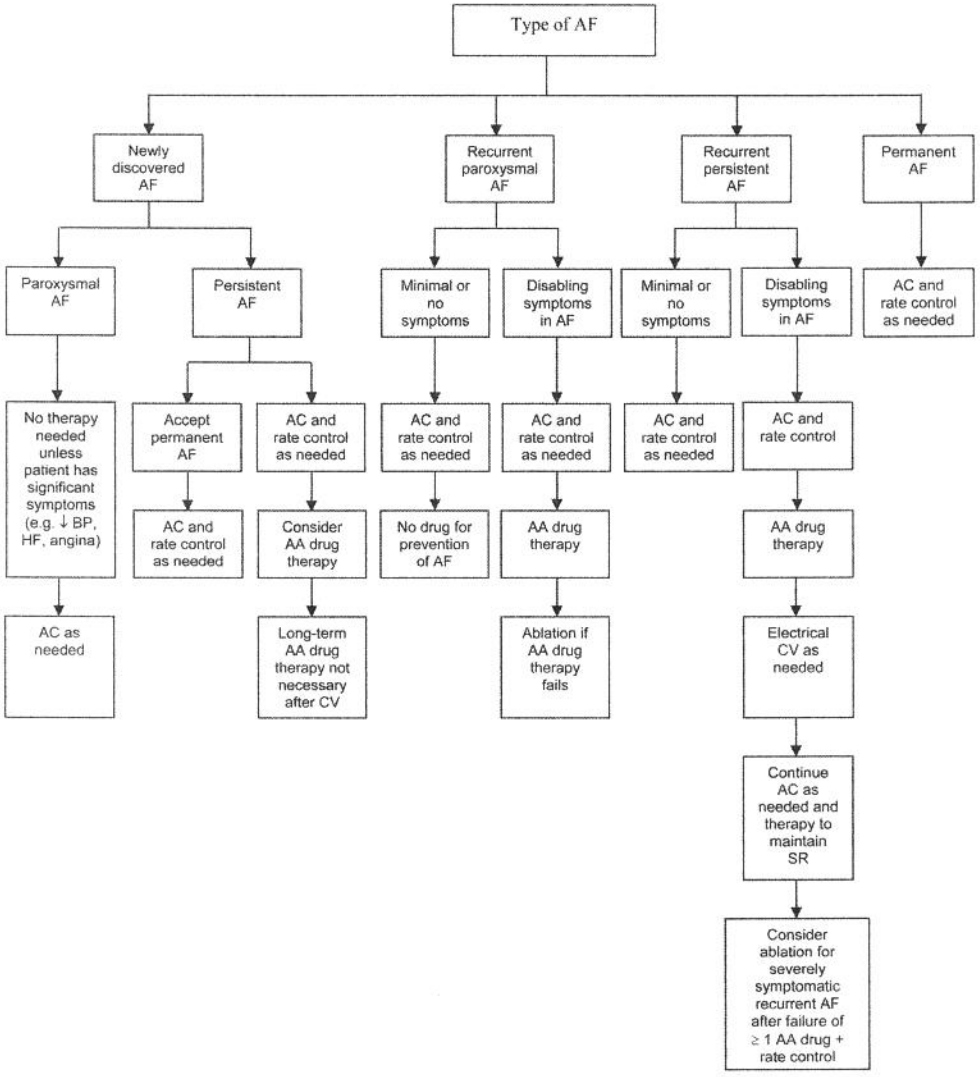

Figure 3-2. Algorithm for chronic management of atrial fibrillation.
AA = antiarrhythmic; AC = anticoagulation; AF = atrial fibrillation; BP = blood pressure; CV = cardioversion; HF = heart failure; SR = sinus rhythm.
Adapted with permission from the American College of Cardiology and American Heart Association, Inc. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). J Am Coll Cardiol 2006;48:e149–246.

have proven efficacy in this setting include dofetilide, flecainide, ibutilide, propafenone, or amiodarone (oral or intravenous). The class Ia antiarrhythmic drugs have limited efficacy in this setting. Sotalol is not effective for cardioversion of paroxysmal or persistent AF. Selection of an antiarrhythmic drug for cardioversion should be based on the presence of structural heart disease. In the absence of structural heart disease, the use of single, oral loading doses of flecainide or propafenone is reasonable for cardioversion. Ibutilide can also be used as an alternative drug in this patient population. In patients with underlying structural heart disease, all three of these antiarrhythmic drugs should be avoided because of the increased risk of proarrhythmia, and amiodarone or dofetilide should be used alternatively. In patients with AF that is longer than 7 days in duration, only dofetilide, amiodarone, and ibutilide have proven efficacy for cardioversion. Class Ia and Ic antiarrhythmic drugs have limited efficacy in this setting.

According to the ACC/AHA/ESC guidelines, the use of antiarrhythmic drug therapy to maintain sinus rhythm is reasonable in patients with recurrent paroxysmal or persistent AF who develop intolerable symptoms during episodes of AF. An algorithm that can be used to guide the selection of antiarrhythmic drug therapy to maintain sinus rhythm in these patient populations is depicted in Figure 3-3. Compared with previous guidelines, the updated guidelines did not include the class Ia antiarrhythmic drugs as part of this algorithm. In fact, the role of these antiarrhythmic drugs for restoring or maintaining sinus rhythm has been deemphasized throughout the guidelines because they are considered less effective or incompletely studied for these purposes. In reality, these drugs would be

considered as last-line antiarrhythmic therapy in patients without structural heart disease or in those with hypertension (without significant LV hypertrophy) or coronary artery disease (with normal LV systolic function).

Prevention of Thromboembolic Events. The ACC/AHA/ESC guidelines and the guidelines derived from the Seventh ACCP Consensus Conference on Antithrombotic Therapy provide recommendations regarding the most appropriate antithrombotic strategy for patients with AF. Both sets of guidelines provide relatively consistent recommendations regarding antithrombotic therapy in patients with AF who are undergoing cardioversion. For these patients, determining the approximate duration of their arrhythmia is important. Patients are at an increased risk for thrombus formation and an embolic event if the duration of AF is 48 hours or longer. Therefore, in patients with AF that is at least 48 hours or of unknown duration, warfarin (target INR 2.5; range 2–3) should be administered for 3 weeks before and for at least 4 weeks after pharmacological or electrical cardioversion. An alternative strategy, using a transesophageal echocardiogram (TEE) to guide anticoagulation for cardioversion, has also been suggested for this patient population. If no thrombus is visualized during the TEE, cardioversion can be performed. However, intravenous unfractionated heparin should be administered during the TEE and cardioversion to prevent the formation of thrombi during the peri-cardioversion or post-cardioversion periods. If cardioversion is successful, warfarin should be initiated and continued for at least 4 weeks. If a thrombus is visualized during the TEE, cardioversion must be postponed and the patient must be anticoagulated for an indefinite period. For patients with AF of less than 48 hours duration, cardioversion can be performed without the 3 weeks of pre-cardioversion anticoagulation therapy; however, either intravenous unfractionated heparin or a low-molecular-weight heparin (administered subcutaneously at treatment doses) should be initiated at presentation before cardioversion. If these patients have risk factors for stroke, a TEE could alternatively be performed before cardioversion to exclude the presence of thrombus; in addition, these patients should also be considered for at least 4 weeks of post-cardioversion anticoagulation therapy.

Recommendations for chronic antithrombotic therapy in patients with AF differ slightly between the two sets of guidelines. According to both sets of guidelines, risk stratification is an essential process in determining the most appropriate oral antithrombotic therapy for patients with paroxysmal, persistent, or permanent AF. The most apparent difference between the guidelines is that the high-risk, moderate-risk, and low-risk categories are not uniform. However, from a practical standpoint, when evaluating the ACC/AHA/ESC guidelines, most patients with AF who have one of the moderate-risk factors usually have at least

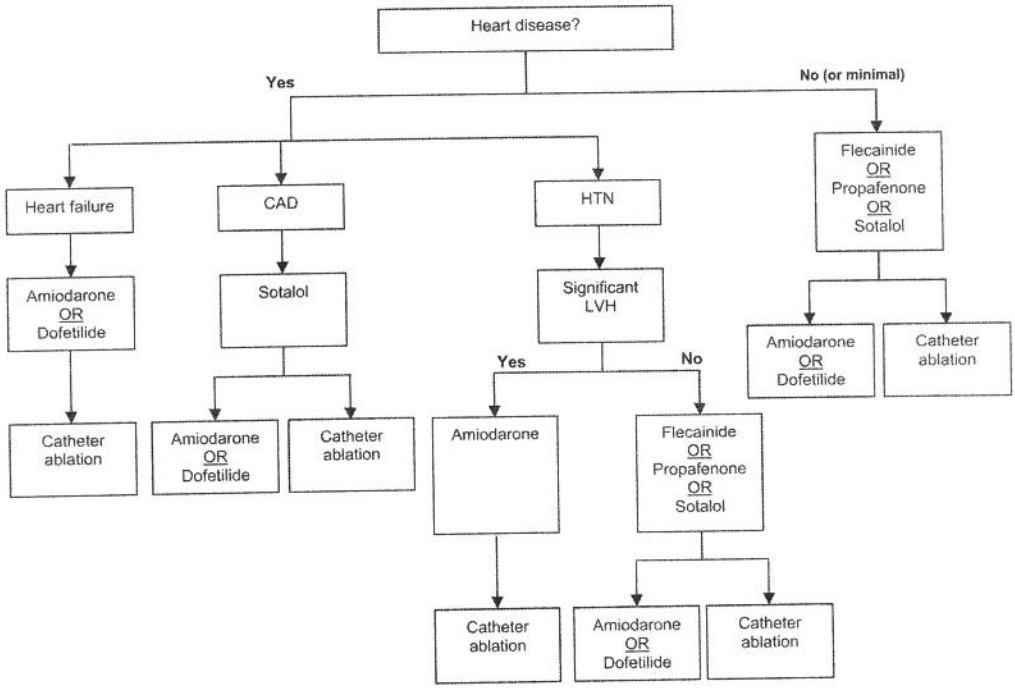

Figure 3-3. Algorithm for selecting antiarrhythmic drug therapy for maintenance of sinus rhythm in patients with recurrent paroxysmal or recurrent persistent atrial fibrillation.[a]

[a]Within each of the boxes, the drugs are listed alphabetically and not in order of suggested use. However, the sequence of the boxes does imply the order of suggested use.

CAD = coronary artery disease; HTN = hypertension; LVH = left ventricular hypertrophy.

Adapted with permission from the American College of Cardiology and American Heart Association, Inc. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). J Am Coll Cardiol 2006;48:e149–246.

another of these risk factors, which ultimately makes the antithrombotic therapy recommendations from both sets of guidelines relatively consistent. Recommendations from both sets of guidelines for selecting the most appropriate chronic antithrombotic therapy in patients with AF are outlined in Table 3-1. When deciding whether to initiate anticoagulant therapy, it is important to remember that the PIAF, RACE, AFFIRM, STAF, and HOT-CAFE trials suggest that patients with AF and other risk factors for stroke continue to be at risk for stroke even when maintained in sinus rhythm. Therefore, antithrombotic therapy should be considered for all patients with AF regardless of whether a rate-control or rhythm-control strategy is pursued. In addition, based on data from the above clinical trials, restoration of sinus rhythm does not warrant discontinuation of antithrombotic therapy.

Monitoring

Patients with AF should have their heart rate and blood pressure monitored to assess the efficacy and safety of the drugs that are used for ventricular rate control. The goal heart rate should be less than 80 beats/minute at rest and less than 100 beats/minute with exercise. A 12-lead electrocardiogram should also be performed regularly to

Table 3-1. Treatment Guidelines for Preventing Thromboembolism in Paroxysmal, Persistent, or Permanent Atrial Fibrillation

	ACCP Guidelines	ACC/AHA/ESC Guidelines
Risk Factors		
High-Risk Factors	Prior stroke, TIA or systemic embolism Age > 75 years Hypertension Diabetes mellitus Moderate or severely impaired LV systolic function and/or congestive HF Rheumatic mitral valve stenosis Prosthetic heart valve	Prior stroke, TIA, or systemic embolism Rheumatic mitral valve stenosis Prosthetic heart valve
Moderate-Risk Factors	Age = 65–75 years	Age ≥ 75 years Hypertension Impaired LV systolic function (LVEF ≤ 35%) or HF Diabetes mellitus
Less-Validated/Weaker Risk Factors	NA	Age 65–74 years Female gender Coronary artery disease Thyrotoxicosis
Low-Risk Factors	Age < 65 years	Age < 65 years
Antithrombotic Therapy		
High-Risk Patient	≥ 1 of the above high-risk factors: Warfarin (target INR 2.5; range = 2–3)[a]	≥ 1 of the above high-risk factors: Warfarin (target INR 2.5; range = 2–3)[a] > 1 of the above moderate-risk factors: Warfarin (target INR 2.5; range = 2–3
Moderate-Risk Patient	With the above moderate-risk factor, but no high-risk factors: Warfarin (target INR 2.5; range = 2–3) OR Aspirin 325 mg/day	Only 1 of the above moderate-risk factors: Warfarin (target INR 2.5; range = 2–3 OR Aspirin 81–325 mg/day
Patients with Less-Validated/ Weaker Risk Factors	NA	≥ 1 of the above less-validated/weaker risk factors: Warfarin (target INR 2.5; range = 2–3) OR Aspirin 81–325 mg/day
Low-Risk Patient	With the above low-risk factor, but no high-risk factors: Aspirin 325 mg/day	With the above low-risk factor, but no other risk factors: Aspirin 81–325 mg/day

[a]The target INR for patients with prosthetic heart valves should be based upon the type of valve that is present.
ACC = American College of Cardiology; ACCP = American College of Chest Physicians; AHA = American Heart Association; ESC = European Society of Cardiology; HF = heart failure; INR = international normalized ratio; LV = left ventricular; LVEF = left ventricular ejection fraction; TIA = transient ischemic attack.

Table 3-2. Therapeutic Monitoring of Selected Antiarrhythmic Drugs Used for Management of Atrial Fibrillation

Drug	Usual Oral Dose	Adverse Effects	Drug Interactions/Interventions
Amiodarone[a,b]	Loading dose: 800–1200 mg/day (in 2–3 divided dosages) until 10 g total Maintenance dose: 200 mg/day	See Table 3-3	Digoxin: Initiating digoxin → 0.125 mg/day (normal renal function); 0.125 mg every other day (renal dysfunction) Already on digoxin → ↓ digoxin dose by 50% Warfarin: Initiating warfarin → 2.5 mg/day Already on warfarin: Amiodarone 400 mg/day → ↓ warfarin dose by 40% Amiodarone 300 mg/day → ↓ warfarin dose by 35% Amiodarone 200 mg/day → ↓ warfarin dose by 30% Amiodarone 100 mg/day → ↓ warfarin dose by 25% Lovastatin → Maximum dose 40 mg/day Simvastatin → Maximum dose 20 mg/day Can alternatively use pravastatin or fluvastatin (not metabolized by CYP 3A4)
Digoxin	0.125–0.25 mg/day Therapeutic range: AF: 0.8–2 ng/mL HF: 0.5–1 ng/mL	Heart block, atrial/ ventricular arrhythmias visual disturbances (e.g., yellow/green halos, blurred vision), nausea, vomiting, anorexia, diarrhea	Amiodarone (See above under Amiodarone) Clarithromycin, cyclosporine, erythromycin, propafenone, quinidine, verapamil → Closely monitor digoxin concentrations
Dofetilide[c]	Initial dose based on CrCl: CrCl > 60 mL/minute: 500 mcg twice daily CrCl 40–60 mL/minute: 250 mcg twice daily CrCl 20–39 mL/minute: 125 mcg twice daily CrCl < 20 mL/minute: Contraindicated Dose must also be adjusted based on QTc interval	Torsades de pointes, headache, dizziness, insomnia, chest pain, nausea, diarrhea, dyspnea	Cimetidine, hydrochlorothiazide, ketoconazole, megestrol, prochlorperazine, QTc-prolonging drugs, trimethoprim/sulfamethoxazole, verapamil → Dofetilide contraindicated Metformin, potent inhibitors of CYP3A4 isoenzyme (e.g., azole antifungals, protease inhibitors, calcium channel blockers) → Use together with caution
Sotalol	80–160 mg twice daily Dosing interval must be adjusted in renal insufficiency: CrCl 40–60 mL/minute: Every 24 hours CrCl < 40 mL/minute: Contraindicated	Torsades de pointes, bradycardia, heart block, palpitations, fatigue, dizziness, dyspnea, bronchospasm, heart failure exacerbation, nausea, vomiting, diarrhea	QTc-prolonging drugs → Avoid concomitant use

[a]Lower daily dose can be used during the loading period (e.g. 600–800 mg/day in 1–2 divided dosages); it may be possible to maintain some patients on doses as low as 100 mg/day.
[b]Amiodarone is a substrate of CYP3A4 isoenzyme and potent inhibitor of CYP1A2, 2C9, 2D6, and 3A4 isoenzymes.
[c]Dofetilide is also contraindicated if baseline QTc interval is greater than 440 msec.
AF = atrial fibrillation; CrCl = creatinine clearance; CYP = cytochrome P450; HF = heart failure.

Table 3-3. Guidelines for Monitoring Chronic Amiodarone Therapy

Adverse Effect	Monitoring Parameters	Monitoring Frequency	Management
Pulmonary			
Pulmonary fibrosis	Chest radiograph Pulmonary function tests (including DLCO)	Baseline, then every 12 months as needed, if symptoms develop	Discontinue amiodarone immediately; initiate corticosteroid therapy
Thyroid			
Hypothyroidism	Thyroid function tests	Baseline, then every 6 months	Thyroid hormone supplementation
Hyperthyroidism	Thyroid function tests	Baseline, then every 6 months	Antithyroid drugs
Ophthalmologic			
Optic neuritis/neuropathy	Ophthalmologic examination	Baseline, then every 12 months	Discontinue amiodarone immediately
Corneal microdeposits	Slit-lamp examination	Routine monitoring not necessary	No treatment necessary
Hepatic/Gastrointestinal			
Increased hepatic transaminases	LFTs	Baseline, then every 6 months	Consider lowering the dose or discontinuing amiodarone if LFTs greater than 3 x normal
Nausea, vomiting, anorexia, abdominal pain	History/physical examination	At each office visit	Lower the dose; take with food; take in divided doses
Cardiovascular[a]			
Bradycardia/heart block	ECG/physical examination	Baseline, then every 3-6 months	Lower the dose, if possible, or discontinue amiodarone if severe
Neurologic			
Tremors, ataxia, peripheral neuropathy	History/physical examination	At each office visit	Lower the dose, if possible, or discontinue amiodarone if severe
Dermatologic			
Photosensitivity/blue-grey skin discoloration	History/physical examination	At each office visit	Advise patients to wear sunblock while outdoors

[a]Although amiodarone can prolong the QT interval, torsades de pointes is rare (incidence less than 1%).
DLCO = diffusing capacity of the lung for carbon monoxide; ECG = electrocardiogram; LFT = liver function test.

assess for recurrence of the arrhythmia and to measure the PR interval (especially for AV nodal-blocking drugs), QRS duration (especially for class I antiarrhythmic drugs), and QTc interval (especially for class Ia and III antiarrhythmic drugs). If the AF recurs while the patient is receiving antiarrhythmic drug therapy, no change in therapy may be needed if episodes are infrequent and well tolerated. However, if recurrences become frequent or are poorly tolerated by the patient, using an alternative antiarrhythmic drug or switching to a rate-control strategy should be considered. Recommended oral doses and monitoring parameters, as well as the most clinically relevant drug interactions of selected antiarrhythmic drugs used in the management of AF are presented in Table 3-2. Due to the number of adverse effects that may be associated with amiodarone use, recommended monitoring guidelines and management strategies for this antiarrhythmic drug are outlined separately (Table 3-3). To inform patients of the potential adverse effects and drug interactions associated with amiodarone, the Food and Drug Administration (FDA) recently stipulated that a medication guide, developed by the manufacturer, must be dispensed with each prescription of this antiarrhythmic drug.

According to the manufacturer's recommendations, to initiate dofetilide therapy, patients must be hospitalized and placed on telemetry for at least 3 days. In addition, dofetilide can only be used by prescribers and institutions that have received the necessary education regarding the appropriate dosing and monitoring of this antiarrhythmic drug. On discharge from the hospital, patients can have their dofetilide prescription filled either though a single mail-order pharmacy (currently PharmaCare Specialty Pharmacy mail-order program) or at retail pharmacies that have enrolled in the Tikosyn in Pharmacy System (TIPS) program established by the manufacturer. Pharmacists can help patients find a pharmacy that participates in the TIPS program or ensure that a prescription has been faxed to the mail-order pharmacy before patients are discharged from the hospital.

Sotalol is currently available as two different products, sotalol AF (Betapace AF) and sotalol (Betapace, Sorine). The former product should be used to treat AF or atrial flutter while the latter products should be used to treat life-threatening ventricular arrhythmias. Even though the chemical entity is the same between the two products, the FDA required different brand names because the dosing regimens and safety information differ for each indication. The recommended maximum daily dose for sotalol AF (320 mg/day) is lower than for sotalol (640 mg/day). In addition, only sotalol AF contains a patient package insert that should be dispensed with each prescription to inform patients of the potential risks and benefits of this drug for the treatment of AF or atrial flutter. As with dofetilide, the manufacturer's recommendations for sotalol AF (and for sotalol) state that patients must be hospitalized and placed on telemetry for at least 3 days when initiating or reinitiating therapy.

Ventricular Arrhythmias/ Asystole/Pulseless Electrical Activity

Epidemiology

Sudden cardiac death is defined as natural death caused by cardiac causes that is marked by a sudden loss of consciousness that develops within 1 hour of the onset of an abrupt change in clinical symptoms. Sudden cardiac death accounts for more than 300,000 deaths per year in the United States and contributes to nearly 50% of all deaths from cardiovascular causes. Although the majority of cases are believed to be due to ventricular fibrillation (VF), SCD can also occur as a result of pulseless ventricular tachycardia (VT), PEA, or asystole. More than 80% of SCD events occur in individuals with coronary artery disease, with 20% occurring in patients having acute MI. Life-threatening ventricular arrhythmias also occur commonly in patients with LV dysfunction. Survival rates for out-of-hospital cardiac arrest are typically low and range from 2% to 25% based on the geographic area of the United States. For patients who do survive an episode of cardiac arrest, even after implantation of an implantable cardioverter defibrillator (ICD), recurrence rates of SCD still remain about 1%–2% each year.

Therapeutic Goals/Outcomes

In patients with an acute onset of ventricular arrhythmia, treatment goals are to treat the potential cause (including MI or HF) of the arrhythmia, terminate the arrhythmia, and restore hemodynamic stability. Goals of chronically treating patients with ventricular arrhythmias include preventing an initial or recurrent episode of SCD and improving quality of life.

Quality Patient Care

Pharmacological Therapy

Acute Management of Ventricular Arrhythmias/Asystole/Pulseless Electrical Activity

Most data in recent years regarding the acute management of pulseless VT/VF, asystole, or PEA has focused on the use of the vasopressors, epinephrine and vasopressin. Vasopressin may possess several advantages compared with epinephrine, most of which have been demonstrated in animal models. Vasopressin's half-life of about 10–20 minutes is considerably longer than the 3–5-minute half-life of epinephrine, which suggests that its vasopressor effects may be more sustained than those of epinephrine during CPR. Vasopressin use has been associated with a greater increase in cerebral and myocardial perfusion compared with epinephrine. Unlike epinephrine, vasopressin maintains its vasoconstrictive effects under acidotic and hypoxic conditions, which suggests that this drug may continue to work during prolonged cardiac arrest situations. Because of its lack of β-adrenergic activity, vasopressin does not appear to increase myocardial oxygen consumption, which is in contrast to the effects of epinephrine. Based on relatively limited clinical evidence that vasopressin may be associated with improved outcomes compared with epinephrine, it was included in the treatment algorithm for pulseless VT/VF as an alternative to epinephrine in the Guidelines 2000 for CPR and Emergency Cardiovascular Care (ECC).

After these guidelines were published, additional data regarding the efficacy of vasopressin for pulseless VT/VF as well as for asystole and PEA emerged. One of these trials, which compared vasopressin 40 units to epinephrine 1 mg in 200 inpatients with VF, PEA or asystole, demonstrated no significant difference between the treatment groups with regard to the proportion of patients who survived at 1 hour or to hospital discharge.

Most recently, the largest trial to evaluate the efficacy of vasopressin was published. In this trial, 1186 patients with out-of-hospital cardiac arrest who presented with VF, PEA, or asystole were randomized to initially receive either vasopressin 40 units or epinephrine 1 mg. If return of spontaneous circulation was not achieved within 3 minutes, an additional dose of study drug was administered. If resuscitation was still required, epinephrine was subsequently used in both treatment groups. As with the previous trial, there were no significant differences in rates of survival to hospital admission or to hospital discharge between the vasopressin and epinephrine groups in the VF or PEA groups. However, both of these end points were significantly higher in patients with asystole who received vasopressin compared with those who received epinephrine. Although these particular results were statistically significant, the overall prognosis for patients in this subgroup was still relatively dismal, with only 12 out of 257 (4.7%) and 4 out of 262 (1.5%) patients in the vasopressin and epinephrine groups, respectively, surviving to hospital discharge. In a subset of 732 patients who failed to achieve return of spontaneous circulation, additional administration of epinephrine, at a median dose of 5 mg, resulted in significantly higher rates of survival to hospital admission and discharge in the vasopressin group compared with the epinephrine group. Several mechanisms have been proposed to explain the potential benefits of vasopressin in these various subgroups. Given the acidotic and hypoxic conditions that are usually present during asystole, the persistent vasoconstrictive effects of vasopressin and epinephrine's loss of effect under these conditions may have contributed to the beneficial outcomes observed in the vasopressin group. In addition, the benefits observed when patients were treated with epinephrine after vasopressin suggest that these drugs may enhance the vasopressor effects of each other, especially under conditions of prolonged ischemia. Although these subgroup findings are intriguing, confirmation of these potential benefits is warranted because they were derived from a post hoc analysis.

Chronic Management of Ventricular Arrhythmias

Update on Recent Clinical Trials. ***Omega-3 Fatty Acids.*** In addition to the evidence that has recently emerged regarding the potential benefits of omega-3 fatty acids in the prevention of AF, two recent trials have shed some light on the potential antiarrhythmic drug effects of these supplements in patients with a history of life-threatening

ventricular arrhythmias. Previous trials have demonstrated that dietary changes or supplements to increase the intake of omega-3 fatty acids in patients with recent MI has been associated with a significant reduction in the risk of SCD. However, the conflicting results of the most recently conducted trials have cast an air of uncertainty as to whether omega-3 fatty acids should be uniformly recommended for all patients at risk for life-threatening ventricular arrhythmias.

The first of these studies to be published enrolled 200 patients who had received an ICD because of a recent episode of sustained VT or VF that was not due to acute MI. These patients were randomized to receive either fish oil 1.8 g/day (composed of 73% omega-3 fatty acids) or placebo (olive oil) and were followed up for a median of 718 days. Although more patients in the fish oil group than in the placebo group received ICD therapy for VT/VF at 6, 12, and 24 months, these differences were not statistically significant. However, in the subgroup of 133 patients whose indication for receiving the ICD was sustained VT, fish oil was associated with a significantly higher incidence of ICD therapy for VT/VF compared with placebo. Despite these arrhythmic events, there was no significant difference in mortality between the treatment groups. Therefore, the study results suggest that fish oil may actually be proarrhythmic in patients who have received an ICD for secondary prevention of SCD, particularly in patients whose qualifying arrhythmia is sustained VT. When comparing results of this study to those that previously showed the benefit of omega-3 fatty acids, it is important to remember that the enrolled patient populations differ, especially with regard to time of onset of MI. Although the majority of patients in this particular trial had a history of coronary heart disease, based on the inclusion criteria, the episode of sustained VT/VF that qualified them for ICD implantation did not occur in the setting of MI. In contrast, all patients in the previously conducted studies that demonstrated the potential antiarrhythmic benefits of omega-3 fatty acids had a recent MI. Therefore, fish oil may exert its antiarrhythmic effects primarily in the setting of acute ischemia and VF, but not when the ventricular arrhythmia is of nonischemic origin and is most likely due to reentry induced by myocardial scarring.

The other study that evaluated the potential antiarrhythmic effects of fish oil was also conducted in patients who had received an ICD for the secondary prevention of SCD, but had conflicting results. A total of 402 patients, who had received an ICD within the previous year because of cardiac arrest, sustained VT, or syncope with inducible sustained VT or VF, were randomized to receive either fish oil 4 g/day (composed of 65% omega-3 fatty acids) or placebo (olive oil) for 12 months. The rate of noncompliance was relatively high in this study (35%), but did not differ between treatment groups. In the intention-to-treat analysis, although patients in the fish oil group experienced a 28% reduction in the risk of ICD therapy for VT/VF or all-cause mortality at 12 months compared with placebo, this finding was not statistically significant. However, results of the on-treatment analysis, which only included patients who had been compliant for at least 11 months, revealed a significant risk reduction of 38% with regard to this end point in the fish oil group. Overall, the main limitations of this trial included its relatively high noncompliance rate and the difficulties experienced by investigators in obtaining complete sets of electrocardiographic data to document arrhythmic events.

Given the conflicting results of these trials, it is difficult to make a unanimous recommendation to initiate fish oil therapy in all patients at risk for life-threatening ventricular arrhythmias. Although fish oil appears to have antiarrhythmic benefits in patients with a recent MI, from the recent data, it appears that we cannot necessarily extrapolate these positive results to all patients with coronary heart disease. In addition, because the ICD population is not necessarily uniform, with some patients being at higher risk for fatal ventricular arrhythmias than others, it is possible that only certain subgroups of patients may derive benefit from fish oil while others do not. Nonetheless, given the lack of a consensus for the use of fish oil in patients with ICDs, it appears that a larger trial that is powered to evaluate the effects of this supplement in a variety of subgroups is warranted.

Prevention of Implantable Cardioverter Defibrillator Shocks. Although ICDs reduce mortality in a broad range of patients at risk for sustained ventricular arrhythmias, shocks delivered by these devices can cause not only pain and anxiety for the patient but also drainage of the battery life of the device. Currently, concomitant antiarrhythmic therapy is administered in up to 70% of patients with an ICD. Antiarrhythmic therapy can be initiated in these patients for many reasons including the following: 1) decreasing episodes of VT or VF to subsequently reduce the frequency of appropriate shocks; 2) reducing the rate of VT so that it can be terminated with antitachycardia pacing; 3) decreasing episodes of supraventricular arrhythmias that may trigger inappropriate shocks; and 4) prolonging the battery life of the device. Despite these benefits, there are potential risks associated with the initiation of antiarrhythmic therapy in these patients, including interference with ICD function and development of adverse effects. Antiarrhythmic drugs can cause proarrhythmia, which can lead to an increase in ICD shocks. Certain antiarrhythmic drugs also elevate the defibrillation threshold, which would increase the amount of energy required to defibrillate the heart.

Although sotalol has undergone more clinical evaluation for this purpose than amiodarone, in clinical practice, amiodarone is used more often as adjunctive therapy in patients with ICDs. Most recently, the efficacy of these antiarrhythmic drugs was compared with that of β-blockers for preventing ICD shocks in the Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients trial. A total of 412 patients who had received an ICD for secondary prevention within 21 days of enrollment were randomized to one of the following treatment groups: β-blocker alone, amiodarone plus a β-blocker, or sotalol alone. After 1 year of treatment, patients in the amiodarone plus β-blocker group experienced significantly fewer ICD shocks than patients in either the β-blocker or sotalol groups. Although there was a trend, sotalol did not significantly reduce the risk of ICD shocks compared with the β-blocker group. Not surprising was the increased incidence of pulmonary

toxicity, hypothyroidism, and symptomatic bradycardia in the amiodarone group. Overall, the trial results raise the question of whether concomitant antiarrhythmic drug therapy should be initiated at the time of ICD implantation. It is important to keep in mind that the trial results can only be applied to a secondary prevention population because it is believed that patients with primary prevention ICD therapy are at a lower risk for shocks due to ventricular arrhythmia. In the secondary prevention population, the decision of whether to initiate empiric antiarrhythmic therapy should be individualized, taking into consideration the relative risk versus benefit of the treatment regimen.

Nonpharmacological Therapy

Over the past decade, numerous trials have established the ICD as an effective treatment not only for the secondary prevention of SCD in patients who have been resuscitated from cardiac arrest or had sustained VT but also for the primary prevention of SCD in high-risk patients. Specifically, the results of three trials (which have been previously discussed in detail), the Antiarrhythmics Versus Implantable Defibrillators, Cardiac Arrest Study Hamburg, and Canadian Implantable Defibrillator Study, clearly support ICDs as first-line therapy for the secondary prevention of SCD. Because only a small percentage of patients who experience a cardiac arrest survive to benefit from an ICD for secondary prevention, the focus of most of the recent clinical investigations has been on the use of ICDs for primary prevention of SCD. The results of many of these major trials, including the Multicenter Automatic Defibrillator Implantation Trial (MADIT-I), Multicenter Unsustained Tachycardia Trial (MADIT-II), Amiodarone versus Implantable Defibrillator Randomized Trial, and the Cardiomyopathy Trial have been previously discussed. The most recent primary prevention ICD trials include the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation trial, and the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT), all of which were performed in various types of patients with a LVEF of 35% or less. Given their important implications in the management of HF, results of these trials are discussed in the Chronic Heart Failure Management chapter.

Indications for ICD therapy have been significantly expanded over the past several years, primarily because of the impressive results of MADIT-II and SCD-HeFT. Based on this broadening of indications, it is estimated that more than 500,000 Medicare beneficiaries will be eligible to receive a prophylactic ICD. Given the significant costs of these devices, the potential economic effect of implanting ICDs, especially in the primary prevention setting, should be considered. Most recently, the cost-effectiveness of ICD therapy was evaluated in patients who would be represented in each of the eight primary prevention trials that have been published thus far. When considering only those six trials in which ICD therapy improved survival compared with control (excluding CABG Patch Trial and DINAMIT), the incremental cost-effectiveness ratios ranged from $34,000 to $70,200 per quality-adjusted life-year gained, which is within the $50,000–$100,000 range that is considered to be economically acceptable. In sensitivity analyses, the incremental cost-effectiveness of the ICD became more favorable when the survival benefit of the device increased (when used in higher-risk patients), the cost of the ICD was reduced, the replacement of ICD generators occurred less frequently, and the quality of life of the patient improved. In fact, as long as the mortality benefit of the ICD exceeded 7 years, the cost-effectiveness of the ICD remained below $100,000.

Treatment Plan

Management of Cardiac Arrest

In 2005, the AHA guidelines for CPR and ECC were updated. These guidelines were based on the most extensive review of the resuscitation literature that has been published. Although these guidelines provide treatment recommendations for numerous arrhythmias and life-threatening cardiopulmonary conditions, only the recommendations for treating the three cardiac arrest rhythms, pulseless VT/VF, asystole, and PEA, are discussed below. For all of these arrest rhythms, there have been slight changes in the recommendations for obtaining access for drug administration. Although intravenous access is preferred, the guidelines recommend the intraosseous route as an alternative if intravenous access cannot be established. Intraosseous access can be used not only for administration of drugs and fluids, but also for obtaining blood for laboratory monitoring. If neither intravenous nor intraosseous access can be established, the endotracheal route can be used for administering only certain drugs (i.e., atropine, lidocaine, epinephrine, and vasopressin).

Pulseless Ventricular Tachycardia/Ventricular Fibrillation. The most significant changes in the treatment algorithm for pulseless VT/VF in the 2005 AHA Guidelines for CPR and ECC involve issues regarding administration of CPR and defibrillation. Although the previous guidelines emphasized immediate defibrillation in these patients, recent studies demonstrated that the provision of CPR before defibrillation was associated with improved survival rates, especially when more than 4–5 minutes had elapsed between the time of collapse to delivery of the shock. Therefore, in the event of an unwitnessed arrest, which usually occurs in the out-of-hospital setting, five cycles (or 2 minutes) of CPR should be given before defibrillation. When the arrest is witnessed and a defibrillator is readily available, defibrillation can be administered immediately after two rescue breaths are provided without the initial need for CPR. When attempting defibrillation, the updated guidelines recommend the delivery of only one shock, which is in contrast to the three-shock sequence previously recommended. Although the efficacy of these defibrillation strategies have not been directly compared in clinical trials, the move toward using only one shock is based on the increased use of biphasic defibrillators, which have a higher first-shock efficacy than monophasic defibrillators. After the delivery of one shock, instead of taking the time to evaluate the pulse and rhythm, CPR should be resumed immediately. This recommendation was based on evidence that demonstrated that a reduction in the interval between defibrillation and CPR by as little as 15 seconds can increase the probability of defibrillation success. After delivery of five cycles (or 2 minutes) of CPR, the pulse and

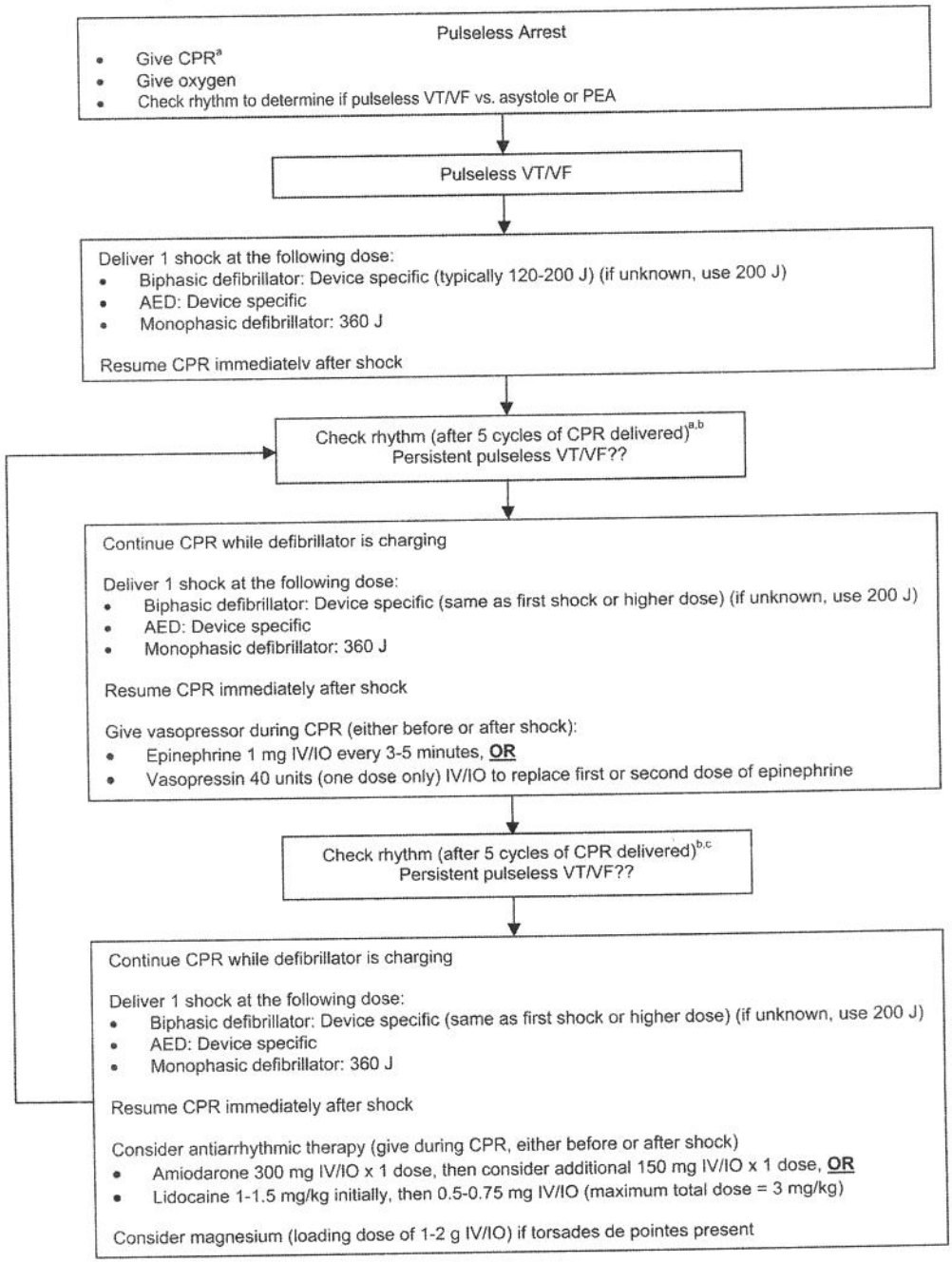

Figure 3-4. Algorithm for treatment of pulseless ventricular tachycardia/ventricular fibrillation.
[a]If arrest is witnessed and defibrillator is readily available, 2 rescue breaths can be given before defibrillation. If arrest is unwitnessed, 5 cycles of CPR should be administered before defibrillation.
[b]One cycle of CPR = 30 chest compressions then 2 breaths; 5 cycles about 2 minutes
[c]After advanced airway established, cycles of CPR no longer need to be given. Instead, continuous chest compressions should be given without pauses for breaths. Give 8–10 breaths/minute.
AED = automated external defibrillator; CPR = cardiopulmonary resuscitation; IO = intraosseous; IV = intravenous; J = joules; PEA = pulseless electrical activity; VT = ventricular tachycardia; VF = ventricular fibrillation.
Adapted with permission from the American Heart Association. 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2005;112(suppl 1):IV-58–IV-66.

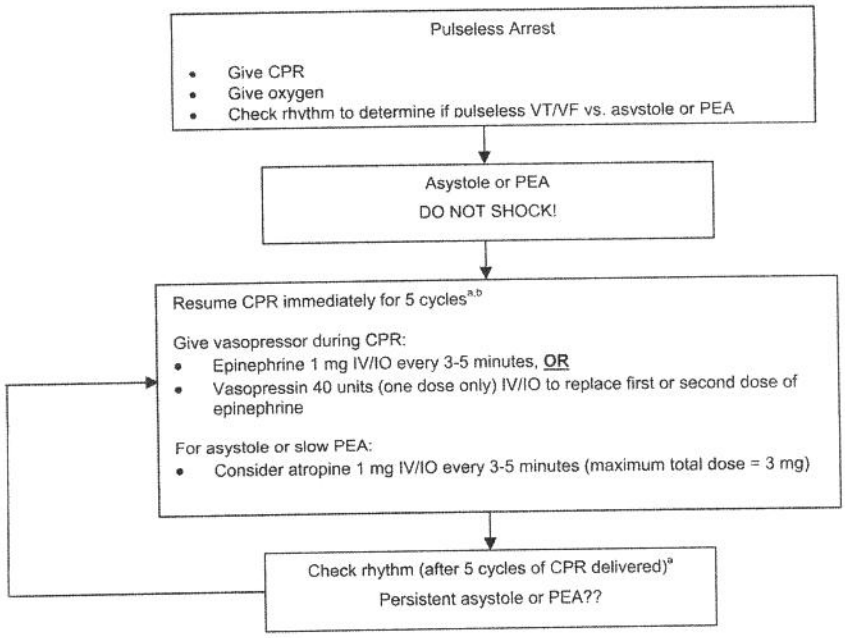

Figure 3-5. Algorithm for treatment of asystole and pulseless electrical activity.
[a]One cycle of CPR = 30 chest compressions then 2 breaths; 5 cycles about 2 minutes.
[b]After advanced airway established, cycles of CPR no longer need to be given. Instead, continuous chest compressions should be given without pauses for breaths. Give 8–10 breaths/minute.
CPR = cardiopulmonary resuscitation; IO = intraosseous; IV = intravenous; PEA = pulseless electrical activity; VT = ventricular tachycardia; VF = ventricular fibrillation.
Adapted with permission from the American Heart Association. 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2005;112(suppl 1):IV-58–IV-66.

rhythm should then be checked. At this time, if pulseless VT/VF is still present, CPR should be resumed until the defibrillator is charged, at which time one shock should be delivered again and followed by administration of five cycles (or 2 minutes) of CPR. This general sequence of resuscitation should be continued for as long as the pulseless VT/VF persists.

With regard to the use of pharmacological therapy for pulseless VT/VF, there continues to be a lack of evidence, which demonstrates an increased rate of survival to hospital discharge with the administration of vasopressors or antiarrhythmic drugs. However, despite the paucity of data, both vasopressors and antiarrhythmic drugs continue to be included in the treatment algorithm for this cardiac arrest rhythm. Given the emphasis that the guidelines have placed on minimizing interruptions in chest compressions, drugs should be administered during CPR either before or after a shock. Although the evidence does not clearly define the most appropriate time to administer pharmacological therapy in relation to defibrillation and CPR, the guidelines recommend that vasopressor therapy can be initiated if pulseless VT/VF persists after delivery of one or two shocks plus CPR. Recommended vasopressors include either epinephrine administered every 3–5 minutes or one dose of vasopressin that can be given to replace either the first or second dose of epinephrine. Antiarrhythmic therapy can then be initiated if pulseless VT/VF persists after delivery of two or three shocks plus CPR and after administration of a vasopressor. Amiodarone and lidocaine continue to be first-line and second-line antiarrhythmic drug therapies, respectively, in this algorithm. Procainamide is no longer recommended for treating pulseless VT/VF because of limited evidence and the need for a prolonged infusion. Magnesium can be administered if torsades de pointes with a prolonged QT interval is present. Figure 3-4 summarizes the treatment approach for pulseless VT/VF.

Asystole and Pulseless Electrical Activity. Although the management of asystole and PEA was addressed in separate treatment algorithms in the previous guidelines, a unified algorithm has been developed for treating these cardiac arrest rhythms in the 2005 AHA Guidelines for CPR and ECC. For both arrhythmias, underlying conditions (e.g., hypovolemia, hypoxia, acidosis, hypokalemia, hyperkalemia, hypoglycemia, hypothermia, drug overdoses, cardiac tamponade, tension pneumothorax, MI, pulmonary embolism, or trauma) must be identified promptly and reversed if possible. Defibrillation has no role in the treatment of these arrhythmias. Instead, the initial focus should be placed on administering CPR. Once either asystole or PEA is confirmed, five cycles (or 2 minutes) of CPR should be delivered and followed by administration of a vasopressor once access has been established. Although epinephrine was previously the sole vasopressor recommended for the treatment of these arrhythmias, vasopressin has now been added to the treatment algorithm. As with pulseless VT/VF, either epinephrine can be administered every 3–5 minutes or one dose of vasopressin can be given to replace the first or second dose of

Table 3-4. Implantable Cardioverter Defibrillator Indications Covered by the Centers for Medicare and Medicaid Services

Secondary Prevention Indications

- Documented episode of cardiac arrest due to VF, not due to a transient or reversible cause
- Documented sustained VT, either spontaneous or induced by an EPS, not associated with acute MI and not due to a transient or reversible cause

Primary Prevention Indications (subject to ICD Registry requirement)

- Documented familial or inherited conditions with a high risk of life-threatening VT , such as long QT syndrome or hypertrophic cardiomyopathy
- Coronary artery disease with documented prior MI, measured LVEF of 35% or less, and inducible, sustained VT or VF at EPS[a] **(MADIT indication)**
- Documented prior MI (more than 40 days before ICD insertion) and measured LVEF of 30% or less **(MADIT II indication)**
- Ischemic dilated cardiomyopathy, documented prior MI (more than 40 days before ICD insertion), NYHA Class II and III HF, and measured LVEF of 35% or less **(SCD-HeFT indication)**
- Nonischemic dilated cardiomyopathy longer than 9 months, NYHA Class II and III HF, and measured LVEF of 35% or less **(SCD-HeFT indication)**
- Patients who meet all current CMS coverage requirements for a cardiac resynchronization therapy device and have NYHA Class IV HF **(COMPANION indication)**
- Patients with nonischemic dilated cardiomyopathy longer than 3 months but less than 9 months, NYHA Class II or III HF, and measured LVEF of 35% or less[b] **(SCD-HeFT indication)**

[a]The MI must have occurred more than 40 days prior to ICD insertion. The EPS must be performed more than 4 weeks after the qualifying MI.
[b]These patients cannot be entered into the current ICD Registry. For this indication, to be covered by CMS, patients must be enrolled in a trial approved by the Food and Drug Administration or an Institutional Review Board.
CMS = Centers for Medicare and Medicaid Services; COMPANION = Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; EPS = electrophysiology study; HF = heart failure; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; MADIT = Multicenter Automatic Defibrillator Implantation Trial; MI = myocardial infarction; NYHA = New York Heart Association; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial; VF = ventricular fibrillation; VT = ventricular tachyarrhythmia.

epinephrine. Atropine can also be given for either asystole or a slow PEA. After drug administration, CPR should be continued for five cycles (or 2 minutes) and then the rhythm and pulse should be checked. If asystole or PEA persist, CPR should be immediately resumed for five cycles (or 2 minutes) and the above drug therapy can be repeated, if applicable. Transcutaneous pacing is not currently recommended for patients with asystole. Figure 3-5 summarizes the treatment approach for asystole and PEA.

Chronic Management of Ventricular Arrhythmias

Primary Prevention of Sudden Cardiac Death

Based on the results of the SCD-HeFT, in early 2005, the Centers for Medicare and Medicaid Services (CMS) expanded the reimbursement-eligibility criteria for patients receiving ICDs for primary prevention. Based on these criteria, ICDs are covered in certain patients with nonischemic cardiomyopathy for the first time. Table 3-4 includes the list of covered indications as established by CMS. Along with this expanded coverage, CMS also implemented an ICD registry requirement, whereby data for nearly all patients who receive an ICD for primary prevention will have to be entered into a national registry so that the institution can receive payment. Data entry is required for all these patients except for those with the indication of nonischemic dilated cardiomyopathy for 3–9 months, NYHA class II or III HF, and measured LVEF of 35% or less. In this particular patient subset, the ICD will only be covered by Medicare if the patient is enrolled in a trial approved by either the FDA or an Institutional Review Board.

Conclusion

Although the management of arrhythmias in the chronic setting has begun to shift toward the use of nonpharmacological strategies in the past several years, antiarrhythmic drugs still continue to have a role in the overall treatment of these rhythm disturbances. Pharmacists can play a significant role in the acute and chronic management of supraventricular and ventricular arrhythmias by assisting prescribers with the appropriate selection and monitoring of antiarrhythmic drug therapy. Pharmacists also need to be aware of the important drug interactions that can potentially affect antiarrhythmics so that patient safety can be optimized. As clinical trials and updated guidelines for the treatment of cardiac arrhythmias continue to emerge in the literature, pharmacists involved in the management of these patients need to keep updated on this information so that they can continue to have a significant impact on patient outcomes.

Annotated Bibliography

1. Wang TJ, Massaro J, Levy D, Vasan RS, Wolf PA, D'Agostino RB, et al. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. JAMA 2003;290:1049–56.

   This study, derived from data from the Framingham Heart Study, examined the predictors of the outcomes of stroke and stroke or death in patients with new-onset atrial fibrillation (AF). Based on this data, point-based scoring systems were developed to estimate a patient's 5-year risk of developing either of these outcomes. These scoring systems are similar to the Framingham risk score that was developed to assess a patient's 10-year risk of experiencing death or a coronary heart disease event. In comparison to other risk stratification schemes for predicting the risk of stroke in patients with AF, this particular scoring system takes into consideration many variables when arriving at a score and had a longer follow-up time. In addition, the predicted 5-year stroke rates in this patient population were closely correlated with the actual event rates, which attests to the internal validity of the risk score. Overall, this point-based scoring system has the potential to be an important tool for clinicians to use to estimate a patient's absolute risk of stroke so that appropriate decisions regarding anticoagulation therapy can be made.

2. Singh BN, Singh SN, Reda DJ, Tang XC, Lopez B, Harris CL, et al. Amiodarone versus sotalol for atrial fibrillation. N Engl J Med 2005;352:1861–72.

This is currently the largest double-blind, placebo-controlled study to directly compare the efficacy of amiodarone and sotalol in patients with AF. This study enrolled 665 patients with persistent AF who were therapeutically anticoagulated. If patients did not spontaneously convert to sinus rhythm by day 28, direct current cardioversion was performed. The primary end point was time to first recurrence of AF after sinus rhythm had been restored. The majority of patients in this study (about 62%) had symptomatic AF at baseline. Although the rates of spontaneous conversion by day 28 were similar between the amiodarone and sotalol groups (27.1% vs. 24.2%, respectively), amiodarone was significantly better than sotalol in maintaining sinus rhythm (median time to first recurrence of AF: 487 days vs. 74 days, respectively). In subset analyses, amiodarone's superiority over sotalol in maintaining sinus rhythm persisted regardless of the duration of AF or the presence (or absence) of symptoms. However, in the subgroup of patients with ischemic heart disease, there was no significant difference between these antiarrhythmics with regard to this end point. Significant improvements in exercise tolerance and quality of life were observed in the patients remaining in sinus rhythm compared with those who had persistent AF. There were no significant differences in major adverse events between the treatment groups. Overall, the primary results of this trial suggest that amiodarone is more effective than sotalol at maintaining sinus rhythm in most patients, except for those with ischemic heart disease. However, given that patients in sinus rhythm had significantly greater improvements in quality of life scores and exercise tolerance than patients remaining in persistent AF, perhaps the more important implication of this trial is that rhythm control should still be considered a reasonable strategy, especially for those who may feel better in sinus rhythm.

3. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). J Am Coll Cardiol 2006;48:e149–246.

These evidence-based guidelines serve as a revision of those published in 2001. Recommendations and levels of evidence are provided for each aspect of the management of AF, including controlling ventricular rate, preventing thromboembolism, restoring sinus rhythm, and maintaining sinus rhythm. Overall, some of the most significant changes regarding the treatment of AF include a greater emphasis on catheter ablation as a viable alternative to antiarrhythmic drugs as second-line therapy for managing recurrent paroxysmal or recurrent persistent AF, as well as the recommendation that antithrombotic therapy be included as part of the treatment regimen, regardless of whether a rate-control or rhythm-control strategy is pursued. In addition, these guidelines recommend that rate control be considered a reasonable alternative to a rhythm-control strategy in patients with AF; however, rhythm control does continue to play a role in the management of patients with AF, especially those who have disabling symptoms while in AF. These guidelines also provide recommendations for the treatment of AF in specific patient populations, such as those with structural heart disease, postoperative AF, Wolff-Parkinson-White syndrome, hyperthyroidism, pregnancy, or pulmonary diseases.

4. American College of Chest Physicians Guidelines for the Prevention and Management of Postoperative Atrial Fibrillation after Cardiac Surgery. Chest 2005;128(suppl):1S–64S.

These evidence-based guidelines developed by the American College of Chest Physicians are the first to address the management of patients that develop AF associated with cardiac surgery. Although the American College of Cardiology, American Heart Association, and European Society of Cardiology collaboratively developed guidelines for managing AF in 2001, these recommendations were not specific to the postoperative patient population. These guidelines present a timely review of the epidemiology, risk factors, and associated patient outcomes of postoperative AF. The management of postoperative AF with regard to controlling ventricular rate, restoring and maintaining sinus rhythm, preventing thromboembolic events, and preventing the initial development of AF is reviewed in an evidence-based manner, with official recommendations and levels of evidence being provided for each aspect of therapy.

5. Singer DE, Albers GW, Dalen JE, Go AS, Halperin JL, Manning WJ. Antithrombotic therapy in atrial fibrillation: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126(suppl):429S–56S.

These evidence-based guidelines developed by the American College of Chest Physicians serve as a revision of published in 2001. For most practitioners, recommendations contained within these guidelines represent the standard of care for the use of antithrombotic therapy in patients with AF. As with the previous guidelines, a fairly detailed overview of essentially all the trials that have evaluated various anticoagulant and antiplatelet therapies in patients with chronic AF is presented. Practitioners are provided with a risk-stratification scheme that can be used to determine whether patients with paroxysmal, persistent, or permanent AF are at low risk, intermediate risk, or high risk of stroke, which can be used to determine the most appropriate antithrombotic therapy. These guidelines also provide recommendations regarding the most appropriate antithrombotic therapy in specific patient populations, including those with concomitant AF and valvular heart disease, postoperative AF, and patients undergoing elective cardioversion. A useful and concise summary of all the recommendations made throughout the guideline is provided at the end of the article.

6. 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2005;112(suppl 1):IV-1–IV-211.

These guidelines are based on the evidence evaluation that occurred during the 2005 International Consensus Conference on Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care Science with Treatment Recommendations. Overall, these guidelines provide evidence-based recommendations for the following areas: basic life support, defibrillation, advanced cardiac life support, pediatric basic and advanced life support, neonatal resuscitation, acute coronary syndromes, first aid, and stroke. Compared to the previous guidelines from 2000, the recommendations for the treatment of cardiac arrest within these updated guidelines place more emphasis on providing

high-quality CPR than drug administration. Recognizing that provision of high-quality CPR during cardiac arrest can significantly improve a patient's chance for survival, some of the most significant changes in these guidelines were to increase the number of chest compressions delivered per minute and to reduce interruptions in chest compressions delivered during CPR. Important changes in the treatment algorithms for pulseless ventricular tachycardia (VT)/ventricular fibrillation (VF), asystole, and pulseless electrical activity (PEA) include the following: 1) providing five cycles (or 2 minutes) of CPR before defibrillation for out-of-hospital arrest when either the emergency medical services response time is estimated to be more than 4 minutes or the arrest is unwitnessed; 2) delivering one shock instead of three successive shocks for pulseless VT/VF, followed by immediate resumption of CPR; 3) deleting procainamide from the pulseless VT/VF treatment algorithm; and 4) recommending the use of a single dose of vasopressin as an alternative to epinephrine in the asystole/PEA treatment algorithm.

7. Raitt MH, Connor WE, Morris C, Kron J, Halperin B, Chugh SS, et al. Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators: a randomized controlled trial. JAMA 2005;293:2884–91.

   This is the first of two clinical trials (see Reference 8 for the other trial) that provides conflicting evidence regarding the efficacy of fish oil in patients with implantable cardioverter defibrillators (ICDs). In this particular trial, 200 patients who received an ICD for a recent episode of sustained VT or VF (not due to an acute myocardial infarction) were randomized to receive fish oil or placebo (olive oil). Therefore, most patients received an ICD for secondary prevention. The primary end point was the time to first episode of VT/VF leading to ICD therapy ("shock"). At 6, 12, and 24 months, 46%, 51%, and 65% of patients, respectively, in the fish oil group had ICD therapy for VT/VF compared with 36%, 41%, and 59%, respectively, of patients in the placebo group (p=0.19). However, in a subgroup of 133 patients who received an ICD specifically for VT, 61%, 66%, and 79%, respectively, of patients in the fish oil group experienced ICD therapy for VT/VF at these same time points compared with 37%, 43%, and 65%, respectively, of patients in the placebo group (p=0.007). Although this study was specifically conducted in patients with ICDs, its results were unexpected given that fish oil supplementation has been previously associated with a significant reduction in sudden cardiac death in two large-scale trials which were conducted in a post-myocardial infarction population. Nonetheless, the findings suggest that the potential antiarrhythmic effects of fish oil may vary depending on the type of underlying structural heart disease, with more profound effects occurring perhaps in the setting of ischemically mediated VT/VF.

8. Leaf A, Albert CM, Josephson M, Steinhaus D, Kluger J, Kang JX, et al. Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake. Circulation 2005;112:2762–8.

   Unlike the trial described in Reference 7, this study demonstrated that fish oil supplementation may have beneficial antiarrhythmic effects in patients with ICDs. Patients with secondary prevention ICDs (n=402) were randomized to receive fish oil or placebo (olive oil) for 12 months. The primary end point was time to first ICD event for VT or VF or all-cause mortality based on an intention-to-treat analysis. The mean time from ICD implantation to entry into the study was 1.6 years. At 12 months, the primary end point occurred in 28% and 39% of patients in the fish oil and placebo groups, respectively (p=0.057). When a prespecified secondary analysis was performed to include only patients who were compliant with therapy for at least 11 months (overall noncompliance rate of 35%), there was a 38% reduction in the primary end point with the use of fish oil (p=0.034). It is unclear as to why these studies have disparate findings regarding the efficacy of fish oil supplementation in patients with ICDs. It is possible that different responses to fish oil may occur in various subgroups of patients with ICDs. However, a randomized, prospective analysis that is powered to detect differences among various subgroups needs to be performed to provide further insight into the efficacy of fish oil in patients with ICDs.

9. Wenzel V, Krismer AC, Arntz HR, Sitter H, Stadlbauer KH, Lindner KH. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. N Engl J Med 2004;350:105–13.

   This is the largest study to compare the efficacy of epinephrine and vasopressin in patients with cardiac arrest. In this study, 1186 patients were randomized to receive up to two doses of either vasopressin or epinephrine, followed by an additional dose of epinephrine if spontaneous circulation was not restored. The primary end point was survival to hospital admission while survival to hospital discharge was designated as a secondary end point. The majority of patients in this study had asystole or PEA (60%), whereas 40% had VF. Overall, no significant differences were observed between the treatment groups with regard to either of these end points. When examining the individual subgroups, patients with asystole were significantly more likely to survive to hospital admission (29% vs. 20.3%; p=0.02) and to hospital discharge (4.7% vs. 1.5%; p=0.04) if they had received vasopressin than if they had received epinephrine initially. No significant differences with regard to either of these end points were observed in the subgroups of patients with VF or PEA. In addition, in a post-hoc analysis performed on patients (n=732) in whom spontaneous circulation was not restored with the two doses of study drug, additional treatment with epinephrine was associated with significantly higher rates of survival to either hospital admission (25.7% vs. 16.4%; p=0.002) or discharge (6.2% vs. 1.7%; p=0.002) in the vasopressin group compared to the epinephrine group. The results of this study, in particular, served as the basis for vasopressin being included in the updated treatment algorithm for asystole/PEA in the 2005 American Heart Association Guidelines for CPR and Emergency Cardiovascular Care. However, because the efficacy of vasopressin appeared to be similar to that of epinephrine in patients with VF, the guidelines continue to recommend vasopressin as an alternative to epinephrine in the pulseless VT/VF treatment algorithm.

10. Goldberger Z, Lampert R. Implantable cardioverter-defibrillators: expanding indications and technologies. JAMA 2006;295:809–18.

    This article provides a timely and succinct review of the major clinical trials that have demonstrated the efficacy of the ICD for the primary and secondary prevention of sudden

cardiac death. It also provides an overview of the major clinical trials that have evaluated the efficacy of cardiac resynchronization therapy in patients with advanced heart failure. Pertinent details of each trial are provided in a useful table format, which facilitates the comparison of the similarities and differences between these studies. Basic information regarding the purpose, components, and programming capabilities of ICDs are also provided in this review article.

SELF-ASSESSMENT QUESTIONS

Questions 41 and 42 pertain to the following case.
A.T. is a 68-year-old woman who presents to the cardiology clinic complaining of episodes of dizziness and palpitations. When asked about the duration of symptoms, she states, "I really cannot remember when the symptoms started, but it has been going on for about 2–3 days." She has a history of type 2 diabetes, hypertension, and dyslipidemia. She denies smoking. Her current drugs include glipizide XL 10 mg/day orally, lisinopril 10 mg/day orally, enteric-coated aspirin 81 mg/day orally, and simvastatin 40 mg/day orally. Her vital signs today are blood pressure of 125/75 mm Hg and heart rate of 110 beats/minute. Her physical examination reveals no evidence of jugular venous distention, pedal edema, murmurs, rubs, or gallops. She is alert and oriented to person, place, and time. Her current electrocardiogram (ECG) shows atrial fibrillation (AF) with a ventricular rate of 115 beats per minute and no evidence of left ventricular hypertrophy (LVH). A recent transthoracic echocardiogram performed 1 month ago revealed a left ventricular ejection fraction (LVEF) of 55% with no wall motion abnormalities, LVH, or valvular defects.

41. Which one of the following represents A.T.'s 5-year predicted risk for stroke?
    A. 21%.
    B. 24%.
    C. 28%.
    D. 30%.

42. Which one of the following drug regimens is the most appropriate to prevent thromboembolic events in A.T.?
    A. Aspirin 325 mg/day orally.
    B. Low-dose warfarin titrated to an international normalized ratio (INR) of 1.2–1.5 and aspirin 325 mg/day orally.
    C. Warfarin titrated to an INR of 2–3.
    D. Drug therapy is not indicated.

43. R.W. is a 68-year-old woman who underwent coronary artery bypass graft (CABG) surgery and aortic valve replacement during this hospital admission. On the third postoperative day, she develops AF. At the time the AF develops, her vital signs are blood pressure of 110/70 mm Hg, heart rate of 120 beats/minute, and respiratory rate of 12 breaths/minute. She complains of palpitations, but is otherwise asymptomatic. Her postoperative echocardiogram reveals LVEF of 55%. Which one of the following regimens is most appropriate to control R.W.'s ventricular rate?
    A. Intravenous digoxin.
    B. Intravenous metoprolol.
    C. Intravenous amiodarone.
    D. Intravenous verapamil.

44. J.P. is an 87-year-old female nursing home resident who was admitted to the hospital for treatment of community-acquired pneumonia. She has a history of type 2 diabetes, hypertension, and Stage 5 chronic kidney disease (on hemodialysis). While having her blood pressure checked in the morning, J.P. complains of dizziness and suddenly loses consciousness. Cardiopulmonary resuscitation is immediately initiated. The monitor shows that J.P. is in asystole. Which one of the following interventions is most appropriate for this patient at this time?
    A. Transcutaneous pacing should be initiated.
    B. Intravenous epinephrine 1 mg alternating with intravenous vasopressin 40 units every 3–5 minutes.
    C. Deliver one shock of 200 joules with a biphasic defibrillator, followed by intravenous atropine 1 mg every 3–5 minutes, up to a maximum total dose of 3 mg.
    D. Intravenous epinephrine 1 mg every 3–5 minutes, then intravenous vasopressin 40 units for one dose.

Questions 45 and 46 pertain to the following case.
R.L. is a 40-year-old man who recently received an implantable cardioverter defibrillator (ICD) after being resuscitated from an episode of cardiac arrest due to ventricular fibrillation (VF) that was not related to an acute myocardial infarction (MI). Over the past 2 months, he has received five shocks, which he states have been extremely painful. Interrogation of the ICD reveals that R.L. is having recurrent episodes of ventricular tachycardia (VT). He has a history of nonischemic dilated cardiomyopathy (LVEF of 25%). His current drug include ramipril 5 mg 2 times/day orally, metoprolol CR/XL 150 mg/day orally, furosemide 40 mg/day orally, potassium chloride 20 mEq/day orally every day, and spironolactone 25 mg/day orally. His vital signs are blood pressure of 108/80 mm Hg, heart rate of 72 beats/minute, height 5'9", and weight 190 pounds. Pertinent laboratory values include potassium of 4.6 mEq/L, magnesium of 2.2 mEq/L, and serum creatinine of 1.7 mg/dL.

45. Which one of the following treatment regimens is the best for reducing the frequency of ICD shocks in R.L.?
    A. Initiate oral amiodarone.
    B. Increase the metoprolol CR/XL to 200 mg/day orally.
    C. Initiate sotalol.
    D. Initiate digoxin.

46. After initiating the therapy above in Question 45, R.L. returns to the electrophysiology clinic 3 months later and states that he did not experience any ICD shocks during this time period. However, he recently heard on the nightly news that fish oils are beneficial in patients with heart disease. He asks for your opinion regarding the use of fish oil supplements. Which one of the

following statements is the most appropriate information to pass on to R.L.?

A. Fish oil supplements should be taken by patients with ICDs because they have consistently reduced the risk of recurrent ventricular arrhythmias in these patients.
B. Fish oil supplements should be taken by patients with ICDs because they have reduced the risk of death in these patients.
C. There is a possibility that fish oil supplements may increase the risk of recurrent ventricular arrhythmias in certain patients with ICDs.
D. Fish oil supplements should be avoided in patients with ICDs because they have been associated with an increased risk of death.

47. L.M. is a 55-year-old man who presents to clinic complaining of palpitations that have been occurring for the past 2–3 weeks. He has a history of hypothyroidism, chronic obstructive pulmonary disease, and AF. He underwent successful electrical cardioversion 3 months ago for an episode of persistent AF and has been in sinus rhythm since that time. He has a 30 pack-year history of smoking. His current drugs include levothyroxine 100 mcg/day orally, ipratropium two puffs 4 times/day, salmeterol two puffs 2 times/day, and albuterol two puffs every 4–6 hours as needed. He has required increased use of his albuterol inhaler over the past few weeks since he has been recovering from a bout of bronchitis. His vital signs are blood pressure of 130/80 mm Hg, heart rate of 135 beats/minute, and respiratory rate of 16 breaths/minute. An ECG reveals AF with a ventricular rate of 130 beats/minute. Pertinent laboratory values include serum creatinine of 1.0 mg/dL, potassium of 4.1 mEq/L, magnesium of 2.1 mEq/L, and thyroid-stimulating hormone of 3.0 mIU/L. An echocardiogram performed 3 months ago demonstrated an LVEF of 55%. Which one of the following treatment regimens is the most appropriate for managing L.M.'s condition at this time?

A. Atenolol and warfarin (titrated to an INR of 2–3).
B. Diltiazem and warfarin (titrated to an INR of 2–3).
C. Amiodarone and warfarin (titrated to an INR of 2–3).
D. Discontinue the albuterol and levothyroxine.

48. M.G. is a 48-year-old woman who presents to the internal medicine clinic complaining of palpitations, dizziness, and fatigue, which have worsened over the past month. She has a history of type 2 diabetes, dyslipidemia, MI (LVEF of 50%), and paroxysmal AF. Her current drugs include enteric-coated aspirin 81 mg/day orally, lisinopril 10 mg/day orally, metoprolol CR/XL 100 mg/day orally, pravastatin 80 mg/day orally, warfarin 5 mg/day orally (has been on for 6 months), and glyburide 5 mg 2 times/day orally. Her vital signs are blood pressure of 125/75 mm Hg, heart rate of 72 beats/minute, height 5'7", and weight 140 pounds. Pertinent laboratory values include potassium of 4.5 mEq/L, serum creatinine of 2.2 mg/dL, and INR of 2.5. An ECG reveals AF with a ventricular rate of 70 beats/minute. Which one of the following regimens is the best for managing M.G.'s arrhythmia?

A. Increase the metoprolol CR/XL to 200 mg/day orally.
B. Initiate sotalol.
C. Initiate propafenone.
D. Initiate amiodarone.

49. Which one of the following statements best describes the role of the renin-angiotensin-aldosterone system in the pathophysiology and potential treatment of AF?

A. In comparative trials, the reduction in the risk of developing AF is significantly greater with the use of angiotensin-converting enzyme (ACE) inhibitors compared with angiotensin receptor blockers (ARBs).
B. The significant reductions in AF that have been associated with the use of ACE inhibitors and ARBs in clinical trials have primarily been limited to patients with left ventricular systolic dysfunction or LVH.
C. The renin-angiotensin-aldosterone system promotes electrical, but not structural remodeling in the atria.
D. Angiotensin II prolongs the atrial effective refractory period, which promotes the development of AF.

50. G.K. is a 45-year-old man with a history of nonischemic dilated cardiomyopathy who was recently admitted to the hospital with acute decompensated heart failure. During morning rounds in the coronary care unit, the telemetry monitor suddenly reveals that this patient has developed sustained VT. On entering the patient's room, it appears that G.K. has become unconscious, with no blood pressure or pulse. Telemetry continues to show VT. After administration of the appropriate initial therapy, the medical resident would like to use an antiarrhythmic drug. Which one of the following is the most appropriate first-line antiarrhythmic drug for G.K.?

A. Lidocaine.
B. Procainamide.
C. Amiodarone.
D. Atropine.

51. P.B. is a 51-year-old woman with a history of type 2 diabetes, dyslipidemia, hypertension, and paroxysmal AF. Echocardiogram performed today reveals an LVEF of 60%, no evidence of thrombus, and no LVH. Her drugs include hydrochlorothiazide 25 mg/day orally, metoprolol 50 mg 2 times/day orally, enteric-coated aspirin 81 mg/day orally, pravastatin 40 mg/day orally, warfarin 2.5 mg/day orally (has been on for 6 months), and glyburide 5 mg 2 times/day orally. Pertinent laboratory values include potassium of 4.5 mEq/L, serum creatinine of 2.0 mg/dL, and INR of 2.5. Her physician decides to admit her to the hospital for electrical cardioversion because she has become increasingly symptomatic during episodes of AF. The

cardioversion is successful and the physician would now like to start chronic antiarrhythmic drug therapy in P.B. to maintain her in sinus rhythm. Her current vitals are blood pressure of 130/85 mm Hg, heart rate of 75 beats/minutes, height 5'6", and weight 150 pounds. Which one of the following antiarrhythmic drugs is the best to use in this patient to maintain her in normal sinus rhythm?

A. Dofetilide.
B. Propafenone.
C. Sotalol.
D. Procainamide.

Questions 52 and 53 pertain to the following case.
S.F. is a 65-year-old man with a history of ischemic heart disease (LVEF of 50%) and paroxysmal AF. He is currently in AF. His current drugs include ramipril 5 mg/day orally, metoprolol 100 mg 2 times/day orally, digoxin 0.125 mg/day orally, warfarin 5 mg/day orally, enteric-coated aspirin 81 mg/day orally, and atorvastatin 40 mg/day orally. Pertinent laboratory values include INR of 2.6 (stable for the past 2 months) and digoxin concentration of 1.6 ng/mL (steady-state). S.F.'s cardiologist decides to start amiodarone to convert him to sinus rhythm. The plan is to initiate amiodarone at 400 mg orally 3 times/day for 1 week, followed by a maintenance dose of 200 mg/day orally.

52. Which one of the following is the most appropriate way of adjusting S.F.'s warfarin and digoxin regimens when the amiodarone is initiated?

A. Decrease digoxin dose to 0.125 mg orally every other day; decrease warfarin to 3 mg orally every Monday, Wednesday, Friday, and Saturday alternating with 4 mg orally every Tuesday, Thursday, and Sunday.
B. Maintain digoxin at the current dose; decrease warfarin to 3 mg orally every Monday, Wednesday, Friday, and Saturday alternating with 4 mg orally every Tuesday, Thursday, and Sunday.
C. Decrease digoxin dose to 0.125 mg orally every other day; decrease the warfarin to 2.5 mg/day orally.
D. Maintain digoxin at the current dose; decrease warfarin to 2.5 mg/day orally.

53. Assuming that all of the appropriate tests are performed at baseline, which one of the following is an appropriate way to monitor S.F.'s amiodarone therapy?

A. Amiodarone should be discontinued immediately if a patient develops amiodarone-induced corneal microdeposits.
B. A chest radiograph should be performed only when a patient develops symptoms suggestive of pulmonary fibrosis (e.g., cough or shortness of breath).
C. Liver function tests should be monitored every 6 months to screen for hepatic dysfunction.
D. Amiodarone should be discontinued immediately if a patient develops amiodarone-induced hypothyroidism.

54. G.S. is a 55-year-old man with a history of hypertension and dyslipidemia who presents to the emergency department complaining of palpitations and dizziness that have been occurring for the past 3–4 days. His vital signs are blood pressure of 120/72 mm Hg, heart rate of 115 beats/minute, height 5'8", and weight 175 pounds. His current drugs include hydrochlorothiazide 25 mg/day orally, metoprolol 25 mg orally 2 times/day, and atorvastatin 20 mg/day orally. His physical examination is negative for jugular venous distention, rales, and peripheral edema. An ECG reveals AF with a ventricular rate of 110 beats/minute. G.S. denies any history of AF in the past. His cardiologist would like to admit G.S. to the hospital to proceed with transesophageal echocardiogram (TEE)-guided cardioversion to restore sinus rhythm. Which one of the following regimens is the most appropriate to prevent thromboembolic events in G.S.?

A. Therapeutic intravenous heparin started after successful cardioversion, followed by warfarin (titrated to an INR of 2–3) for at least 4 weeks
B. Therapeutic intravenous heparin started at the time of TEE-guided cardioversion, followed by aspirin 325 mg/day orally for at least 4 weeks after successful cardioversion.
C. Therapeutic intravenous heparin started at the time of TEE-guided cardioversion and continued for 48 hours after successful cardioversion.
D. Therapeutic intravenous heparin started at the time of TEE-guided cardioversion, followed by warfarin (titrated to an INR of 2–3) for at least 4 weeks after successful cardioversion.

55. C.L. is a 48-year-old man who was diagnosed with nonischemic cardiomyopathy (LVEF of 20%) 1 year ago. He currently has symptoms consistent with New York Heart Association class III heart failure. His current drugs include enalapril 10 mg orally 2 times/day, metoprolol CR/XL 200 mg/day orally, digoxin 0.125 mg/day orally, furosemide 40 mg 2 times/day orally, potassium chloride 20 mEq 2 times/day orally, and spironolactone 25 mg/day orally. The medical intern was wondering whether C.L. would benefit from ICD implantation. Which one of the following statements is the most appropriate information to pass on to C.L.?

A. Based on the results of the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial, C.L. would benefit from ICD implantation.
B. Based on the results of the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II), C.L. would benefit from ICD implantation.
C. Implantation of an ICD in C.L. would not be considered a cost-effective strategy.
D. Based on the results of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), C.L. would benefit from ICD implantation

56. W.L., a 54 year-old man, presents to the heart failure clinic complaining of worsening palpitations, shortness

of breath, and fatigue. He also has a history of MI (5 months ago), heart failure (LVEF of 25%), paroxysmal AF, and pulmonary fibrosis secondary to amiodarone (occurred 1 year ago). His current drugs include enteric-coated aspirin 81 mg/day orally, enalapril 10 mg 2 times/day orally, furosemide 40 mg 2 times/day orally, potassium chloride 40 mEq/day orally, carvedilol 25 mg 2 times/day orally, atorvastatin 20 mg/day orally, digoxin 0.125 mg/day orally, and warfarin 4 mg/day orally. He has been stable on this regimen for the past 3 months. His vitals are blood pressure of 115/70 mm Hg, heart rate of 80 beats/minute, height 5'9", and weight 175 pounds. Pertinent laboratory values include potassium of 4.3 mEq/L, serum creatinine of 1.3 mg/dL, digoxin concentration of 0.8 ng/mL, and INR of 2.6. His ECG reveals AF with a ventricular rate of 78 beats/minute. Which one of the following regimens is the best for managing W.L.'s arrhythmia?

A. Amiodarone 400 mg 2 times/day orally until a total of 10 g has been given, followed by 200 mg/day orally.
B. Increase digoxin to 0.25 mg/day orally.
C. Dofetilide 500 mcg 2 times/day orally.
D. Sotalol 80 mg 2 times/day orally.

57. R.F. is a 60-year-old man who presents to the emergency department with crushing substernal chest pain that radiates down his left arm. His ECG shows 2-mm of ST-segment elevation in the anterior leads. While being transported to the cardiac catheterization laboratory, R.F. becomes unconscious. The monitor at that time shows that the patient is in VF. Cardiopulmonary resuscitation and defibrillation are provided; however, the patient remains in VF. Which one of the following drugs is most appropriate to administer at this time to R.F.?

A. Intravenous vasopressin.
B. Intravenous atropine.
C. Intravenous lidocaine.
D. Intravenous adenosine.

Questions 58 and 59 pertain to the following case.
F.P. is a 65-year-old man with a history of hypertension, dyslipidemia, and type 2 diabetes. One week ago, after having worsening dyspnea and chest tightness, he was sent for coronary angiography which revealed three-vessel coronary artery disease and an LVEF of 30%. He is scheduled to undergo CABG surgery in 2 days.

58. Which one of the following regimens is best to prevent postoperative AF in F.P.?

A. Metoprolol.
B. Amiodarone.
C. Verapamil.
D. Digoxin.

59. Despite administration of this prophylactic therapy before CABG surgery, F.P. develops AF 2 days after surgery. At the time the AF develops, he begins complaining of dyspnea and palpitations, and his vital signs are blood pressure of 90/40 mm Hg, heart rate of 135 beats/minute, and respiratory rate of 19 breaths/minute. Which one of the following drugs is most appropriate to treat F.P.'s postoperative AF?

A. Sotalol.
B. Ibutilide.
C. Flecainide.
D. Amiodarone.

60. A 35-year-old homeless man is brought to the emergency department after being involved in a car accident with a tractor trailer. He had to be removed by emergency medical services by the "jaws of life" and has suffered serious internal injuries. On arrival to the emergency department, he has no blood pressure or pulse. However, telemetry shows sinus rhythm at a rate of 50 beats/minute. Five cycles of cardiopulmonary resuscitation are provided. However, the patient's clinical status has not changed. Which one of the following interventions is most appropriate to administer to this patient at this time?

A. Deliver one shock of 200 joules with a biphasic defibrillator.
B. Intravenous epinephrine 1 mg every 3–5 minutes.
C. Amiodarone 300 mg administered via intravenous push.
D. Intravenous isoproterenol continuous infusion.