2014 AHA/ACC/HRS Guideline 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 Heart Rhythm Society

Developed in Collaboration With the Society of Thoracic Surgeons

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Preamble

The medical profession should play a central role in evaluating the evidence related to drugs, devices, and procedures for the detection, management, and prevention of disease. When properly applied, expert analysis of available data on the benefits and risks of these therapies and procedures can improve the quality of care, optimize patient outcomes, and favorably affect costs by focusing resources on the most effective strategies. An organized and directed approach to a thorough review of evidence has resulted in the production of clinical practice guidelines that assist clinicians in selecting the best management strategy for an individual patient. Moreover, clinical practice guidelines can provide a foundation for other applications, such as performance measures, appropriate use criteria, and both quality improvement and clinical decision support tools.

The American College of Cardiology (ACC) and the American Heart Association (AHA) have jointly engaged in the production of guidelines in the area of cardiovascular disease since 1980. The ACC/AHA Task Force on Practice Guidelines (Task Force), whose charge is to develop, update, or revise practice guidelines for cardiovascular diseases and procedures, directs this effort. Writing committees are charged with the task of performing an assessment of the evidence and acting as an independent group of authors to develop, update, or revise written recommendations for clinical practice.

Experts in the subject under consideration are selected from both organizations to examine subject-specific data and write guidelines. Writing committees are specifically charged to perform a literature review; weigh the strength of evidence for or against particular tests, treatments, or procedures; and include estimates of expected health outcomes where such data exist. Patient-specific modifiers, comorbidities, and issues of patient preference that may influence the choice of tests or therapies are considered, as well as frequency of follow-up and cost-effectiveness. When available, information from studies on cost is considered; however, review of data on efficacy and outcomes constitutes the primary basis for preparing recommendations in this guideline.

In analyzing the data, and developing recommendations and supporting text, the writing committee uses evidence-based methodologies developed by the Task Force. The Classification of Recommendation (COR) is an estimate of the size of the treatment effect, with consideration given to risks versus benefits, as well as evidence and/or agreement that a given treatment or procedure is or is not useful/effective or in some situations may cause harm; this is defined in Table 1. The Level of Evidence (LOE) is an estimate of the certainty or precision of the treatment effect. The writing committee reviews and ranks evidence supporting each recommendation, with the weight of evidence ranked as LOE A, B, or C, according to specific definitions that are included in Table 1. Studies are identified as observational, retrospective, prospective, or randomized, as appropriate. For certain conditions for which inadequate data are available, recommendations are based on expert consensus and clinical experience and are ranked as LOE C. When recommendations at LOE C are supported by historical clinical data, appropriate references (including clinical reviews) are cited if available.

For issues with sparse available data, a survey of current practice among the clinician members of the writing committee is the basis for LOE C recommendations and no references are cited.

The schema for COR and LOE is summarized in Table 1, which also provides suggested phrases for writing recommendations within each COR.

A new addition to this methodology is the separation of the Class III recommendations to delineate whether the recommendation is determined to be of “no benefit” or is associated with “harm” to the patient. In addition, in view of the increasing number of comparative effectiveness studies, comparator verbs and suggested phrases for writing recommendations for the comparative effectiveness of one treatment or strategy versus another are included for COR I and IIa, LOE A or B only.

In view of the advances in medical therapy across the spectrum of cardiovascular diseases, the Task Force has designated the term guideline-directed medical therapy to represent optimal medical therapy as defined by ACC/AHA guideline (primarily Class I)–recommended therapies. This new term, guideline-directed medical therapy, is used herein and throughout subsequent guidelines.

Therapies not available in the United States are discussed in the text without a specific COR. For studies performed in large numbers of subjects outside North America, each writing committee reviews the potential impact of different practice patterns and patient populations on the treatment effect and relevance to the ACC/AHA target population to determine whether the findings should inform a specific recommendation.

The ACC/AHA practice guidelines are intended to assist clinicians in clinical decision making by describing a range of generally acceptable approaches to the diagnosis, management, and prevention of specific diseases or conditions. The guidelines attempt to define practices that meet the needs of most patients in most circumstances. The ultimate judgment about care of a particular patient must be made by the clinician and patient in light of all the circumstances presented by that patient. As a result, situations may arise in which deviations from these guidelines may be appropriate. Clinical decision making should involve consideration of the quality and availability of expertise in the area where care is provided. When these guidelines are used as the basis for regulatory or payer decisions, the goal should be improvement in quality of
The Task Force recognizes that situations arise in which additional data are needed to inform patient care more effectively; these areas are identified within each respective guideline when appropriate.

Prescribed courses of treatment in accordance with these recommendations are effective only if followed. Because lack of patient understanding and adherence may adversely affect outcomes, clinicians should make every effort to engage the patient’s active participation in prescribed medical regimens and lifestyles. In addition, patients should be informed of the risks, benefits, and alternatives to a particular treatment and should be involved in shared decision making whenever feasible, particularly for COR IIa and IIb, for which the benefit-to-risk ratio may be lower.

The Task Force makes every effort to avoid actual, potential, or perceived conflicts of interest that may arise as a result of relationships with industry and other entities (RWI) among the members of the writing committee. All writing committee members and peer reviewers of the guideline are required to disclose all current healthcare-related relationships, including those existing 12 months before initiation of the writing effort.

Table 1. Applying Classification of Recommendations and Level of Evidence

<table>
<thead>
<tr>
<th>S I Z E O F T R E A T M E N T E F F E C T</th>
<th>CLASS I</th>
<th>CLASS IIa</th>
<th>CLASS IIb</th>
<th>CLASS III No Benefit or CLASS III Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefit &gt;&gt; Risk Procedure/Treatment SHOULD be performed/administered</td>
<td>Recommendation that procedure or treatment is useful/effective</td>
<td>Recommendation in favor of treatment or procedure being useful/effective</td>
<td>Recommendation’s usefulness/effectiveness less well established</td>
<td>Recommendation that procedure or treatment is not useful/effective and may be harmful</td>
</tr>
<tr>
<td>Benefit &gt;&gt; Risk Additional studies with focused objectives needed</td>
<td>Sufficient evidence from multiple randomized trials or meta-analyses</td>
<td>Some conflicting evidence from multiple randomized trials or meta-analyses</td>
<td>Greater conflicting evidence from multiple randomized trials or meta-analyses</td>
<td>Sufficient evidence from multiple randomized trials or meta-analyses</td>
</tr>
<tr>
<td>IT IS REASONABLE to perform procedure/administer treatment</td>
<td>Procedure/Treatment MAY BE CONSIDERED</td>
<td>Procedure/Treatment MAY BE CONSIDERED</td>
<td>Procedure/Treatment MAY BE CONSIDERED</td>
<td>Procedure/Treatment MAY BE CONSIDERED</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LEVEL A</th>
<th>LEVEL B</th>
<th>LEVEL C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple populations evaluated*</td>
<td>Limited populations evaluated*</td>
<td>Very limited populations evaluated*</td>
</tr>
<tr>
<td>Data derived from multiple randomized clinical trials or meta-analyses</td>
<td>Data derived from a single randomized trial or nonrandomized studies</td>
<td>Only consensus opinion of experts, case studies, or standard of care</td>
</tr>
</tbody>
</table>

**Suggested phrases for writing recommendations**
- should be considered
- is recommended
- is indicated
- is useful/effective/beneficial

**Comparative effectiveness phrases**
- treatment/strategy A is recommended/indicated in preference to treatment B
- treatment/strategy A should be chosen over treatment B

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/effectiveness in different subpopulations, such as sex, age, history of diabetes mellitus, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative-effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.
1. Introduction

1.1. Methodology and Evidence Review

The recommendations listed in this document are, whenever possible, evidence based. An extensive evidence review was conducted, focusing on 2006 through October 2012 and selected other references through March 2014. The relevant data are included in evidence tables in the Online Data Supplement. Searches were extended to studies, reviews, and other evidence conducted in human subjects, published in English, and accessible through PubMed, EMBASE, Cochrane, Agency for Healthcare Research and Quality Reports, and other selected databases relevant to this guideline. Key search words included but were not limited to the following: age, antiarrhythmic, atrial fibrillation, atrial remodeling, atrioventricular conduction, atroventricular node, cardioversion, classification, clinical trial, complications, concealed conduction, cost-effectiveness, defibrillator, demographics, epidemiology, experimental, heart failure, hemodynamics, human, hyperthyroidism, hypothyroidism, meta-analysis, myocardial infarction, pharmacology, postoperative, pregnancy, pulmonary disease, quality of life, rate control, rhythm control, risks, sinus rhythm, symptoms, and tachycardia-mediated cardiomyopathy. Additionally, the writing committee reviewed documents related to atrial fibrillation (AF) previously published by the ACC and AHA. References selected and published in this document are representative and not all-inclusive.

To provide clinicians with a comprehensive set of data, whenever deemed appropriate or when published, the absolute risk difference and number needed to treat or harm are provided in the guideline or data supplement, along with confidence intervals (CI) and data related to the relative treatment effects such as the odds ratio (OR), relative risk (RR), hazard ratio, or incidence rate ratio.

1.2. Organization of the Writing Committee

The 2014 AF writing committee was composed of clinicians with broad expertise related to AF and its treatment, including adult cardiology, electrophysiology, cardiothoracic surgery, and heart failure (HF). The writing committee was assisted by staff from the ACC and AHA. Under the guidance of the Task Force, the Heart Rhythm Society was invited to be a partner organization and provided representation. The writing committee also included a representative from the Society of Thoracic Surgeons. The rigorous methodological policies and procedures noted in the Preamble differentiate ACC/AHA guidelines from other published guidelines and statements.

1.3. Document Review and Approval

This document was reviewed by 2 official reviewers each nominated by the ACC, AHA, and Heart Rhythm Society, as well as 1 reviewer from the Society of Thoracic Surgeons and 43 individual content reviewers (from the ACC Electrophysiology Section Leadership Council, ACC Adult Congenital and Pediatric Cardiology Section Leadership Council, ACC Association of International Governors, ACC Heart Failure and Transplant Section Leadership Council, ACC Imaging Section Leadership Council, ACC Interventional Section Leadership Council, ACC Surgeons’ Council, and the Heart Rhythm Society Scientific Documents Committee). All information on reviewers’ RWI was distributed to the writing committee and is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACC, AHA, and Heart Rhythm Society and endorsed by the Society of Thoracic Surgeons.

1.4. Scope of the Guideline

The task of the 2014 writing committee was to establish revised guidelines for optimum management of AF. The new guideline incorporates new and existing knowledge derived from published clinical trials, basic science, and comprehensive review articles, along with evolving treatment strategies and new drugs. This guideline supersedes the “ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation” and the 2 subsequent focused updates from 2011. In addition, the ACC, AHA, American College of Physicians, and American Academy
of Family Physicians submitted a proposal to the Agency for Healthcare Research and Quality to perform a systematic review on specific questions related to the treatment of AF. The data from that report were reviewed by the writing committee and incorporated where appropriate.7a,7b

The 2014 AF guideline is organized thematically, with recommendations, where appropriate, provided with each section. Some recommendations from earlier guidelines have been eliminated or updated as warranted by new evidence or a better understanding of earlier evidence. In developing the 2014 AF guideline, the writing committee reviewed prior published guidelines and related statements. Table 2 lists these publications and statements deemed pertinent to this effort and is intended for use as a resource.

### 2. Background and Pathophysiology

AF is a common cardiac rhythm disturbance that increases in prevalence with advancing age. Approximately 1% of patients with AF are <60 years of age, whereas up to 12% of patients with AF are 75 to 84 years of age.29 More than one third of patients with AF are ≥80 years of age.30,31 In the United States, the percentage of Medicare fee-for-service beneficiaries with AF in 2010 was reported as 2% for those <65 years of age and 9% for those ≥65 years of age.32 For individuals of European descent, the lifetime risk of developing AF after 40 years of age is 26% for men and 23% for women.33 In African Americans, although risk factors for AF are more prevalent, incidence of AF appears to be lower.34 AF is often associated with structural heart disease and other co-occurring chronic conditions (Table 3; see also [http://www.cms.](http://www.cms.))

<table>
<thead>
<tr>
<th>Title</th>
<th>Organization</th>
<th>Publication Year/Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)</td>
<td>NHLBI</td>
<td>20038</td>
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<tr>
<td>Assessment of Cardiovascular Risk in Asymptomatic Adults</td>
<td>ACC/AHA</td>
<td>20109</td>
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<tr>
<td>Coronary Artery Bypass Graft Surgery</td>
<td>ACC/AHA</td>
<td>201110</td>
</tr>
<tr>
<td>Hypertrophic Cardiomyopathy</td>
<td>ACC/AHA</td>
<td>201111</td>
</tr>
<tr>
<td>Percutaneous Coronary Intervention</td>
<td>ACC/AHA/SCAI</td>
<td>201112</td>
</tr>
<tr>
<td>Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease</td>
<td>AHA/ACC</td>
<td>201113</td>
</tr>
<tr>
<td>Atrial Fibrillation*</td>
<td>CCS</td>
<td>201214</td>
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<tr>
<td>Atrial Fibrillation</td>
<td>ESC</td>
<td>201215</td>
</tr>
<tr>
<td>Stable Ischemic Heart Disease</td>
<td>ACC/AHA/ACP/AATS/PCNA/SCAI/STS</td>
<td>201216</td>
</tr>
<tr>
<td>Antithrombotic Therapy</td>
<td>ACCP</td>
<td>201217</td>
</tr>
<tr>
<td>Device-Based Therapy</td>
<td>ACC/AHA/HRSA</td>
<td>201218</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>ACC/AHA</td>
<td>201319</td>
</tr>
<tr>
<td>ST-Elevation Myocardial Infarction</td>
<td>ACC/AHA</td>
<td>201320</td>
</tr>
<tr>
<td>Unstable Angina/Non-ST-Elevation Myocardial Infarction</td>
<td>ACC/AHA</td>
<td>201414</td>
</tr>
<tr>
<td>Valvular Heart Disease</td>
<td>AHA/ACC</td>
<td>201412</td>
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<tr>
<td>Assessment of Cardiovascular Risk</td>
<td>ACC/AHA</td>
<td>201323</td>
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<tr>
<td>Lifestyle Management to Reduce Cardiovascular Risk</td>
<td>AHA/ACC</td>
<td>201324</td>
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<tr>
<td>Management of Overweight and Obesity in Adults</td>
<td>AHA/ACC/TOS</td>
<td>201325</td>
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<tr>
<td>Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults</td>
<td>ACC/AHA</td>
<td>201326</td>
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<tr>
<td>Treatment of Atrial Fibrillation</td>
<td>AHRQ</td>
<td>201327 a,7b</td>
</tr>
</tbody>
</table>

*Includes the following sections: Catheter Ablation for AF/Atrial Flutter; Prevention and Treatment of AF Following Cardiac Surgery; Rate and Rhythm Management; Prevention of Stroke and Systemic Thromboembolism in AF and Flutter; Management of Recent-Onset AF and Flutter in the Emergency Department; Surgical Therapy; The Use of Antiplatelet Therapy in the Outpatient Setting; and Focused 2012 Update of the CCS AF Guidelines: Recommendations for Stroke Prevention and Rate/Rhythm Control.

AATS indicates American Association for Thoracic Surgery; ACC, American College of Cardiology; ACCP, American College of Chest Physicians; ACP, American College of Physicians; AF, atrial fibrillation; AHA, American Heart Association; AHRQ, Agency for Healthcare Research and Quality; ASA, American Stroke Association; CCS, Canadian Cardiology Society; ECAS, European Cardiac Arrhythmia Society; EHRA, European Heart Rhythm Association; ESC, European Society of Cardiology; HRS, Heart Rhythm Society; JNC, Joint National Committee; NHLBI, National Heart, Lung, and Blood Institute; PCNA, Preventive Cardiovascular Nurses Association; SCAI, Society for Cardiovascular Angiography and Interventions; STS, Society of Thoracic Surgeons; and TOS, The Obesity Society.
Table 3. 10 Most Common Comorbid Chronic Conditions Among Medicare Beneficiaries With AF

<table>
<thead>
<tr>
<th>Condition</th>
<th>Beneficiaries ≥65 y of Age (N=2 426 865) (Mean Number of Conditions=5.8; Median=6)</th>
<th>Beneficiaries &lt;65 y of Age (N=105 878) (Mean Number of Conditions=5.8; Median=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 015 235 83.0</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1 549 125 63.8</td>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1 507 395 62.1</td>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>HF</td>
<td>1 247 748 51.4</td>
<td>HF</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 027 135 42.3</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Arthritis</td>
<td>965 472 39.8</td>
<td>Anemia</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>885 443 36.5</td>
<td>CKD</td>
</tr>
<tr>
<td>CKD</td>
<td>784 631 32.3</td>
<td>Arthritis</td>
</tr>
<tr>
<td>COPD</td>
<td>561 826 23.2</td>
<td>Depression</td>
</tr>
<tr>
<td>Cataracts</td>
<td>546 421 22.5</td>
<td>COPD</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; and HF, heart failure.
Reproduced with permission from the Centers for Medicare & Medicaid Services.44

2.1. Definitions and Pathophysiology of AF

AF is a supraventricular tachyarrhythmia with uncoordinated atrial activation and consequently ineffective atrial contraction.3,26,30 Characteristics on an electrocardiogram (ECG) include 1) irregular R–R intervals (when atrioventricular [AV] conduction is present), 2) absence of distinct repeating P waves, and 3) irregular atrial activity.

Hemodynamic consequences of AF can result from a variable combination of suboptimal ventricular rate control (either too rapid or too slow), loss of coordinated atrial contraction, beat-to-beat variability in ventricular filling, and sympathetic activation.45–47 Consequences for individual patients vary, ranging from no symptoms to fatigue, palpitations, dyspnea, hypotension, syncope, or HF.48 The most common symptom of AF is fatigue. The appearance of AF is often associated with exacerbation of underlying heart disease, either because AF is a cause or consequence of deterioration or because it contributes directly to deterioration.49,50 For example, initially asymptomatic patients may develop tachycardia-induced ventricular dysfunction and HF (tachycardia-induced cardiomyopathy) when the ventricular rate is not adequately controlled.51,52 AF also confers an increased risk of stroke and/or peripheral thromboembolism owing to the formation of atrial thrombi, usually in the left atrial appendage (LAA).

In the absence of an accessory AV pathway, the ventricular rate is determined by the conduction and refractory properties of the AV node and the sequence of wave fronts entering the AV node.53–55 L-type calcium channels are responsible for the major depolarizing current in AV nodal cells. Beta-adrenergic receptor stimulation enhances AV nodal conduction, whereas vagal stimulation (muscarinic receptor activation by acetylcholine) impedes AV nodal conduction.55 Sympathetic activation and vagal withdrawal such as that with exertion or illness accelerates the ventricular rate. Each atrial excitation wave front that depolarizes AV nodal tissue renders those cells refractory for a period of time, an effect called concealed conduction.55 This effect of concealed conduction into the AV node explains why the ventricular rate can be faster and more difficult to slow when fewer atrial wave fronts are entering the AV node, as in atrial flutter, compared with AF.55

Loss of atrial contraction may markedly decrease cardiac output, particularly when diastolic ventricular filling is impaired by mitral stenosis, hypertension, hypertrophic cardiomyopathy (HCM), or restrictive cardiomyopathy.56,57,58 After restoration of sinus rhythm, atrial mechanical function fails to recover in some patients, likely as a consequence of remodeling or underlying atrial disease and duration of AF.58 Ventricular contractility is not constant during AF because of variable diastolic filling time and changes in the force- interval relationship.59,60 Overall, cardiac output may decrease and filling pressures may increase...
AF than for persistent AF. When sinus rhythm is restored of therapy such as catheter ablation are better for paroxysmal AF episodes (Table 4).

Electrophysiological mapping reveals a focal point of origin. An isoelectric segment between P waves (Figure 1) has clinical relevance in that outcomes of therapy such as catheter ablation are better for paroxysmal AF than for persistent AF. When sinus rhythm is restored of therapy such as catheter ablation are better for paroxysmal AF episodes.

Terminology and Definitions

**Term**
- Paroxysmal AF
- Persistent AF
- Long-standing persistent AF
- Permanent AF
- Nonvalvular AF

**Definition**
- **AF** that terminates spontaneously or with intervention within 7 d of onset.
- Continuous AF that is sustained for >7 d.
- Continuous AF >12 mo in duration.
- The term “permanent AF” is used when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm.
- AF in the absence of rheumatic mitral valve, or mitral valve repair.

AF indicates atrial fibrillation.

Compared with a regular rhythm at the same mean rate. In patients undergoing AV nodal ablation, irregular right ventricular (RV) pacing at the same rate as regular ventricular pacing resulted in a 15% reduction in cardiac output. Irregular R-R intervals also promote sympathetic activation.

2.1.1. AF Classification

AF may be described in terms of the duration of episodes using a simplified scheme shown in Table 4. Implanted loop recorders, pacemakers, and defibrillators offer the possibility of reporting frequency, rate, and duration of abnormal atrial rhythms, including AF. Episodes often increase in frequency and duration over time.

Characterization of patients with AF by duration of their AF episodes (Table 4) has clinical relevance in that outcomes of therapy such as catheter ablation are better for paroxysmal AF than for persistent AF. When sinus rhythm is restored by cardioversion, however, the ultimate duration of the AF episode(s) is not known. Furthermore, both paroxysmal and persistent AF may occur in a single individual.

**Lone AF** is a historical descriptor that has been variably applied to younger persons without clinical or echocardiographic evidence of cardiopulmonary disease, hypertension, or diabetes mellitus. Because the definitions are variable, the term lone AF is potentially confusing and should not be used to guide therapeutic decisions.

2.1.1.1. Associated Arrhythmias

Other atrial arrhythmias are often encountered in patients with AF. Atrial flutter is a macroreentrant atrial tachycardia that usually proceeds up the atrial septum, down the lateral atrial wall, and through the cavotricuspid (subeustachian) isthmus between the tricuspid valve annulus and inferior vena cava, where it is commonly targeted for ablation. It is also known as “common atrial flutter” or “cavotricuspid isthmus–dependent atrial flutter.” This sequence of activation (also referred to as “counterclockwise atrial flutter”) produces predominantly negative “sawtooth” flutter waves in ECG leads II, III, and aVF, and a positive deflection in V1 (Figure 1). The atrial rate is typically 240 bpm to 300 bpm, but conduction delays in the atrial circuit due to scars from prior ablation, surgery, or antiarrhythmic drugs can slow the rate to <150 bpm in some patients. When the circuit revolves in the opposite direction, flutter waves typically appear positive in the inferior ECG leads and negative in V1 (reverse typical atrial flutter). Irregular flutter wave morphologies occur in the presence of substantial atrial disease, prior surgery, or radiofrequency catheter ablation; the P-wave morphology is not a reliable indicator of the type of macroreentrant atrial tachycardia in these situations. Atrial flutter is often a persistent rhythm that requires electrical cardioversion or radiofrequency catheter ablation for termination. It is often initiated by a brief episode of atrial tachycardia or by AF.

This relationship between AF and atrial flutter may explain why >80% of patients who undergo radiofrequency catheter ablation of typical atrial flutter will have AF within the following 5 years. AF may be misdiagnosed as atrial flutter when AF activity is prominent on the ECG. Atrial flutter may also arise during treatment with antiarrhythmic agents prescribed to prevent recurrent AF, particularly sodium channel–blocking antiarrhythmic drugs such as flecainide or propafenone. Catheter ablation of the cavotricuspid isthmus is effective for prevention of recurrent atrial flutter in these patients while allowing continued antiarrhythmic treatment to prevent recurrent AF.

Atypical flutter, or “non–cavotricuspid isthmus–dependent macroreentrant atrial tachycardia,” describes macroreentrant atrial tachycardias that are not one of the typical forms of atrial flutter that use the cavotricuspid isthmus. A variety of reentrant circuits have been described, including “perimodal flutter” reentry involving the roof of the left atrium (LA), and reentry around scars in the left or right atrium, often from prior surgery or ablation. Complex reentry circuits with >1 reentry loop or circuit can occur and often coexist with common atrial flutter. These arrhythmias are not abolished by ablation of the cavotricuspid isthmus, but recognition and distinction of these arrhythmias from common atrial flutter usually requires electrophysiological studies.
2.2. Mechanisms of AF and Pathophysiology

AF occurs when structural and/or electrophysiological abnormalities alter atrial tissue to promote abnormal impulse formation and/or propagation (Figure 2). These abnormalities are caused by diverse pathophysiological mechanisms,\(^{28,81,82}\) such that AF represents a final common phenotype for multiple disease pathways and mechanisms that are incompletely understood.

2.2.1. Atrial Structural Abnormalities

Any disturbance of atrial architecture potentially increases susceptibility to AF.\(^{83}\) Such changes (eg, inflammation, fibrosis, hypertrophy) occur most commonly in the setting of underlying heart disease associated with hypertension, coronary artery disease (CAD), valvular heart disease, cardiomyopathies, and HF, which tend to increase LA pressure, cause atrial dilation, and alter wall stress. Similarly, atrial ischemia from CAD and infiltrative diseases such as amyloidosis, hemochromatosis, and sarcoidosis can also promote AF. Extracardiac factors that promote AF include hypertension, sleep apnea, obesity, use of alcohol/drugs, and hyperthyroidism, all of which have pathophysiological effects on atrial cellular structure and/or function. Even in patients with paroxysmal AF without recognized structural heart disease, atrial biopsies have revealed inflammatory infiltrates consistent with myocarditis and fibrosis.\(^{84}\) In addition, prolonged rapid atrial pacing increases arrhythmia susceptibility and forms the basis for a well-studied model of AF. In the atria of patients with established AF and of animals subjected to rapid atrial pacing, there is evidence of myocyte loss from glycogen deposits and of mitochondrial disturbances and gap-junction abnormalities that cause cell necrosis and apoptosis.\(^{85-87}\) These structural abnormalities can heterogeneously alter impulse conduction and/or refractoriness, generating an arrhythmogenic substrate.

Myocardial fibrosis is a common feature of both experimental and human AF.\(^{88}\) The atria are more sensitive to profibrotic signaling and harbor a greater number of fibroblasts than the ventricles. Atrial stretch activates the renin-angiotensin-aldosterone system, which generates multiple downstream profibrotic factors, including transforming growth factor-beta.\(^{1}\) Additional mechanisms, including inflammation and genetic factors, can also promote atrial fibrosis. The canine rapid ventricular pacing model of HF causes extensive atrial fibrosis and increases AF susceptibility.\(^{89}\) Fibrosis also occurs in the rapid atrial pacing model of AF. Late gadolinium-enhancement magnetic resonance imaging is used to image and quantitate atrial fibrosis noninvasively.\(^{90-93}\) Human

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**Figure 1. Atrial tachycardias.** Diagram summarizing types of atrial tachycardias often encountered in patients with a history of AF, including those seen after catheter or surgical ablation procedures. P-wave morphologies are shown for common types of atrial flutter; however, the P-wave morphology is not always a reliable guide to the reentry circuit location or the distinction between common atrial flutter and other macroreentrant atrial tachycardias. \(^*\)Exceptions to P-wave morphology and rate are common in scarred atria. AF indicates atrial fibrillation; bpm, beats per minute; and ECG, electrocardiogram.\(^{72,80}\)
studies show a strong correlation between regions of low voltage on electroanatomic mapping and areas of late enhancement on magnetic resonance imaging. Preliminary results suggest that the severity of atrial fibrosis correlates with the risk of stroke and decreased response to catheter ablation.

2.2.2. Electrophysiological Mechanisms
AF requires both a trigger for initiation and an appropriate anatomic substrate for maintenance, both of which are potential targets for therapy. Several hypotheses have been proposed to explain the electrophysiological mechanisms that initiate and maintain AF. In humans, the situation is complex, and it is likely that multiple mechanisms coexist in an individual patient.

2.2.2.1. Triggers of AF
Ectopic focal discharges often initiate AF. Rapidly firing foci initiating paroxysmal AF arise most commonly from LA myocardial sleeves that extend into the pulmonary veins. These observations led to the development of pulmonary vein isolation as the cornerstone for radiofrequency catheter ablation strategies. Unique anatomic and electrophysiological features of the pulmonary veins and atriopulmonary vein junctions may account for their arrhythmogenic nature. Atrial myocardial fibers are oriented in disparate directions around the pulmonary veins and the posterior LA, with considerable anatomic variability among individuals. Conduction abnormalities that promote reentry are likely due to relatively depolarized resting potentials in pulmonary vein myocytes that promote sodium channel inactivation and to the abrupt changes in fiber orientation. Reentry is further favored by abbreviated action potentials and refractoriness in pulmonary vein myocytes. Isolated pulmonary vein myocytes also demonstrate abnormal automaticity and triggered activity that could promote rapid focal firing. Additional potential sources for abnormal activity include interstitial cells (similar to pacemaker cells in the gastrointestinal tract) and melanocytes, both of which have been identified in pulmonary veins. Although the pulmonary veins are the most common sites for ectopic focal triggers, triggers can also arise elsewhere, including the posterior LA, ligament of Marshall, coronary sinus, veinae cavae, septum, and appendages.

Abnormal intracellular calcium handling may also play a role in AF owing to diastolic calcium leak from the sarcoplasmic reticulum, which can trigger delayed afterdepolarizations.

2.2.2.2. Maintenance of AF
Theories proposed to explain the perpetuation and maintenance of AF include 1) multiple independent reentrant wavelets associated with heterogeneous conduction and refractoriness; 2) ≥1 rapidly firing foci, which may be responsive to activity from cardiac ganglion plexi; and 3) ≥1 rotors, or spiral wave reentrant circuits. With a single rapid focus or rotor excitation, wave fronts may encounter refractory tissue and break up during propagation, resulting in irregular or fibrillatory conduction. Both rapid focal firing and reentry may be operative during AF.

These presumed mechanisms have driven the development of therapies. The atrial maze procedure and ablation lines may interrupt paths for multiple wavelets and spiral reentry. When a biatrial phase mapping approach was used, a limited number of localized, rapid drivers (mean of approximately 2 per patient) were identified in a small group of patients with various types of AF. In most cases, these localized sources appeared to be reentrant, whereas in others they were consistent with focal triggers, and radiofrequency catheter ablation targeting of these sites often terminated or slowed AF. Other investigators, using a noninvasive continuous biatrial mapping system, report contrasting results, observing mostly evidence for multiple wavelets and focal sites rather than rotor activity.
Some investigators targeted regions in which electrogram recordings show rapid complex atrial fractionated electrograms, which are thought to be indicative of the substrate for AF or markers for ganglion plexi (see Section 2.2.2.3 for ablation of AF).\textsuperscript{109} The relation of complex atrial fractionated electrograms to AF remains controversial.

### 2.2.2.3. Role of the Autonomic Nervous System

Autonomic stimulation can provoke AF.\textsuperscript{28,98,115} Activation of the parasympathetic and/or sympathetic limbs can provoke atrial arrhythmias.\textsuperscript{108,116} Acetylcholine activates a specific potassium current, $I_{\text{K,ACH}}$, which heterogeneously shortens atrial action potential duration and refractoriness, increasing susceptibility to reentry. Sympathetic stimulation increases intracellular calcium, which promotes automaticity and triggered activity. Increased parasympathetic and/or sympathetic activity before onset of AF has been observed in some animal models and humans.\textsuperscript{117,118}

Plexi of autonomic ganglia that constitute the intrinsic cardiac autonomic nervous system are located in epicardial fat near the pulmonary vein-LA junctions and the ligament of Marshall. Stimulation of the ganglia in animals elicits repetitive bursts of rapid atrial activity. These plexi are often located proximal to atrial sites where complex atrial fractionated electrograms are recorded. Ablation targeting these regions improved outcomes over pulmonary vein isolation alone in some but not all studies.\textsuperscript{119–121}

In some patients with structurally normal hearts, AF is precipitated during conditions of high-parasympathetic tone, such as during sleep and following meals, and is referred to as “vagally mediated AF.”\textsuperscript{122} Avoidance of drugs, such as digoxin, that enhance parasympathetic tone has been suggested in these patients, but this remains an unproven hypothesis. Catheter ablation targeting ganglion plexi involved in vagal responses abolished AF in only 2 of 7 patients in 1 small series.\textsuperscript{120} Adrenergic stimulation, such as that during exercise, can also provoke AF in some patients.\textsuperscript{123}

### 2.2.3. Pathophysiological Mechanisms

#### 2.2.3.1. Atrial Tachycardia Remodeling

AF often progresses from paroxysmal to persistent over a variable period of time. Cardioresion of AF and subsequent maintenance of sinus rhythm are more likely to be successful when AF duration is ≤6 months.\textsuperscript{124} The progressive nature of AF is consistent with studies demonstrating that AF causes electrical and structural remodeling such that “AF begets AF.”\textsuperscript{125,126}

#### 2.2.3.2. Inflammation and Oxidative Stress

Inflammation (eg, associated with pericarditis and cardiac surgery) may be linked to AF and can be correlated with a rise in plasma concentrations of C-reactive protein.\textsuperscript{81} Inflammatory infiltrates consistent with myocarditis are often present in the atria of patients with AF and in animals with atrial dilation. Plasma concentrations of C-reactive protein and interleukin-6 are elevated in AF; increased C-reactive protein predicts the development of AF and relapse after cardioversion; and genetic variants in the interleukin-6 promoter region may influence the development of postoperative AF. In the canine pericarditis and atrial tachycardia remodeling model, prednisone suppresses AF susceptibility and reduces plasma concentrations of C-reactive protein.\textsuperscript{127}

Aging, environmental stress, inflammation, and C-reactive protein of the renin-angiotensin-aldosterone system can cause oxidative damage in the atrium. Oxidative changes are present in the atrial tissue of patients with AF and are associated with upregulation of genes involved in the production of reactive oxygen species. In human AF and a porcine model of atrial tachypacing, atrial superoxide production increased, with an apparent contribution of NAD(P)H oxidase.\textsuperscript{128} The antioxidant ascorbate attenuated electrical remodeling in the canine atrial tachypacing model and reduced postoperative AF in a small study in humans.\textsuperscript{129}

#### 2.2.3.3. The Renin-Angiotensin-Aldosterone System

Stimulation of the renin-angiotensin-aldosterone system promotes structural and likely electrophysiological effects in the atrium and ventricle that increase arrhythmia susceptibility.\textsuperscript{130–133} In addition to adverse hemodynamic effects, activation of multiple cell signaling cascades promotes increased intracellular calcium, hypertrophy, apoptosis, cytokine release and inflammation, oxidative stress, and production of growth-related factors that also stimulate fibrosis, as well as possible modulation of ion channel and gap-junction dynamics. Components of the renin-angiotensin-aldosterone system (including angiotensin II, angiotensin-converting enzyme [ACE], and aldosterone) are synthesized locally in the atrial myocardium and are increased during atrial tachypacing and AF. Variants in the ACE gene that increase angiotensin II plasma concentrations can elevate risk of AF, whereas selective cardiac overexpression of ACE causes atrial dilation, fibrosis, and increased susceptibility of AF. Therapy with these agents can reduce the occurrence of AF in patients with hypertension or left ventricular (LV) dysfunction but does not help prevent recurrence of AF in the absence of these other indications for these drugs (Section 6.2.1).

Aldosterone plays an important role in angiotensin II-mediated inflammation and fibrosis; in patients with primary hyperaldosteronism, the incidence of AF is increased. In experimental models of HF, spironolactone and eplerenone decreased atrial fibrosis and/or susceptibility of AF. Eplerenone therapy is associated with decreased AF in patients with HF.\textsuperscript{134}

#### 2.2.3.4. Risk Factors and Associated Heart Disease

Multiple clinical risk factors, electrocardiographic and echocardiographic features, and biochemical markers are associated with an increased risk of AF (Table 5). One epidemiological analysis found that 56% of the population-attributable risk of AF could be explained by ≥1 common risk factor.\textsuperscript{135} Thus, it may be possible to prevent some cases of AF through risk factor modification such as blood pressure control or weight loss.

Many potentially “reversible” causes of AF have been reported, including binge drinking, cardiothoracic and non-cardiac surgery, myocardial infarction (MI), pericarditis, myocarditis, hyperthyroidism, electrocution, pneumonia, and pulmonary embolism.\textsuperscript{10,49,136–138} AF that occurs in the setting of Wolff-Parkinson-White (WPW) syndrome, AV nodal reentrant tachycardia, or atrial ectopic tachycardia may resolve after catheter ablation for these arrhythmias.\textsuperscript{12} It is important to recognize that sparse data support the notion that patients with AF that occurs in the setting of 1 of these potentially “reversible” conditions are, in fact, cured of AF after effective treatment or elimination of the condition. Because long-term follow-up data are not available in these clinical scenarios and AF may recur, these patients should receive careful follow-up.

See Online Data Supplements 1 and 2 for additional data on electrophysiological and pathophysiological mechanisms.
3. Clinical Evaluation: Recommendation

3.1. Electrocardiographic documentation is recommended to establish the diagnosis of AF. (Level of Evidence: C)

The diagnosis of AF in a patient based on the patient’s clinical history and physical examination and is confirmed by ECG, ambulatory rhythm monitoring (eg, telemetry, Holter monitor, event recorders), implanted loop recorders, pacemakers or defibrillators, or, in rare cases, by electrophysiological study. The clinical evaluations, including additional studies that may be required, are summarized in Appendix 4.

3.1.1. Clinical History and Physical Examination

3.1.1.1. Clinical History

3.1.1.2. Physical Examination

3.1.2. Investigations

3.1.2.1. ECG

An ECG, or other electrocardiographic recording, is the essential tool for confirming AF. A chest radiograph should be done if pulmonary disease or HF is suspected and may also detect enlargement of the cardiac chambers. As part of the initial evaluation, all patients with AF should have a 2-dimensional transthoracic echocardiogram to detect underlying structural heart disease, assess cardiac function, and evaluate atrial size. Additional laboratory evaluation should include assessment of serum electrolytes and of thyroid, renal, and hepatic function, and a blood count.

3.1.2.2. Transesophageal Echocardiography (TEE)

TEE is the most sensitive and specific technique to detect LA thrombi as a potential source of systemic embolism in AF and can be used to guide the timing of cardioversion or catheter ablation procedures (Section 6.1.1). TEE can also identify features associated with an increased risk of LA thrombus formation, including reduced LAA flow velocity, spontaneous LA contrast, and aortic atheroma. In 5% to 15% of patients with AF, TEE before planned cardioversion revealed an LA or LAA thrombus.164,165

3.1.2.3. Additional Investigation of Selected Patients With AF: Transesophageal Echocardiography

Transesophageal Echocardiography (TEE): TEE is the most sensitive and specific technique to detect LA thrombi as a potential source of systemic embolism in AF and can be used to guide the timing of cardioversion or catheter ablation procedures (Section 6.1.1). TEE can also identify features associated with an increased risk of LA thrombus formation, including reduced LAA flow velocity, spontaneous LA contrast, and aortic atheroma. In 5% to 15% of patients with AF, TEE before planned cardioversion revealed an LA or LAA thrombus.164,165

3.1.2.4. Electrophysiological Study

An electrophysiological study can be helpful when initiation of AF is due to a supraventricular tachycardia, such as AV node reentrant tachycardia, AV reentry involving an accessory pathway, or ectopic atrial tachycardia. Ablation of the supraventricular tachycardia may prevent or reduce recurrences of AF. Electrophysiological study is often warranted in patients with a delta wave on the surface ECG indicating pre-excitation. Some patients with AF also have atrial flutter that may benefit from treatment with radiofrequency catheter ablation. AF associated with rapid ventricular rates and a wide-complex QRS (aberrant conduction) may sometimes be mislabeled as ventricular tachycardia, and an electrophysiological study can help establish the correct diagnosis.

3.1.2.5. Additional Investigation of Selected Patients With AF: Plasma Levels of B-Type Natriuretic Peptide or N-Terminal Pro-B-Type Natriuretic Peptide

Plasma levels of B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide may be elevated in patients with paroxysmal and persistent AF in the absence of clinical HF, and levels decrease rapidly after restoration of sinus rhythm. A sleep study may be useful if sleep apnea is suspected.166

3.1.3. Rhythm Monitoring and Stress Testing

Prolonged or frequent monitoring may be necessary to reveal episodes of asymptomatic AF. Electrocardiography, ambulatory rhythm monitoring (eg, telemetry, Holter monitor, and event recorders), and exercise testing can be useful to judge the adequacy of rate control. Patient-activated electrocardiographic event recorders can help assess the relation to symptoms, whereas auto-triggered event recorders may detect asymptomatic episodes.
These technologies may also provide valuable information to guide drug dosage for rate control or rhythm management.

4. Prevention of Thromboembolism

4.1. Risk-Based Antithrombotic Therapy: Recommendations

See Table 6 for a summary of recommendations from this section.

Class I

1. In patients with AF, antithrombotic therapy should be individualized based on shared decision making after discussion of the absolute risks and RRs of stroke and bleeding and the patient’s values and preferences. (Level of Evidence: C)

2. Selection of antithrombotic therapy should be based on the risk of thromboembolism irrespective of whether the AF pattern is paroxysmal, persistent, or permanent.167–170 (Level of Evidence: B)

3. In patients with nonvalvular AF, the CHA2DS2-VASc score is recommended for assessment of stroke risk.171–173 (Level of Evidence: B)

4. For patients with AF who have mechanical heart valves, warfarin is recommended, and the target INR intensity (2.0 to 3.0 or 2.5 to 3.5) should be based on the

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Table 6. Summary of Recommendations for Risk-Based Antithrombotic Therapy

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombotic therapy based on shared decision making, discussion of risks of stroke and bleeding, and patient’s preferences</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Selection of antithrombotic therapy based on risk of thromboembolism</td>
<td>I</td>
<td>B</td>
<td>167–170</td>
</tr>
<tr>
<td>CHA2DS2-VASc score recommended to assess stroke risk</td>
<td>I</td>
<td>B</td>
<td>171–173</td>
</tr>
<tr>
<td>Warfarin recommended for mechanical heart valves and target INR intensity based on type and location of prosthesis</td>
<td>I</td>
<td>B</td>
<td>174–176</td>
</tr>
<tr>
<td>With prior stroke, TIA, or CHA2DS2-VASc score ≥2, oral anticoagulants recommended. Options include:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>I</td>
<td>A</td>
<td>171–173</td>
</tr>
<tr>
<td>Dabigatran, rivaroxaban, or apixaban</td>
<td>I</td>
<td>B</td>
<td>177–179</td>
</tr>
<tr>
<td>With warfarin, determine INR at least weekly during initiation of therapy and monthly when stable</td>
<td>I</td>
<td>A</td>
<td>180–182</td>
</tr>
<tr>
<td>Direct thrombin or factor Xa inhibitor recommended if unable to maintain therapeutic INR</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Reevaluate the need for anticoagulation at periodic intervals</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Bridging therapy with UFH or LMWH recommended with a mechanical heart valve if warfarin is interrupted. Bridging therapy should balance risks of stroke and bleeding</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>For patients without mechanical heart valves, bridging therapy decisions should balance stroke and bleeding risks against duration of time patient will not be anticoagulated</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Evaluate renal function before initiation of direct thrombin or factor Xa inhibitors, and reevaluate when clinically indicated and at least annually</td>
<td>I</td>
<td>B</td>
<td>183–185</td>
</tr>
<tr>
<td>For atrial flutter, antithrombotic therapy is recommended as for AF</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>With nonvalvular AF and CHA2DS2-VASc score of 0, it is reasonable to omit antithrombotic therapy</td>
<td>I1a</td>
<td>B</td>
<td>183, 184</td>
</tr>
<tr>
<td>With CHA2DS2-VASc score ≥2 and end-stage CKD (CrCl &lt;15 mL/min) or on hemodialysis, it is reasonable to prescribe warfarin for oral anticoagulation</td>
<td>I1a</td>
<td>B</td>
<td>185</td>
</tr>
<tr>
<td>With nonvalvular AF and a CHA2DS2-VASc score of 1, no antithrombotic therapy or treatment with oral anticoagulant or aspirin may be considered</td>
<td>I1b</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>With moderate-to-severe CKD and CHA2DS2-VASc scores ≥2, reduced doses of direct thrombin or factor Xa inhibitors may be considered</td>
<td>I1b</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>For PCI, BMS may be considered to minimize duration of DAPT</td>
<td>I1b</td>
<td>B</td>
<td>186</td>
</tr>
<tr>
<td>After coronary revascularization in patients with CHA2DS2-VASc score ≥2, it may be reasonable to use clopidogrel concurrently with oral anticoagulants but without aspirin</td>
<td>I1b</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Direct thrombin dabigatran and factor Xa inhibitor rivaroxaban are not recommended in patients with AF and end-stage CKD or on dialysis because of a lack of evidence from clinical trials regarding the balance of risks and benefits</td>
<td>I1b</td>
<td>B</td>
<td>177–179, 187–189</td>
</tr>
<tr>
<td>Direct thrombin inhibitor dabigatran should not be used with a mechanical heart valve</td>
<td>I1b</td>
<td>C</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*See the 2011 PCI guideline for type of stent and duration of DAPT recommendations.12

AF indicates atrial fibrillation; BMS, bare-metal stent; CHA2DS2-VASc, Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, Prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65 to 74 years, Sex category; CKD, chronic kidney disease; COR, Class of Recommendation; CrCl, creatinine clearance; DAPT, dual antiplatelet therapy; INR, international normalized ratio; LMWH, low-molecular-weight heparin; LOE, Level of Evidence; N/A, not applicable; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; and UFH, unfractionated heparin.

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*CHA2DS2-VASc indicates Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, Prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65 to 74 years, Sex category.
type and location of the prosthesis.174–176 (Level of Evidence: B)

5. For patients with nonvalvular AF with prior stroke, transient ischemic attack (TIA), or a CHA2DS2-VASc score of 2 or greater, oral anticoagulants are recommended. Options include warfarin (INR 2.0 to 3.0)177–179 (Level of Evidence: A), dabigatran187 (Level of Evidence: B), rivaroxaban188 (Level of Evidence: B), or apixaban.189 (Level of Evidence: B)

6. Among patients treated with warfarin, the INR should be determined at least weekly during initiation of antithrombotic therapy and at least monthly when anticoagulation (INR in range) is stable.190–192 (Level of Evidence: A)

7. For patients with nonvalvular AF unable to maintain a therapeutic INR level with warfarin, use of a direct thrombin or factor Xa inhibitor (dabigatran, rivaroxaban, or apixaban) is recommended. (Level of Evidence: C)

8. Reevaluation of the need for and choice of antithrombotic therapy at periodic intervals is recommended to reassess stroke and bleeding risks. (Level of Evidence: C)

9. Bridging therapy with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) is recommended for patients with AF and a mechanical heart valve undergoing procedures that require interruption of warfarin. Decisions on bridging therapy should balance the risks of stroke and bleeding. (Level of Evidence: C)

10. For patients with AF without mechanical heart valves who require interruption of warfarin or new anticoagulants for procedures, decisions about bridging therapy (LMWH or UFH) should balance the risks of stroke and bleeding and the duration of time a patient will not be anticoagulated. (Level of Evidence: C)

11. Renal function should be evaluated before initiation of direct thrombin or factor Xa inhibitors and should be reevaluated when clinically indicated and at least annually.193–195 (Level of Evidence: B)

12. For patients with atrial flutter, antithrombotic therapy is recommended according to the same risk profile used for AF. (Level of Evidence: C)

Class IIa

1. For patients with nonvalvular AF and a CHA2DS2-VASc score of 0, it is reasonable to omit antithrombotic therapy.183,184 (Level of Evidence: B)

2. For patients with nonvalvular AF with a CHA2DS2-VASc score of 2 or greater and who have end-stage chronic kidney disease (CKD) (creatinine clearance [CrCl] <15 ml/min) or are on hemodialysis, it is reasonable to prescribe warfarin (INR 2.0 to 3.0) for oral anticoagulation.185 (Level of Evidence: B)

Class IIb

1. For patients with nonvalvular AF and a CHA2DS2-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered. (Level of Evidence: C)

2. For patients with nonvalvular AF and moderate-to-severe CKD with CHA2DS2-VASc scores of 2 or greater, treatment with reduced doses of direct thrombin or factor Xa inhibitors may be considered (eg, dabigatran, rivaroxaban, or apixaban), but safety and efficacy have not been established. (Level of Evidence: C)

3. In patients with AF undergoing percutaneous coronary intervention,† bare-metal stents may be considered to minimize the required duration of dual antiplatelet therapy. Anticoagulation may be interrupted at the time of the procedure to reduce the risk of bleeding at the site of peripheral arterial puncture. (Level of Evidence: C)

4. Following coronary revascularization (percutaneous or surgical) in patients with AF and a CHA2DS2-VASc score of 2 or greater, it may be reasonable to use clopidogrel (75 mg once daily) concurrently with oral anticoagulants but without aspirin.190 (Level of Evidence: B)

Class III: No Benefit

1. The direct thrombin inhibitor dabigatran and the factor Xa inhibitor rivaroxaban are not recommended in patients with AF and end-stage CKD or on dialysis because of the lack of evidence from clinical trials regarding the balance of risks and benefits.177–179,187–189 (Level of Evidence: C)

Class III: Harm

1. The direct thrombin inhibitor dabigatran should not be used in patients with AF and a mechanical heart valve.190 (Level of Evidence: B)

4.1.1. Selecting an Antithrombotic Regimen—Balancing Risks and Benefits

AF, whether paroxysmal, persistent, or permanent and whether symptomatic or silent, significantly increases the risk of thromboembolic ischemic stroke.191–194 Nonvalvular AF increases the risk of stroke 20 times195 over that of patients in sinus rhythm. Thromboembolism occurring with AF is associated with a greater risk of recurrent stroke, more severe disability, and mortality.196,197 Silent AF is also associated with ischemic stroke.191–193 The appropriate use of antithrombotic therapy and the control of other risk factors, including hypertension and hypercholesterolemia, substantially reduce stroke risk.

Antithrombotic agents routinely used for the prevention of thromboembolism in patients with nonvalvular AF include anticoagulant drugs (UFH and LMWH, warfarin, and direct thrombin and factor Xa inhibitors) and antiplatelet drugs (aspirin and clopidogrel). Although anticoagulants have been effective in reducing ischemic stroke in multiple randomized controlled trials (RCTs), their use is associated with an increased risk of bleeding, ranging from minor bleeding to fatal intracranial or extracranial hemorrhage. Platelet inhibitors (alone or in combination) are less effective than warfarin, are better tolerated by some patients, and are associated with a lower risk of intracerebral hemorrhage. However, they have similar overall rates of major bleeding in

†See the 2011 percutaneous coronary intervention guideline for type of stent and duration of dual antiplatelet therapy recommendations.12
Table 7. Comparison of the CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-VASc Risk Stratification Scores for Subjects With Nonvalvular AF

<table>
<thead>
<tr>
<th>CHADS\textsubscript{2}</th>
<th>CHA\textsubscript{2}DS\textsubscript{2}-VASc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>Adjusted Stroke Rate (% per y)</td>
</tr>
<tr>
<td>Congestive HF</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 y</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
</tr>
<tr>
<td>Maximum score</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHA\textsubscript{2}DS\textsubscript{2}-VASc</th>
<th>Adjusted Stroke Rate (% per y)</th>
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<tbody>
<tr>
<td>Congestive HF</td>
<td>1</td>
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</tr>
<tr>
<td>Age ≥75 y</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Maximum score</td>
<td>9</td>
</tr>
</tbody>
</table>

*These adjusted stroke rates are based on data for hospitalized patients with AF and were published in 2001.201 Because stroke rates are decreasing, actual stroke rates in contemporary nonhospitalized cohorts might vary from these estimates.

†Adjusted stroke rate scores are based on data from Lip and colleagues.115,151,152,202,203 Actual rates of stroke in contemporary cohorts might vary from these estimates.

AF indicates atrial fibrillation; CHADS\textsubscript{2}, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Prior Stroke or TIA or Thromboembolism (doubled); CHA\textsubscript{2}DS\textsubscript{2}-VASc, Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, Prior Stroke or TIA or Thromboembolism (doubled), Vascular disease, Age 65 to 74 years, Sex category; HF, heart failure; MI, myocardial infarction; PAD, peripheral artery disease; TE, thromboembolism; and TIA, transient ischemic attack.201,203

some studies.184,199,197–198 Careful consideration is required to balance the benefits and risks of bleeding in each individual patient.

4.1.1.1. Risk Stratification Schemes (CHADS\textsubscript{2}, CHA\textsubscript{2}DS\textsubscript{2}-VASc, and HAS-BLED)

One meta-analysis has stratified ischemic stroke risk among patients with nonvalvular AF using the following point scoring systems: AF Investigators200; CHADS\textsubscript{2}, (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Prior Stroke or TIA or Thromboembolism [doubled]); CHA\textsubscript{2}DS\textsubscript{2}-VASc (Congestive heart failure, Hypertension, Age ≥75 years [doubled], Diabetes mellitus, Prior Stroke or TIA or thromboembolism [doubled], Vascular disease, Age 65 to 74 years, Sex category) (Table 7).

The CHADS\textsubscript{2} score has been validated in multiple nonvalvular AF cohorts, with findings indicating an increase in stroke rate of approximately 2.0% for each 1-point increase in CHADS\textsubscript{2} score (from 1.9% with a score of 0 to 18.2% with a score of 6).201,204 A limitation of the CHADS\textsubscript{2} score is that a score of 1 is considered an “intermediate” risk and those at lowest risk may not be well identified. Furthermore, patients whose only risk factor is a CHADS\textsubscript{2} score of 2 due to prior stroke may have a greater risk than a score of 2 would indicate.

When compared with the CHADS\textsubscript{2} score, the CHA\textsubscript{2}DS\textsubscript{2}-VASc score15 for nonvalvular AF has a broader score range (0 to 9) and includes a larger number of risk factors (female sex, 65 to 74 years of age, and vascular disease).202,203 In this scheme, women cannot achieve a CHA\textsubscript{2}DS\textsubscript{2}-VASc score of 0. In a nationwide Danish registry from 1997 to 2008, the CHA\textsubscript{2}DS\textsubscript{2}-VASc index better discriminated stroke risk among subjects with a baseline CHADS\textsubscript{2} score of 0 to 1 with an improved predictive ability.172 In another study among patients with AF, the CHA\textsubscript{2}DS\textsubscript{2}-VASc score more clearly defined anticoagulation recommendations than the CHADS\textsubscript{2} score did.173 More patients, particularly older women, were redistributed from the low- to high-risk categories. In a study of Swedish patients with nonvalvular AF, women again had a moderately increased stroke risk compared with men; however, women younger than 65 years of age and without other AF risk factors had a low risk for stroke, and it was concluded that anticoagulant treatment was not required.205 However, the continued evolution of AF-related thromboembolic risk evaluation is needed.

Bleeding risk scores to quantify hemorrhage risk include HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly), RIETE (Computerized Registry of Patients With Venous Thromboembolism), and ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation).206–208 Although these scores may be helpful in defining patients at elevated bleeding risk, their clinical utility is insufficient for use as evidence for the recommendations in this guideline. The RIETE score was developed from a large venous thromboembolism cohort and includes 2 points for recent bleeding, 1.5 points for abnormal creatinine levels or anemia, and 1 point for each of the following: >75 years of age, cancer, or pulmonary embolism at baseline. The ATRIA score assigns points to the following variables: anemia, 3; severe renal disease, 3; >75 years of age, 2; prior hemorrhage, 1; and hypertension, 1.

HAS-BLED14,30 is a score based on the presence of hypertension (systolic blood pressure >160 mm Hg), abnormal liver or renal function, history of stroke or bleeding, labile INRs, elderly age (≥65 years), use of drugs that promote bleeding, or alcohol excess.209 A score ≥3 indicates potentially “high risk” for bleeding and may require closer observation of a patient for adverse risks, closer monitoring of INRs, or differential dose selections of oral anticoagulants or aspirin. HAS-BLED is better at discriminating risk than the HEMORR2HAGES or ATRIA scoring systems are, but all 3 scores had C indexes <0.70 in the receiver operating curves, indicating only modest performance and poor predictive accuracy.210
4.2. Antithrombotic Options

Antithrombotic medications prevent strokes and systemic emboli among patients with AF in part by reducing the formation of platelet-rich or thrombotic clots in the LA or LAA, from which the clots can embolize through the systemic circulation to the brain or other sites. Stroke prevention trials (Figure 3) compared warfarin or aspirin with placebo and compared aspirin with warfarin or clopidogrel and aspirin. Warfarin was also compared with dual antiplatelet agents (clopidogrel and aspirin). Trials have also compared direct thrombin inhibitors and factor Xa inhibitors with warfarin and, in 1 case, with aspirin. Both primary and secondary stroke prevention have been evaluated. The selection of an antithrombotic agent should be based on shared decision making that takes into account risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including time in the INR therapeutic range if the patient has been on warfarin, irrespective of whether the AF pattern is paroxysmal, persistent, or permanent.

Meta-analyses have summarized the effect of antithrombotic therapies for stroke prevention in nonvalvular AF. The largest meta-analysis identified 29 RCTs from 1996 to 2007 that tested antithrombotic therapies of >12 weeks’ duration among 28,044 patients. Nine trials were double-blind designs with a mean follow-up of 1.5 years per patient. The average age of the subjects was 71 years, and 35% of the subjects were women. Among 12 of the trials, 3003 subjects were randomized to placebo or control, with an average stroke rate of 4.1% per year among the primary prevention studies and 13% per year among those with prior stroke or TIA.

4.2.1. Antiplatelet Agents

No studies, with the exception of the SPAF (Stroke Prevention in Atrial Fibrillation)-1 trial, show benefit for aspirin alone in preventing stroke among patients with AF. Antiplatelet
therapy was compared with placebo or no treatment in 8 trials with a total of 4876 subjects. Among these 8 trials compared different doses of aspirin ranging from 25 mg twice a day to 1300 mg once a day. For primary prevention, aspirin was associated with a 19% reduction (95% CI: −1% to 35%) in stroke incidence with an absolute risk reduction of 0.8% per year (number needed to treat: 125). The 95% CI encompassed 0, which includes the possibility that aspirin has no real effect on stroke reduction. For secondary prevention among those with TIA or strokes, aspirin was associated with an absolute risk reduction of 2.5% per year and a corresponding number needed to treat of 40. It is important to recognize that the 19% reduction in stroke incidence observed in this meta-analysis was driven by positive results from only 1 of these RCTs—the SPAF-1 trial. In this trial, aspirin was prescribed at 325 mg once daily, and the impact of aspirin was very heterogeneous between groups. Aspirin was ineffective in preventing strokes in those >75 years of age and did not prevent severe strokes. Moreover, aspirin has not been studied in a population at low risk of AF.

Clopidogrel plus aspirin was evaluated for stroke prevention in the ACTIVE (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events)-W trial. This trial was terminated early (before planned follow-up was completed) on the recommendation of the Data Safety and Monitoring Board because the combination of antiplatelet agents, clopidogrel (75 mg once daily) plus aspirin (75 mg to 100 mg once daily), proved inferior to warfarin (target INR 2.0 to 3.0) in patients with a mean CHADS 2 score of 2. Monitoring Board because the combination of antithrombotic agents was associated with significant reductions in all strokes, ischemic stroke, and the combined endpoint of stroke, MI, or vascular death. With an ischemic stroke rate of 4% per year in the control group, the absolute risk reduction was about 2.6% per year for those with no prior stroke or TIA, or about 25 ischemic strokes prevented in 1 year per 1000 subjects treated with warfarin. The RR reductions were consistent across the trials. Intracranial hemorrhage was not significantly increased among the subjects randomized to warfarin, but the patient numbers were small and the CI wide.

For nonvalvular AF, 2 separate Cochrane Collaboration reviews evaluated the efficacy and safety of oral anticoagulants compared with antiplatelet agents. One review included those with no history of stroke or TIA and the other those with a history of stroke or TIA. Among 9598 subjects with AF, the majority (90%) of whom had no prior stroke or TIA, oral anticoagulants were associated with a significant reduction in all strokes and ischemic strokes compared with antiplatelet agents. Assuming an absolute stroke risk of 4% per year with antiplatelet agents, approximately 19 strokes could be prevented per year for every 1000 patients with AF treated with oral anticoagulants. The risk of intracranial hemorrhage was significantly increased among those treated with oral anticoagulants, but major extracranial hemorrhages were not significantly different. After excluding the ACTIVE-W trial, which used clopidogrel and aspirin as the antiplatelet agent comparison, oral anticoagulants were significantly associated with an increased risk of bleeding (OR: 1.90; 95% CI: 1.07 to 3.39). Similarly, among patients with a prior history of stroke or TIA, oral anticoagulants compared with antiplatelet agents were associated with significant reductions in all major vascular events and recurrent stroke. Bleeding risks—including for any intracranial bleeds and major extracranial bleeds—were increased with oral anticoagulants.

The BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged) study also evaluated the efficacy of warfarin among
higher-risk elderly subjects >75 years of age. BAFTA was designed to compare warfarin with aspirin for the prevention of fatal and nonfatal stroke, intracranial hemorrhage, and other clinically significant arterial embolism in a primary care population of patients ≥75 years of age who had AF. Warfarin was superior in preventing stroke or systemic embolism without a significant increase in bleeding risk. The annual risk of extracranial hemorrhage was 1.4% in the warfarin group and 1.6% in the aspirin group.

Despite strong evidence for the efficacy of warfarin, several limitations have led to it being underused. The narrow therapeutic window and increased risk of bleeding, including in the brain, have hindered broader use, especially among the elderly. Interactions with other drugs, effects of alterations in diet, and the requirement for close monitoring with frequent blood tests have also made the dosing of warfarin challenging for clinicians and patients. Even in well-conducted clinical trials, the time in therapeutic range (TTR) of those taking warfarin was reported as 55% to 66%, whereas in some community settings, TTR has been reported as approximately 50%. Despite underutilization of warfarin among eligible patients due to a variety of factors, a meta-analysis of contemporary studies found risk of stroke or systemic embolism estimated to be at 1.66% per year for warfarin in patients with AF (Figure 5).

See Online Data Supplements 4 and 5 for additional data on warfarin and antiplatelet therapy.

4.2.2.2. New Target-specific Oral Anticoagulants

**Dabigatran** is the first new oral anticoagulant approved by the US Food and Drug Administration (FDA) to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF and is a direct thrombin inhibitor. Its site of action in the coagulation cascade is shown in Figure 4. Dabigatran was compared with warfarin in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial, which was an open-label randomized comparison of dabigatran (110 mg or 150 mg twice daily in a blinded fashion) with adjusted-dose warfarin in 18,113 patients over a median follow-up period of 2 years. The mean CHADS2 score was 2.1 and the primary outcome was stroke (of any type) and systemic embolism, with any major hemorrhage being the primary safety outcome. Half of the patients were naïve to oral anticoagulants. The mean TTR for those randomized to warfarin was 64%. The primary outcome was assessed first for noninferiority followed by superiority.
For the primary outcomes, dabigatran 150 mg twice daily was superior to warfarin, and dabigatran 110 mg twice daily was noninferior to warfarin. When dabigatran was compared with warfarin, the risk of hemorrhagic strokes was also significantly lower (74% lower) with both the 110 mg and 150 mg doses. Major bleeding was significantly decreased with the 110 mg dose but not with the 150 mg dose. Both doses had lower rates of intracranial bleeding and life-threatening bleeding, whereas gastrointestinal bleeding was higher in the 150 mg dose (1.6% versus 1.0% per year) group. Dyspepsia was more frequent for both doses. For secondary prevention of stroke, the results were similar to the primary analysis but statistically weaker because of smaller sample size.225

Dabigatran is renally excreted, and patients with a CrCl of <30 mL/min were excluded from the RE-LY trial. CKD is associated with increased bleeding risk during both dabigatran therapy and warfarin therapy.226 The FDA approved the higher dose of 150 mg twice daily but not the lower dose of 110 mg twice daily. The FDA also approved a dose of 75 mg twice daily for those with low CrCl (15 mL/min to 30 mL/min) based on pharmacological modeling, but that dose was never clinically studied.

The RE-LY trial included subjects distributed equally across stroke risk strata (CHADS$_2$ score 0 to 1 in 31.8% of subjects, 2 in 35.6%, and >2 in 32.5%). For the primary efficacy endpoint and intracranial bleeding, there was similar efficacy across the range of CHADS$_2$ scores.177 In patients <75 years of age, both doses of dabigatran were associated with less intracranial and extracranial bleeding than warfarin; in patients ≥75 years of age, both doses reduced intracranial bleeding. However, extracranial bleeding was similar or more frequent compared with warfarin.227 Higher CHADS$_2$ scores were associated with increased risks for stroke or systemic embolism, bleeding, and death in patients with AF receiving oral anticoagulants.228

The benefits of dabigatran compared with warfarin in terms of efficacy and safety were similar in patient groups with paroxysmal, persistent, and permanent AF.169 An FDA postmarket analysis of gastrointestinal and intracranial bleeding of dabigatran compared with warfarin indicates that bleeding rates do not appear to be higher for dabigatran.229

A post hoc analysis of 1989 electrical cardioversions found a very low rate of stroke within 30 days after the procedure (0.6% for warfarin, 0.3% for dabigatran 150 mg twice daily, and 0.8% for dabigatran 110 mg twice daily).230 Most subjects were treated with their assigned medication for ≥3 weeks before cardioversion. TEE was performed in 25% of subjects. There was no significant difference in the incidence of LAA thrombus (1.1% for warfarin; and for dabigatran, 1.2% for 150 mg twice daily and 1.8% for 110 mg twice daily).230 In the RE-LY trial, there appeared to be an imbalance of MIs: 0.8%, 0.8%, and 0.6% per year for patients randomized to dabigatran 150 mg twice daily, dabigatran 110 mg twice daily, or warfarin, respectively (P=0.09).72 Absolute events were low in a population in which 31% of randomized patients had objective evidence of CAD. A meta-analysis of a dabigatran RCT found a statistically significant increase in risk of MI and acute coronary syndromes (ACSs) in patients randomized to dabigatran.231 Interpretation of these results should be made with caution, given the multiple limitations of this type of analysis, which include the use of different controls and different patient populations.

**Rivaroxaban** is the second new oral anticoagulant approved by the FDA for reduction of risk of stroke and systemic embolism in patients with nonvalvular AF and is a direct factor Xa inhibitor (Figure 4). It should be administered as a single daily
dose with the evening meal to ensure adequate absorption. It is predominantly excreted by the kidneys. The evidence leading to approval was based on the RCT ROCKET AF (Rivaroxaban Versus Warfarin in Nonvalvular Atrial Fibrillation), which compared rivaroxaban (20 mg once daily, 15 mg once daily if CrCl was 30 mL/min to 49 mL/min) with warfarin among 14,264 patients. ROCKET AF differed from RE-LY in that it selected higher-risk patients with AF (≥2 risk factors for stroke compared with 1 risk factor). Patients in ROCKET AF were older and had a greater mean CHADS2 score of 3.47. Similar to other AF trials, the primary outcome was any stroke or systemic embolism, and the primary hypothesis was noninferiority. Although the primary analysis was prespecified as a per-protocol analysis, the intention-to-treat analysis was also presented. The main safety outcome was clinically relevant bleeding events. This was a double-blind trial, and the patients receiving warfarin had a lower mean TTR of 55%. The trial demonstrated noninferiority for rivaroxaban compared with warfarin; however, in the intention-to-treat analysis, superiority was not achieved (P=0.12). Major bleeding was similar for rivaroxaban and warfarin, but less fatal bleeding and less intracranial hemorrhage were found for rivaroxaban. At the end of the trial, patients transitioning to open-label therapy had more strokes with rivaroxaban than with warfarin. However, the risk of stroke or noncentral nervous system embolism after elective temporary discontinuation of rivaroxaban compared with warfarin in the ROCKET AF trial did not differ significantly in a post hoc analysis. The risk of stroke was similar for patients assigned to rivaroxaban and warfarin. In ROCKET AF, a decline in renal function was an independent predictor of stroke risk.

Apixaban is the third new oral anticoagulant approved by the FDA for reduction of risk of stroke and systemic embolism with nonvalvular AF and is another direct factor Xa inhibitor (Figure 4). It is predominantly eliminated hepatically and is highly protein bound. It has been investigated in 2 clinical trials. In the ARISTOTLE (Apixaban Versus Warfarin in Patients With Atrial Fibrillation) trial, apixaban (5 mg twice daily) was compared with warfarin in a double-blind RCT of 18,201 patients with AF and a mean CHADS2 score of 2.1. Apixaban 2.5 mg twice daily was used among patients with ≥2 of the following conditions: ≥80 years of age, weight ≤60 kg, or a serum creatinine level ≥1.5 mg/dL. As with the other new anticoagulant trials, the primary outcome was any stroke or systemic embolism and the primary safety outcome was major bleeding. Patients were followed for a mean of 1.8 years, and the mean age was 70 years. For patients treated with warfarin, the TTR was 62%. Apixaban was significantly better than warfarin, with fewer overall strokes (both ischemic and hemorrhagic), systemic emboli, and major bleeding events. Patients treated with apixaban had significantly fewer intracranial bleeds, but gastrointestinal bleeding complications were similar between the 2 study groups. Patients treated with apixaban had fewer deaths than those on warfarin. In ARISTOTLE, the benefit of apixaban was independent of type of AF, risk profile, CHADS2 or CHA2DS2-VASc score, and whether there was a prior stroke.

Apixaban was also compared with aspirin in the AVERROES study, a double-blind study of 5,599 patients deemed unsuitable for warfarin therapy. The mean CHADS2 score was 2, and 36% of the subjects had a CHADS2 score of 0 to 1. After a mean follow-up of 1.1 years, the study was prematurely terminated due to the superiority of apixaban compared with aspirin for preventing the occurrence of any stroke or systemic embolism, whereas bleeding risk between the 2 treatments was similar.

Patients with severe and end-stage CKD (serum creatinine >2.5 mg/dL or CrCl <25 mL/min) were excluded from the ARISTOTLE and AVERROES trials. On the basis of the new pharmacokinetic profiles in a limited data set, prescribing recommendations for apixaban were revised for use in patients with end-stage CKD who were maintained on stable hemodialysis with the recommended dose of 5 mg twice daily with a reduction in dose to 2.5 mg twice daily for either age ≥80 years or body weight ≤60 kg. For patients with severe or end-stage CKD not on dialysis, a dose recommendation was not provided. There are no published data for the use of apixaban in these clinical settings.

Other factor Xa inhibitors, including edoxaban and betrixaban, are under evaluation but not yet approved by the FDA.

4.2.2.3. Considerations in Selecting Anticoagulants

Selection of agents for antithrombotic therapy depends on a large number of variables, including clinical factors, clinician and patient preference, and, in some circumstances, cost. The new agents are currently considerably more expensive than warfarin. However, dietary limitations and the need for repeated INR testing are eliminated with the new agents. If patients are stable, their condition is easily controlled, and they are satisfied with warfarin therapy, it is not necessary to change to a new agent. However, it is important to discuss this option with patients who are candidates for the new agents.

All 3 new oral anticoagulants represent important advances over warfarin because they have more predictable pharmacological profiles, fewer drug–drug interactions, an absence of major dietary effects, and less risk of intracranial bleeding than warfarin. They have rapid onset and offset of action so that bridging with parenteral anticoagulant therapy is not needed during initiation, and bridging may not be needed in patients on chronic therapy requiring brief interruption of anticoagulation for invasive procedures. However, strict compliance with these new oral anticoagulants is critical. Missing even 1 dose could result in a period without protection from thromboembolism. As a result, the FDA issued black box warnings that discontinuation of these new agents can increase the risk of thromboembolism and that coverage with another anticoagulant may be needed. In addition, reversal agents, while in development, are not available, although the short half-lives lessen the need for an antidote. Although dose adjustments may be warranted for those with CKD or body weight extremes, these new agents do not require regular monitoring of INR or activated partial thromboplastin time.

Importantly, patients with mechanical heart valves or hemon-dynamically significant mitral stenosis were excluded from all 3 major trials (RE-LY, ROCKET AF, and ARISTOTLE), therefore, these patients should be managed with warfarin. Patients with aortic stenosis or aortic insufficiency who, in the estimation of the local RCT principal investigator, would not need a surgical procedure before the conclusion of the trial were included. The RE-ALIGN (Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran...
Table 8. Dose Selection of Oral Anticoagulant Options for Patients With Nonvalvular AF and CKD (Based on Prescribing Information for the United States)*

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>Warfarin*238</th>
<th>Dabigatran†177</th>
<th>Rivaroxaban†178</th>
<th>Apixaban†179</th>
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</thead>
<tbody>
<tr>
<td>Normal/mild impairment</td>
<td>Dose adjusted for INR 2.0–3.0 (CrCl &gt;30 mL/min)</td>
<td>150 mg BID</td>
<td>20 mg QD with the evening meal (CrCl &gt;50 mL/min)</td>
<td>5.0 or 2.5 mg BID‡</td>
</tr>
<tr>
<td>Moderate impairment</td>
<td>Dose adjusted for INR 2.0–3.0 (CrCl &gt;30 mL/min)</td>
<td>150 mg BID</td>
<td>15 mg QD with the evening meal (CrCl 30–50 mL/min)</td>
<td>5.0 or 2.5 mg BID‡</td>
</tr>
<tr>
<td>Severe impairment</td>
<td>Dose adjusted for INR 2.0–3.0 (CrCl &lt;15 mL/min)</td>
<td>75 mg BID</td>
<td>15 mg QD with the evening meal (CrCl 15–30 mL/min)</td>
<td>No recommendation.</td>
</tr>
<tr>
<td>End-stage CKD not on dialysis</td>
<td>Dose adjusted for INR 2.0–3.0 (CrCl &lt;15 mL/min)</td>
<td>Not recommended‡</td>
<td>Not recommended‡</td>
<td>No recommendation.</td>
</tr>
<tr>
<td>End-stage CKD on dialysis</td>
<td>Dose adjusted for INR 2.0–3.0 (CrCl &lt;15 mL/min)</td>
<td>Not recommended‡</td>
<td>Not recommended‡</td>
<td>No recommendation.</td>
</tr>
</tbody>
</table>

*Renal function should be evaluated before initiation of direct thrombin or factor Xa inhibitors and should be reevaluated when clinically indicated and at least annually. CrCl should be measured using the Cockcroft-Gault method.
†The concomitant use of P-glycoprotein inducers or inhibitors with dabigatran or the concomitant use of dual P-glycoprotein and strong CYP3A4 inducers or inhibitors with either rivaroxaban or apixaban, particularly in the setting of CKD, may require dosing adjustment or avoidance of concomitant drug use (see the FDA drug label at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202155s002lbl.pdf, Section 8.6).
‡Use apixaban 2.5 mg BID if any 2 patient characteristics are present: Cr ≥1.5 mg/dL, ≥80 y of age, body weight ≤60 kg.179 Apixaban is not recommended in patients with severe hepatic impairment.
§Dose-adjusted warfarin has been used, but observational data on safety and efficacy are conflicting.
¶No published studies support a dose for this level of renal function.
#In patients with end-stage CKD on stable hemodialysis, prescribing information indicates the use of apixaban 5 mg BID with dose reduction to 2.5 mg BID if the patient is ≥80 y of age or body weight is ≤60 kg.
 AF indicates atrial fibrillation; BID, twice daily; CKD, chronic kidney disease; Cr, creatinine; CrCl, creatinine clearance; FDA, Food and Drug Administration; INR, international normalized ratio; and QD, once daily.

Exetilate (HYPHEN BioMed, Neuville-sur-Oise, France) is approved in France for the treatment of nonvalvular AF and is available for patients with moderate renal impairment (CrCl 30–50 mL/min). However, the presence of atrial flutter may possibly increase the level of exetilate due to its long half-life. Exetilate is also contraindicated in patients with severe renal impairment (CrCl <15 mL/min) and patients with end-stage CKD due to the risk of life-threatening bleeding.

The price of an effective anticoagulant is the risk of bleeding, which, if extracranial, is usually not life-threatening. Although INR and activated partial thromboplastin time increase with dabigatran, this is not in a linear fashion and cannot be used to monitor the level of anticoagulation. The Hemoclot (HYPHEN BioMed, Neuville-sur-Oise, France) thrombin clotting time is a more accurate measure of anticoagulation levels, but the test is not approved in the United States and is not widely available elsewhere.239 If bleeding or overdose occurs, the anticoagulant agent should be discontinued. The use of activated charcoal to reduce absorption may be considered. Dabigatran is dialyzable, but apixaban and rivaroxaban are not, and both are highly plasma protein bound.

Dabigatran, rivaroxaban, and apixaban are substrates for the efflux transporter P-glycoprotein. P-glycoprotein inhibitors, such as ketoconazole, verapamil, amiodarone, dorne-darone, quinidine, and clarithromycin, may increase plasma concentrations. In addition, P-glycoprotein inducers (such as phenytoin, carbamazepine, rifampin, and St. John’s wort) can decrease levels of these drugs to subtherapeutic blood levels, and coadministration should be avoided. Absorbed dabigatran etexilate is “pumped” back into the intestinal tract. Dabigatran also can cause dyspepsia. Coprescription with a proton pump inhibitor can mildly reduce dabigatran peak concentrations; however, dose adjustment is not warranted.239 Rivaroxaban and apixaban are contraindicated with drugs that are combined P-glycoprotein and strong P450 3A4 (CYP3A4) inducers.

Although the new oral anticoagulant trials were similar in design and inclusion/exclusion criteria, it is difficult to make comparisons between the agents to judge differential efficacy in the absence of direct comparisons.

4.2.2.4. Silent AF and Stroke

Clinically unrecognized and asymptomatic AF is a potentially important cause of stroke, supporting efforts for early detection of AF in at-risk individuals. Episodes of asymptomatic
AF are potentially detectable from implantable arrhythmia management devices (pacemakers or defibrillators) that have an atrial lead and can be programmed to record the number, duration, and frequency of atrial rates that exceed a certain threshold and, in some cases, also provide stored electrograms for analysis. These devices typically report “atrial high-rate events.” Whether the high-rate event is AF, atrial flutter, or an atrial tachycardia is not necessarily discernible. Patients receiving arrhythmia management devices often have risk factors for AF. Atrial high-rate episodes have been observed in 10% to 28% of patients who have no prior history of AF.\(^1\)!\(^{61,191}\)

The ASSERT (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial) trial enrolled 2580 patients ≥65 years of age with hypertension and no history of AF in whom a pacemaker or defibrillator was recently implanted. During the first 3 months, 10% of subjects had atrial high-rate episodes of >190 bpm for >6 minutes.\(^61\) These high-rate episodes were associated with a >5-fold increase in subsequent diagnosis of atrial arrhythmia on ECG and a 1.60% per year rate of stroke or systemic embolism compared with a 0.69% per year rate for those without high-rate episodes during the first 3 months. In a subgroup analysis of the MOST (Mode Selection Trial in Sinus Node Dysfunction) trial, patients with atrial high-rate episodes (rate >220 bpm for >10 beats detected by a pacemaker) were more than 2 times as likely to die or have a stroke and 6 times as likely to be subsequently diagnosed with AF as similar patients without atrial high-rate events.\(^193\)

In a prospective study of 2486 patients receiving arrhythmia management devices who had ≥1 AF risk factor for stroke—20% of whom had a history of AF—patients with atrial tachycardia/AF burden (defined as the longest total atrial tachycardia/AF duration on any given day during the prior 30-day period) >5.5 hours had a thromboembolism rate of 2.4% per year compared with 1.1% per year for those with less or no atrial tachycardia/AF burden.\(^194\) In a study of 560 patients with HF, the recording of atrial high-rate episodes lasting >3.8 hours in 1 day was associated with a 9-fold increased thromboembolic event rate.\(^240\)

Additional studies are needed to further clarify the relationship between stroke risk and atrial high-rate episodes detected by implanted devices and to define key characteristics of atrial high-rate episodes in patients who warrant further investigation or potentially therapy.\(^192,194\)

### 4.3. Interruption and Bridging Anticoagulation

Interruption of anticoagulation is often considered for patients with AF who have episodes of bleeding or require surgical or interventional procedures associated with a bleeding risk. There is sparse evidence on which to base specific recommendations on bridging oral anticoagulants among patients with nonvalvular AF with adjusted-dose heparin or LMWH\(^241\); however, additional studies (eg, BRIDGE [Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery]) are ongoing.\(^242\) The duration of interruption and timing of resumption of anticoagulation after the procedure are guided by individualized consideration of the risk of thrombotic events and the severity of the operative and perioperative bleeding risk. For patients who are treated with warfarin and who are at low risk of thromboemboli or those who are back in normal sinus rhythm and are undergoing surgical or diagnostic procedures that carry a risk of bleeding, stopping warfarin for up to 1 week and allowing the INR to normalize without substituting UFH is a recognized approach. Warfarin is then resumed after adequate hemostasis has been achieved. For patients at higher risk of thromboembolism (mechanical valves, prior stroke, CHA\(_2\)DS\(_2\)-VASc score ≥2), bridging with UFH or LMWH is a common practice, although data for LMWH are limited.\(^22\) An increasingly common approach, especially for pacemaker or implantable cardioverter-defibrillator implantation, catheter ablation, coronary angiography, and other vascular interventions, is to perform the procedure without interrupting warfarin.\(^1\)!\(^{241,243-247}\)

Radiofrequency catheter ablation of AF performed with a therapeutic INR does not increase bleeding risk and reduces the risk of emboli.\(^1\)!\(^{243,244}\) Pacemaker or defibrillator implantation with a therapeutic INR has a lower risk of postoperative bleeding than discontinuing warfarin and initiating bridging anticoagulation with UFH or LMWH and may be considered in those patients requiring device implantation who also have a moderate-to-high thromboembolic risk.\(^1\)!\(^{241,245-250}\)

For oral factor Xa inhibitors and direct thrombin inhibitors, there is limited experience with drug withdrawal before surgical procedures.\(^241\) In the ROCKET AF trial, rivaroxaban was held for 2 days before elective surgery or invasive procedure and for 24 hours before semiurgent procedures.\(^60\) The increased risk of bleeding should be weighed carefully against the urgency of surgery or an invasive procedure. Interruption of anticoagulation should be guided by the pharmacological properties of the drug. The timing of resumption should take into account the fact that anticoagulation, in contrast to warfarin, is achieved promptly and that reversal agents are not yet available for these agents, which complicates management if bleeding occurs. For elective surgery, holding these agents for 1 day (2 doses for dabigatran and apixaban; 1 dose for rivaroxaban) before the procedure is generally sufficient for patients with normal renal function.\(^250\) Also, for patients with normal renal function, the need for complete hemostasis (eg, for spinal puncture, spinal/epidural catheter, or major surgery) will require discontinuation for ≥48 hours. An activated partial thromboplastin time for dabigatran and prothrombin time for apixaban and rivaroxaban may provide useful information; a level close to control suggests a low serum concentration of these agents. For patients undergoing catheter ablation or any procedure in which perforation of the heart chamber is possible, these new agents must be used with caution because of the lack of approved antidotes in the event of cardiac tamponade. In some cases, activated prothrombin complex concentrate and recombinant factor VIIa have been used to reverse the anticoagulant effects of these new agents. Specific reversal agents are not currently available but are in development. Whether hemostasis will be easier and safer for coronary interventions done by a radial artery approach rather than a femoral approach is not known. The use of bare-metal stents
or coronary artery bypass surgery in preference to drug-eluting stents where concomitant long-term use of dual antiplatelet agents is anticipated and might increase bleeding risk is a reasonable consideration when long-term therapy with these anticoagulants is desired.

In patients undergoing percutaneous coronary intervention, dual antiplatelet therapy with aspirin and clopidogrel is indicated to prevent stent thrombosis. The combination of oral anticoagulants and antiplatelet therapy (“triple therapy”) is associated with a high annual risk of fatal and nonfatal bleeding episodes. Recently, in patients taking oral anticoagulants undergoing percutaneous coronary intervention, the efficacy and safety of antiplatelet therapy with aspirin and clopidogrel versus clopidogrel alone were studied. The use of clopidogrel without aspirin was associated with a reduction in bleeding and no increase in the rate of thrombotic events.

4.4. Nonpharmacological Stroke Prevention

4.4.1. Percutaneous Approaches to Occlude the LAA

The LAA is the primary source for thromboembolism in AF. Exclusion of the LAA, both surgically and with devices, has been attempted with the goal of reducing thromboembolism in patients with AF. There are 2 general approaches to occlude the LAA using percutaneous strategies. The first involves implantable devices that are inserted percutaneously into the LAA with the goal of occluding or plugging the LAA. Devices for LAA occlusion include the WATCHMAN device (Boston Scientific, Natick, MA) and the Amplatzer cardiac plug (St. Jude Medical, Plymouth, MN). The WATCHMAN device is deployed percutaneously via transseptal puncture and has a polyethylene membrane that covers a self-expanding nitinol cage with barbs to anchor the device in the LAA. The early findings for the WATCHMAN device suggest noninferiority to warfarin for the composite endpoint of stroke, systemic embolism, and cardiovascular death; however, early adverse events occur in approximately 10% of patients, including pericardial bleeding. Longer-term follow-up of the WATCHMAN device at 1588 patient-years suggests noninferiority of this device to warfarin. A subsequent registry study demonstrated that the WATCHMAN device achieved noninferiority in patients who could not receive warfarin. Lastly, data from subsequent experience with the WATCHMAN device suggest that the earlier device-related complications were mitigated with increasing operator experience.

The Amplatzer cardiac plug, which has Conformité Européenne Mark approval, consists of a small proximal disc, a central polyester patch, and a larger distal disc with hooks to anchor the device in the LAA. It does not require anticoagulation. A European-based trial found a 96% success rate for deployment/implantation but with a 7% incidence of serious complications. The second strategy is to tie off the LAA using an epicardial snare, referred to as the LARIAT device (SentreHEART, Redwood City, CA). This device received FDA approval in 2009 for facilitation of suture placement and knot tying for use in surgical applications in which soft tissues are being approximated. It has been adapted for use in AF and combines a percutaneous epicardial and endocardial approach. The initial experience with this device appeared promising, with 97% acute obliteration of the LAA as confirmed by TEE and a favorable safety profile. The long-term outcomes of use of the LARIAT device, requiring RCTs to study reduced stroke risk and safety, are not yet defined. The device requires subxiphoid pericardial access that may not be achievable in the presence of pericardial adhesions, it can provoke pericarditis that can be severe, and it is not achievable for all LAA anatomies. It is not yet clear if occluding the LAA with the LARIAT device lowers stroke risk. Additional devices are in development.

4.4.2. Cardiac Surgery—LAA Occlusion/Excision: Recommendation

Class IIb

1. Surgical excision of the LAA may be considered in patients undergoing cardiac surgery. (Level of Evidence: C)

Surgical-based procedures to exclude the LAA during cardiac surgery are controversial for several reasons. What should seem technically simple and reproducible—removal of the LAA—yields inconsistent results, and the anatomy of the LAA is quite variable. The circumflex coronary artery lies proximate to the base of the LAA, and epicardial and endocardial-based surgical techniques to occlude the LAA are often inadequate because of surgeons’ concern about damage to the circumflex artery during a suture-based closure of the appendage. Epicardial techniques include simple suture ligation, oversewing the base without excision, excising the appendage and oversewing the base, and surgical stapling and excision. One device, the Gillinov-Cosgrove clip LAA exclusion system, has FDA approval. Endocardial techniques include inversion of the appendage, amputation, and then oversewing the base from the endocardial aspect.

The results of surgical occlusion of the LAA remain suboptimal, with echocardiographic follow-up suggesting incomplete occlusion in ≥50% of subjects. In the largest study to examine the success of LAA ligation, 2546 patients undergoing TEE between 1993 and 2004 were retrospectively examined; 137 patients underwent a surgical attempt at LAA occlusion. Of these 137 patients, 52 underwent excision and 85 underwent exclusion (by either suture or stapling). TEE-defined unsuccessful closures were characterized by either persistent flow into the LAA, a remnant stump of >1.0 cm of the LAA, or color Doppler flow into the LAA. Overall, 55 of 137 closures were successful (40%). Success varied with the technique used: for excision, the success rate was 73%; for suture exclusion, 23%; and for stapling, 0%. Particularly noteworthy is that thrombus was identified in ≥25% of patients with unsuccessful LAA occlusion with suture exclusion or stapled LAA remnants. This latter finding constitutes important data guiding the continued need for anticoagulation in patients who have undergone surgical LAA ligation.

It is unclear whether occlusion of the LAA at the time of concomitant heart surgery contributes to the success and
efficacy of occlusion in terms of stroke prevention. The LAAOS (Left Atrial Appendage Occlusion Study) randomized 77 patients with risk factors for stroke to LAA closure or control at the time of coronary artery bypass surgery. During this trial, suture-based or staple-based occlusion was permitted; the success of LAA closure in the suture group was 45% versus 72% in the stapled group. Nine appendage tears occurred during the trial (1 control and 8 treatments), but these tears did not contribute to mortality or morbidity. There were 2 thromboembolic events in the occlusion group and none in the control. The authors concluded that LAA occlusion could be performed safely; however, larger randomized studies are needed to determine whether LAA occlusion could reduce stroke risk in patients with risk factors for AF who undergo non-AF-related cardiac surgery. In a retrospective cohort of 205 patients with echocardiography following mitral valve replacement, 58 patients underwent LAA ligation as judged by transthoracic echocardiogram. Of these 58 patients, 52 had a complete ligation of the LAA, as defined by lack of color Doppler flow from the body of the LA into the appendage, and 6 had persistent flow. The principal finding was that lack of and incomplete LAA occlusion were both strongly associated with the occurrence of a thromboembolic event.

In summary, the current data on LA occlusion at the time of concomitant cardiac surgery reveal a lack of clear consensus because of the inconsistency of techniques used for surgical excision, the highly variable rates of successful LAA occlusion, and the unknown impact of LAA occlusion on future thromboembolic events.

5. Rate Control: Recommendations

See Table 9 for a summary of recommendations for this section.

Class I

1. Control of the ventricular rate using a beta blocker or nondihydropyridine calcium channel antagonist is recommended for patients with paroxysmal, persistent, or permanent AF (Level of Evidence: B)

2. Intravenous administration of a beta blocker or nondihydropyridine calcium channel blocker is recommended to slow the ventricular heart rate in the acute setting in patients without pre-excitation. In hemodynamically unstable patients, electrical cardioversion is indicated (Level of Evidence: B)

3. In patients who experience AF-related symptoms during activity, the adequacy of heart rate control should be assessed during exertion, adjusting pharmacological treatment as necessary to keep the ventricular rate within the physiological range (Level of Evidence: C)

Class IIa

1. A heart rate control (resting heart rate <80 bpm) strategy is reasonable for symptomatic management of AF (Level of Evidence: B)

2. Intravenous amiodarone can be useful for rate control in critically ill patients without pre-excitation (Level of Evidence: B)

3. AV nodal ablation with permanent ventricular pacing is reasonable to control heart rate when

Table 9. Summary of Recommendations for Rate Control

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control ventricular rate using a beta blocker or nondihydropyridine calcium channel antagonist for paroxysmal, persistent, or permanent AF</td>
<td>I</td>
<td>B</td>
<td>267–269</td>
</tr>
<tr>
<td>IV beta blocker or nondihydropyridine calcium channel blocker is recommended to slow ventricular heart rate in the acute setting in patients without pre-excitation. In hemodynamically unstable patients, electrical cardioversion is indicated</td>
<td>I</td>
<td>B</td>
<td>270–273</td>
</tr>
<tr>
<td>For AF, assess heart rate control during exertion, adjusting pharmacological treatment as necessary</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>A heart rate control (resting heart rate &lt;80 bpm) strategy is reasonable for symptomatic management of AF</td>
<td>IIa</td>
<td>B</td>
<td>269, 274</td>
</tr>
<tr>
<td>IV amiodarone can be useful for rate control in critically ill patients without pre-excitation</td>
<td>IIa</td>
<td>B</td>
<td>275–277</td>
</tr>
<tr>
<td>AV nodal ablation with permanent ventricular pacing is reasonable when pharmacological therapy is inadequate and rhythm control is not achievable</td>
<td>IIa</td>
<td>B</td>
<td>278–280</td>
</tr>
<tr>
<td>A lenient rate-control strategy (resting heart rate &lt;110 bpm) may be reasonable when patients remain asymptomatic and LV systolic function is preserved</td>
<td>IIb</td>
<td>B</td>
<td>274</td>
</tr>
<tr>
<td>Oral amiodarone may be useful for ventricular rate control when other measures are unsuccessful or contraindicated</td>
<td>IIb</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>AV nodal ablation should not be performed without prior attempts to achieve rate control with medications</td>
<td>III: Harm</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Nondihydropyridine calcium channel antagonists should not be used in decompensated HF</td>
<td>III: Harm</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>With pre-excitation and AF, digoxin, nondihydropyridine calcium channel antagonists, or amiodarone should not be administered</td>
<td>III: Harm</td>
<td>B</td>
<td>281</td>
</tr>
<tr>
<td>Dronedarone should not be used to control ventricular rate with permanent AF</td>
<td>III: Harm</td>
<td>B</td>
<td>282, 283</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; AV, atrioventricular; bpm, beats per minute; COR, Class of Recommendation; HF, heart failure; IV, intravenous; LOE, Level of Evidence; LV, left ventricular; and N/A, not applicable.
pharmacological therapy is inadequate and rhythm control is not achievable.\textsuperscript{274–280} (Level of Evidence: B)

Class IIb

1. A lenient rate-control strategy (resting heart rate \(<110\ \text{bpm})\) may be reasonable as long as patients remain asymptomatic and LV systolic function is preserved.\textsuperscript{274} (Level of Evidence: B)

2. Oral amiodarone may be useful for ventricular rate control when other measures are unsuccessful or contraindicated. (Level of Evidence: C)

Class III: Harm

1. AV nodal ablation with permanent ventricular pacing should not be performed to improve rate control without prior attempts to achieve rate control with medications. (Level of Evidence: C)

2. Nondihydropyridine calcium channel antagonists should not be used in patients with decompensated HF as these may lead to further hemodynamic compromise. (Level of Evidence: C)

3. In patients with pre-excitation and AF, digoxin, nondihydropyridine calcium channel antagonists, or intravenous amiodarone should not be administered as they may increase the ventricular response and may result in ventricular fibrillation.\textsuperscript{281} (Level of Evidence: C)

4. Dronedarone should not be used to control the ventricular rate in patients with permanent AF as it increases the risk of the combined endpoint of stroke, MI, systemic embolism, or cardiovascular death.\textsuperscript{282,283} (Level of Evidence: B)

Rate control in AF is an important strategy. It impacts quality of life, reduces morbidity, and decreases the potential for developing tachycardia-induced cardiomyopathy. Multiple agents, including beta blockers, nondihydropyridine calcium channel blockers, digoxin, and certain antiarrhythmic drugs, including amiodarone and sotalol, have been evaluated with regard to efficacy in attaining rate control. This information is summarized in Table 10. When considering which agent(s) to use, clinicians must consider the patient’s degree of symptoms, hemodynamic status, presence or absence of HF, and potential precipitants of AF. When evaluating the evidence supporting different agents, clinicians must recognize that most clinical trials were performed in the 1980s and 1990s and have study design limitations that include variable endpoints, small sample sizes, and single-site study and observational trial designs. Issues to consider include the acuity of attaining rate control, which agent(s) to administer, and the degree of rate control required. Over the last 40 years, several themes have emerged. In general, beta blockers are the most common agents used for rate control, followed by nondihydropyridine calcium channel blockers, digoxin, and amiodarone. Patient comorbidities must be understood to avoid medications that may precipitate adverse events such as decompensation of HF, exacerbation of chronic obstructive pulmonary disease, or acceleration of conduction in patients with pre-excitation.

When rapid control of ventricular rate during AF is required, intravenous medications or electrical cardioversion may be used. Electrical cardioversion is preferred in patients with decompensated HF, ongoing myocardial ischemia, or hypotension, although this may carry an increased thromboembolic risk in patients with inadequate anticoagulation or for whom AF is of uncertain duration. In hemodynamically stable patients with a rapid ventricular response, oral medications may be administered.

5.1. Specific Pharmacological Agents for Rate Control

5.1.1. Beta-Adrenergic Receptor Blockers

By blocking sympathetic tone, beta blockers are useful for ventricular rate control in patients with AF. Beta blockers, including esmolol, propranolol, and metoprolol, are effective when administered intravenously in the setting of acute AF.\textsuperscript{270,273,284} Orally administered beta blockers, including atenolol, metoprolol, nadolol, propranolol, as well as the antiarrhythmic drug sotalol, have all been effectively used for ongoing ventricular
rate control in patients with chronic AF. There is less published literature on rate control of AF with additional beta blockers. In the AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) study, beta blockers were the most effective and commonly used drug class for rate control (70% on beta blocker versus 54% on calcium channel blocker). In patients with HF, carvedilol had efficacy for heart rate control and, in combination with digoxin, resulted in improved LV function. Combination therapy of beta blockers with other agents, including digoxin, is effective in ventricular rate control; however, drugs should be titrated to avoid excessive bradycardia.

See Online Data Supplement 6 for additional data on beta blockers.

5.1.2. Nondihydropyridine Calcium Channel Blockers
Diltiazem and verapamil have direct AV nodal effects, blocking L-type calcium channels, and are used for ventricular rate control in both acute and chronic AF. In the setting of acute AF, intravenous administration of diltiazem was safe and effective in controlling ventricular response in 83% of patients. Intravenous verapamil is also effective in establishing acute ventricular rate control. Unless immediate rate control is required or an enteral route of administration is not available, oral administration is appropriate. Both verapamil and diltiazem reduce resting and exercise heart rate and can improve exercise tolerance. These nondihydropyridine calcium channel blockers should not be used in patients with LV systolic dysfunction and decompensated HF because of their negative inotropic effects, but they may be used in patients with HF with preserved LV systolic function. In addition, these agents should not be used in patients with pre-excitation and AF due to the potential for shortening bypass tract refractoriness, which may accelerate the ventricular rate to precipitate hypotension or ventricular fibrillation (Section 7.8).

See Online Data Supplement 7 for additional data on nondihydropyridine calcium channel blockers.

5.1.3. Digoxin
Digoxin is not usually first-line therapy for ventricular rate control in patients with AF, despite its common use. Although intravenous digoxin does slow the ventricular response, onset of action requires >1 hour and the effect does not peak until approximately 6 hours after initial administration. Therefore, it is not an optimal agent when rapid rate control is desired. During chronic oral therapy, digoxin reduces the resting heart rate, but it is ineffective at controlling the ventricular response during exercise. Digoxin may be combined with beta blockers or nondihydropyridine calcium channel blockers to improve ventricular rate control during exercise, and it has been used in HF as 1 of the few rate control agents that does not have negative inotropic effects. Adverse effects of digoxin include AV block, ventricular arrhythmias, and, infrequently, aggravation of sinus node dysfunction. Dose adjustment is required in patients with renal dysfunction, the elderly, and in the presence of drugs that reduce its excretion, such as amiodarone, propafenone, or nondihydropyridine calcium channel blockers. Therefore, periodic assessment of serum levels is warranted in many patients. Studies finding an association between digoxin therapy and mortality raise further concern about its use, particularly long term. In the AFFIRM trial, digoxin was associated with an increase in mortality, which in post hoc analysis was irrespective of sex or HF. Arrhythmias, which are dose related, are a potential source of mortality; in the DIG (Digitalis Investigation Group) trial, serum levels >0.9 ng/mL were associated with increased mortality. However, in another AFFIRM subgroup propensity-matched analysis with paroxysmal and persistent AF, there was no increase in mortality or hospitalization in those taking digoxin as baseline initial therapy. Because it can shorten cardiac action potential duration, digoxin should not be used as sole therapy in patients with pre-excitation.

See Online Data Supplement 8 for additional data on digoxin.

5.1.4. Other Pharmacological Agents for Rate Control
Amiodarone exerts sympatholytic and calcium antagonistic properties that can depress AV nodal conduction. Although intravenous amiodarone can be used in critically ill patients without pre-excitation to attain ventricular rate control, it is less effective than nondihydropyridine calcium channel blockers and requires a longer time to achieve rate control (7 hours versus 3 hours for diltiazem). There are limited data on the efficacy of oral therapy with amiodarone for rate control during persistent AF, but in 1 small trial it had similar efficacy to digoxin. Amiodarone is uniquely lipid soluble. Its onset of action can be accelerated by a high-dose amiodarone-loading regimen, but there is the potential for worsening hemodynamics in patients with recent decompensated HF or hypotension. Intravenous amiodarone does not have the same electrophysiological effects as oral amiodarone, and intravenous amiodarone has the potential to accelerate the ventricular response and precipitate fatal arrhythmias in patients with AF and pre-excitation. Amiodarone has many potential toxicities and drug interactions that limit its long-term use for control of ventricular rate.

Dronedarone, which lacks iodine moieties of amiodarone, slows the resting rate in AF by an average of 12 bpm and also improves exercise heart rate control; however, it should not be used for rate control in permanent AF, as it was found to increase rates of HF, stroke, cardiovascular death, and unplanned hospitalization. Furthermore, dronedarone should not be used for ventricular rate control in patients with HF and LV systolic dysfunction because it increases the likelihood of the combined endpoint of stroke, MI, systemic embolism, or cardiovascular death.

See Online Data Supplement 9 for additional data on pharmacological agents for rate control.

5.2. AV Nodal Ablation
AV nodal ablation with permanent pacemaker implantation effectively controls and regularizes ventricular heart rate and, in selected patients, improves symptoms. Patients most likely to benefit include those with tachycardia-induced cardiomyopathy with ventricular rate control refractory to medical therapy. AV nodal ablation is usually reserved for elderly patients, because it leads to pacemaker dependency. Patients with symptoms refractory to medical therapy who are treated with AV nodal ablation and permanent pacemaker implantation have an improvement in cardiac symptoms, quality of life, and health care utilization. With this approach, no
rate-control medications are necessary, but anticoagulation to prevent thromboembolism is required, based on the patient’s stroke risk as assessed by the CHA2DS2-VASc system. When this approach is under consideration, the patient must receive counseling to understand that this is an irreversible measure that results in a lifelong pacemaker dependency with its potential complications. Time permitting, pacemaker implantation may be performed 4 to 6 weeks before the AV node ablation to ensure proper pacemaker function, because malfunction due to lead dislodgment can be catastrophic. Sudden death secondary to torsades de pointes or ventricular fibrillation has been reported after AV junction ablation. This outcome is possibly related to increased dispersion of ventricular refractoriness produced by sudden heart rate slowing and ventricular pacing. After ablation, the ventricular pacing rate is usually set between 90 bpm and 100 bpm and then gradually tapered over several months. RV apical pacing also creates a ventricular activation sequence that can lead to depressed ventricular function. In patients with left ventricular ejection fraction (LVEF) <35% and symptoms of HF, implantation of a biventricular pacing system is recommended. This procedure should also be considered for patients with less severe ventricular dysfunction. In the BLOCK HF (Biventricular Versus Right Ventricular Pacing in Heart Failure Patients With Atrioventricular Block) trial, patients with advanced AV block with LVEF <50% had improved clinical outcomes when treated with a biventricular pacemaker compared with RV apical pacing. An upgrade to a biventricular pacing system should be considered for patients who have undergone AV nodal ablation coupled with an RV pacing system who develop moderate-to-severe LV systolic dysfunction.

See Online Data Supplement 10 for additional data on AV junction ablation.

5.3. Selecting and Applying a Rate-Control Strategy

5.3.1. Broad Considerations in Rate Control

The optimal heart rate targets for rate control are controversial. The target used in the AFFIRM trial was a resting heart rate of either ≤80 bpm or averaging ≤100 bpm on ambulatory monitoring, without a rate >100% of the maximum age-adjusted predicted exercise heart rate. These conditions were achieved in 58% of patients during initial drug therapy. One RCT, the RACE (Rate Control Efficacy in Permanent Atrial Fibrillation)-II trial, assessed lenient versus strict rate control. In this trial, 614 patients with permanent AF were randomized to a lenient rate-control (resting heart rate <110 bpm) strategy or a strict rate-control (resting heart rate <80 bpm) strategy. At 3 years, the primary composite endpoint of cardiovascular death, hospitalization for HF, stroke, embolism, bleeding, or life-threatening arrhythmic events was similar between the 2 groups (12.9% lenient rate control versus 14.9% strict rate control); thus, a strict rate-control strategy did not improve outcomes. Several considerations warrant a

![Figure 6. Approach to selecting drug therapy for ventricular rate control.](http://circ.ahajournals.org/)
cautious approach to extrapolating these findings to the general AF population. The majority of patients in the RACE-II trial had preserved LV systolic function. RACE-II was a single noninferiority trial with a 90% CI for a composite endpoint. The resting heart rate achieved in both groups only differed by 10 bpm, and 78% of patients in the lenient control group had resting rates <100 bpm. This single RCT does not provide sufficient evidence to assess definitive results of the impact on all-cause mortality, HF symptoms, hospitalizations, or quality of life. The degree of rate control, however, remains an area of uncertainty and controversy that requires further study.

See Online Data Supplement 11 for additional data on rate control.

5.3.2. Individual Patient Considerations

Optimal ventricular rate control may differ and is impacted by the degree of patient symptoms and comorbidities, including the presence of valvular heart disease, LV systolic dysfunction, HF, and presence of pre-excitation. Figure 6 provides a brief outline of the approach(es) to rate control in different patient populations.

6. Rhythm Control

Long-term AF management may attempt to restore and maintain sinus rhythm, commonly referred to as “a rhythm-control strategy,” using a combination of approaches, including cardioversion, antiarrhythmic drugs, and radiofrequency catheter ablation in the setting of appropriate anticoagulation and rate control. RCTs comparing outcomes of a rhythm-control strategy using antiarrhythmic drugs with a rate-control strategy in patients with AF failed to show a superiority of rhythm control on mortality for either strategy.269,313 Furthermore, when applied in patients who are candidates for both treatment strategies (rhythm or rate control), a rhythm-control strategy results in more hospitalizations. Therefore, the routine use of a rhythm-control strategy is not warranted for some patients. Catheter ablation has not been studied in this context.

Although an initial rate-control strategy is reasonable for many patients, several considerations favor pursuing a rhythm-control strategy. Successful sinus rhythm maintenance is associated with improvements in symptoms and quality of life for some patients.314,315 Persistent symptoms associated with AF remain the most compelling indication for a rhythm-control strategy. Other factors that may favor attempts at rhythm control include difficulty in achieving adequate rate control, younger patient age, tachycardia-mediated cardiomyopathy, first episode of AF, AF precipitated by an acute illness, and patient preference. AF progresses from paroxysmal to persistent in many patients and subsequently results in electrical and structural remodeling that becomes irreversible with time.126,316 For this reason, acceptance of AF as permanent in a patient may render future rhythm-control therapies less effective. This may be more relevant for a younger patient who wishes to remain a candidate for future developments in rhythm-control therapies. Early intervention with a rhythm-control strategy to prevent progression of AF may be beneficial.317-319

6.1. Electrical and Pharmacological Cardioversion of AF and Atrial Flutter

See Table 11 for a summary of recommendations from this section.

6.1.1. Prevention of Thromboembolism: Recommendations

Class I

1. For patients with AF or atrial flutter of 48 hours’ duration or longer, or when the duration of AF is unknown, anticoagulation with warfarin (INR 2.0 to 3.0) is recommended for at least 3 weeks before and 4 weeks after cardioversion, regardless of the CHA2DS2-VASc score and the method (electrical or pharmacological) used to restore sinus rhythm.320-323 (Level of Evidence: B)

2. For patients with AF or atrial flutter of more than 48 hours’ duration or unknown duration that requires immediate cardioversion for hemodynamic instability, anticoagulation should be initiated as soon as possible and continued for at least 4 weeks after cardioversion unless contraindicated. (Level of Evidence: C)

3. For patients with AF or atrial flutter of less than 48 hours’ duration and with high risk of stroke, intravenous heparin or LMWH, or administration of a factor Xa or direct thrombin inhibitor, is recommended as soon as possible before or immediately after cardioversion, followed by long-term anticoagulation therapy. (Level of Evidence: C)

4. Following cardioversion for AF of any duration, the decision about long-term anticoagulation therapy should be based on the thromboembolic risk profile (Section 4). (Level of Evidence: C)

Class IIA

1. For patients with AF or atrial flutter of 48 hours’ duration or longer or of unknown duration who have not been anticoagulated for the preceding 3 weeks, it is reasonable to perform TEE before cardioversion and proceed with cardioversion if no LA thrombus is identified, including in the LAA, provided that anticoagulation is achieved before TEE and maintained after cardioversion for at least 4 weeks.164 (Level of Evidence: B)

2. For patients with AF or atrial flutter of 48 hours’ duration or longer or when duration of AF is unknown, anticoagulation with dabigatran, rivaroxaban, or apixaban is reasonable for at least 3 weeks before and 4 weeks after cardioversion.390,324,325 (Level of Evidence: C)

Class IIB

1. For patients with AF or atrial flutter of less than 48 hours’ duration who are at low thromboembolic risk, anticoagulation (intravenous heparin, LMWH, or a new oral anticoagulant) or no antithrombotic therapy may be considered for cardioversion, without the need for postcardioversion oral anticoagulation.326 (Level of Evidence: C)
6.1.2. Direct-Current Cardioversion: Recommendations

Class I

1. In pursuing a rhythm-control strategy, cardioversion is recommended for patients with AF or atrial flutter as a method to restore sinus rhythm. If cardioversion is unsuccessful, repeated attempts at direct-current cardioversion may be made after adjusting the location of the electrodes, applying pressure over the electrodes or following administration of an antiarrhythmic medication.327 (Level of Evidence: B)

2. Cardioversion is recommended when a rapid ventricular response to AF or atrial flutter does not respond promptly to pharmacological therapies and contributes to ongoing myocardial ischemia, hypotension, or HF. (Level of Evidence: C)

3. Cardioversion is recommended for patients with AF or atrial flutter and pre-excitation when tachycardia is associated with hemodynamic instability. (Level of Evidence: C)

Class IIa

1. It is reasonable to perform repeated cardioversions in patients with persistent AF, provided that sinus rhythm can be maintained for a clinically meaningful time period between procedures. Severity of AF symptoms and patient preference should be considered when embarking on a strategy requiring serial cardioversion procedures. (Level of Evidence: C)

6.1.3. Pharmacological Cardioversion: Recommendations

Class I

1. Flecainide, dofetilide, propafenone, and IV ibutilide are useful for cardioversion of AF or atrial flutter, provided contraindications to the selected drug are absent.328–333 (Level of Evidence: A)

Class IIa

1. Amiodarone is reasonable for pharmacological cardioversion of AF 334, 335 (Level of Evidence: A)

2. Propafenone or flecainide (“pill-in-the-pocket”) to terminate AF out of hospital is reasonable once observed to be safe in a monitored setting.328 (Level of Evidence: B)

Dofetilide should not be initiated out of hospital III: Harm B 332, 336

AF indicates atrial fibrillation; COR, Class of Recommendation; IV, intravenous; LA, left atrial; LMWH, low-molecular-weight heparin; LOE, Level of Evidence; N/A, not applicable; RVR, rapid ventricular response; and TEE, transesophageal echocardiography.
2. Propafenone or flecainide ("pill-in-the-pocket") in addition to a beta blocker or nondihydropyridine calcium channel antagonist is reasonable to terminate AF outside the hospital once this treatment has been observed to be safe in a monitored setting for selected patients.\(^{326}\) (Level of Evidence: B)

**Class III: Harm**

1. Dofetilide therapy should not be initiated out of hospital because of the risk of excessive QT prolongation that can cause torsades de pointes.\(^{322,326}\) (Level of Evidence: B)

Direct-current cardioversion involves the delivery of an electrical shock synchronized with the QRS complex to avoid inducing ventricular fibrillation that can occur when a shock is delivered during ventricular repolarization on the T wave. It is clinically relevant to differentiate between a cardioversion in which sinus rhythm was not restored, even transiently, and a cardioversion in which sinus rhythm was restored but AF recurs. In the former scenario, approaches that improve energy delivery and may allow for successful cardioversion include increasing shock strength, delivering a biphasic rather than monophasic waveform, changing the shock vector by altering the electrode pad position, improving energy transfer via pressure on the anterior electrode pad, or using a drug such as ibutilide to lower the defibrillation threshold. In the latter scenario, when sinus rhythm is restored but AF returns, pretreatment with selected antiarrhythmic drugs may increase the likelihood of maintenance of sinus rhythm.\(^{327,337}\)

A number of technical factors influence cardioversion efficacy, including energy, waveform, and electrode placement.\(^{7a,7b}\) A biphasic waveform is more effective than a monophasic waveform.\(^{338}\) Anteroposterior electrode placement is superior to anterolateral placement in some but not all studies.\(^{7a,7b,339}\) If an attempt at cardioversion using 1 electrode placement fails, another attempt using the alternative placement is recommended. The initial use of a higher-energy shock is more effective and may minimize the number of shocks required as well as the duration of sedation.\(^{340}\) Risks associated with cardioversion include thromboembolism, sedation-related complications, ventricular tachycardia and fibrillation, bradyarrhythmias, skin burn or irritation from electrodes, muscle soreness, and reprogramming or altering implanted cardiac device function. Elective cardioversion should not be performed in patients with evidence of digoxin toxicity, severe hypokalemia, or other electrolyte imbalances until these factors are corrected.

Appropriate anticoagulation management around the time of cardioversion is essential for reducing thromboembolic risk. Results of observational studies suggest that thromboembolic risk after cardioversion is highest in the first 72 hours and that the majority of events occur within 10 days.\(^{341,342}\) Thromboembolism after cardioversion can be due to migration of thrombi present at the time of cardioversion or to the formation and subsequent migration of de novo thrombi that form while atrial function is still depressed in the postcardioversion period. In this guideline, the Class I recommendation for anticoagulation with warfarin for ≥3 weeks before and continuing for ≥4 weeks after cardioversion is based on pathophysiological and observational data.\(^{322,323}\) For new oral anticoagulants, available data supporting similar use at cardioversion consist of subgroup analyses of dabigatran from RE-LY, rivaroxaban from ROCKET AF, and apixaban from ARISTOTLE in patients who were receiving long-term anticoagulation (>3 weeks) around the time of cardioversion.\(^{230,324,325}\)

TEE guidance is an alternative to 3 weeks of anticoagulation before cardioversion.\(^{164,343}\) Therapeutic anticoagulation is achieved and followed by TEE; if no thrombus is seen (including in the LAA), cardioversion is performed and anticoagulation is continued for ≥4 weeks. The absence of LA thrombus on TEE does not preclude the need for anticoagulation during and after cardioversion. In the ACUTE (Assessment of Cardioversion Using Transesophageal Echocardiography) trial, hospitalized patients were typically started on intravenous heparin before cardioversion, whereas outpatients were typically started on warfarin 5 days before cardioversion and anticoagulation status was verified at the time of cardioversion.\(^{346}\) Alternative strategies for achieving rapid anticoagulation include administration of LMWH\(^{344}\) or a new oral anticoagulant. If a thrombus is identified on TEE, the cardioversion should be postponed, followed by ≥3 to 4 weeks of anticoagulation. Repeat TEE to ensure thrombus resolution is an option before another cardioversion attempt.\(^{322}\) If a thrombus remains on repeat TEE, an alternative strategy such as rate control in conjunction with appropriate anticoagulation may be considered.

Data on cardioversion risks for atrial flutter are limited. Atrial flutter, however, can be associated with thrombi and episodes of AF. Therefore, it is recommended that the anti-coagulation management strategy for cardioversion of atrial flutter be the same as for AF.

In patients with AF clearly of <48 hours’ duration, it is common practice to perform cardioversion without TEE or antecedent anticoagulation.\(^{345}\) No RCTs comparing anticoagulation strategies in patients with AF duration of <48 hours exist.\(^{342}\) If high-risk features are present, such as mitral stenosis or prior history of thromboembolism, long-term anticoagulation should be considered. Decisions about whether to initiate long-term systemic anticoagulation at the time of cardioversion in a patient with AF of <48 hours’ duration should be based on the patient’s long-term risk of stroke using the CHA\(_2\)DS\(_2\)-VASc risk score discussed in Section 4.1.

For patients with AF requiring emergency cardioversion because of hemodynamic instability, initiation of anticoagulation should not delay interventions to stabilize the patient. No RCTs have evaluated optimal anticoagulation strategies in this patient population. It is reasonable to administer heparin (intravenous bolus of UFH followed by infusion, or LMWH) or new anticoagulant and to continue this after cardioversion unless contraindicated. For patients with AF or atrial flutter of ≥48 hours’ duration or uncertain duration, oral anticoagulation is recommended for ≥4 weeks after emergency cardioversion (similar to patients undergoing elective cardioversion). If warfarin is used, bridging with UFH or LMWH is indicated until the INR is therapeutic. For patients with AF and thromboembolic risk factors, oral long-term anticoagulation is recommended.

Antiarrhythmic drugs can be administered for attempted conversion of AF to sinus rhythm or to facilitate electrical cardioversion. Pharmacological cardioversion is most likely
effective when initiated within 7 days after onset of an episode of AF. The most commonly effective antiarrhythmic drugs are specified in Table 12. In patients with recent-onset AF, intravenous administration of ibutilide restored sinus rhythm in about 50% of patients, with an average conversion time of <30 minutes. The rates of successful termination were higher in patients with atrial flutter than in those with AF.346 Pretreatment with ibutilide also improves the efficacy of transthoracic electrical cardioversion of AF.327 The major risk is excessive QT prolongation, which can cause polymorphic ventricular tachycardia/torsades de pointes. The latter occurs in up to 3% to 4% of patients. Electrocardiographic monitoring should be continued for ≥4 hours after administration, and resuscitation equipment must be immediately available. Ibutilide should be avoided in patients with QT prolongation, marked hypokalemia, or a very low ejection fraction (EF) (<30%) because of the risk of ventricular proarrhythmia.327 The major risk is excessive QT prolongation, which can cause polymorphic ventricular tachycardia/torsades de pointes. The latter occurs in up to 3% to 4% of patients. Electrocardiographic monitoring should be continued for ≥4 hours after administration, and resuscitation equipment must be immediately available. Ibutilide should be avoided in patients with QT prolongation, marked hypokalemia, or a very low ejection fraction (EF) (<30%) because of the risk of ventricular proarrhythmia.327

Table 12. Recommended Drug Doses for Pharmacological Cardioversion of AF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of Administration</th>
<th>Dosage</th>
<th>Potential Adverse Effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone*</td>
<td>Oral</td>
<td>600–800 mg daily in divided doses to a total load of up to 10 g, then 200 mg QD as maintenance</td>
<td>Phlebitis (IV), hypotension, bradycardia, QT prolongation, torsades de pointes (rare), GI upset, constipation, increased INR</td>
<td>334, 335</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>Oral</td>
<td>150 mg over 10 min, then 1 mg/min for 6 h, then 0.5 mg/min for 18 h or change to oral dosing</td>
<td>QT prolongation, torsades de pointes; adjust dose for renal function, body size, and age</td>
<td>332</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>Oral</td>
<td>200–300 mg × 1†</td>
<td>Hypotension, atrial flutter with 1:1 AV conduction, ventricular proarrhythmia; avoid in patients with CAD and significant structural heart disease</td>
<td>328</td>
</tr>
<tr>
<td>Flecainide</td>
<td>Oral</td>
<td>400–600 mg × 1†</td>
<td>Hypotension, atrial flutter with 1:1 AV conduction, ventricular proarrhythmia; avoid in patients with CAD and significant structural heart disease</td>
<td>328, 330</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>IV</td>
<td>1 mg over 10 min; may repeat 1 mg once if necessary (if weight &lt;60 kg, use 0.01 mg/kg)</td>
<td>QT prolongation, torsades de pointes, hypotension</td>
<td>329, 333, 346</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Oral</td>
<td>450–600 mg × 1†</td>
<td>Hypotension, atrial flutter with 1:1 AV conduction, ventricular proarrhythmia; avoid in patients with CAD and significant structural heart disease</td>
<td>328, 330</td>
</tr>
</tbody>
</table>

*Multiple dosing schemes exist for the use of amiodarone.
†Recommended given in conjunction with a beta blocker or nondihydropyridine calcium channel antagonist administered ≥30 minutes before administering the Vaughan Williams class IC agent.328

AF indicates atrial fibrillation; AV, atrioventricular; BID, twice a day; CAD, coronary artery disease; CI, confidence interval; CrCl, creatinine clearance; GI, gastrointestinal; INR, international normalized ratio; IV, intravenous; and QD, once daily.

Adapted with permission from Fuster et al.4

6.2. Pharmacological Agents for Preventing AF and Maintaining Sinus Rhythm

6.2.1. Antiarrhythmic Drugs to Maintain Sinus Rhythm: Recommendations

Class I

1. Before initiating antiarrhythmic drug therapy, treatment of precipitating or reversible causes of AF is recommended. (Level of Evidence: C)

2. The following antiarrhythmic drugs are recommended in patients with AF to maintain sinus rhythm, depending on underlying heart disease and comorbidities (Level of Evidence: A):
   a. Amiodarone314,347–349
   b. Dofetilide350,352
   c. Dronedarone150,152
   d. Flecainide347,353
   e. Propafenone347,354,357
   f. Sotalol347,355,358

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3. The risks of the antiarrhythmic drug, including proarrhythmia, should be considered before initiating therapy with each drug. (Level of Evidence: C)

4. Because of its potential toxicities, amiodarone should only be used after consideration of risks and when other agents have failed or are contraindicated. (Level of Evidence: C)

Class IIa

1. A rhythm-control strategy with pharmacological therapy can be useful in patients with AF for the treatment of tachycardia-induced cardiomyopathy. (Level of Evidence: C)

Class IIb

1. It may be reasonable to continue current antiarrhythmic drug therapy in the setting of infrequent, well-tolerated recurrences of AF when the drug has reduced the frequency or symptoms of AF. (Level of Evidence: C)

Class III: Harm

1. Antiarrhythmic drugs for rhythm control should not be continued when AF becomes permanent (Level of Evidence: C), including dronedarone. (Level of Evidence: B)

2. Dronedarone should not be used for treatment of AF in patients with New York Heart Association (NYHA) class III and IV HF or patients who have had an episode of decompensated HF in the past 4 weeks. (Level of Evidence: B)

When a rhythm-control strategy is desired, antiarrhythmic drug therapy may be selected to reduce the frequency and duration of AF and improve quality of life. Before antiarrhythmic drug treatment is initiated, reversible precipitants of AF should be identified and corrected. After the first episode of AF that resolves, it is reasonable to address the underlying causes of AF and need for anticoagulation, and to not initiate antiarrhythmic drug treatment until warranted by recurrences of AF. Decisions about anticoagulation should be based on the individual patient’s stroke risk profile and not on the response to antiarrhythmic drug therapy. Antiarrhythmic drug efficacy is modest, and asymptomatic AF recurrences are common. Therefore, a rhythm-control strategy should not result in cessation of antithrombotic therapy, rate-control therapy, or treatment of underlying heart disease.

Drug selection is guided to a greater extent by safety concerns than by drug efficacy. A common approach is to identify available drug choices by first eliminating, on the basis of clinical parameters, drugs that have absolute or relative contraindications. Patients with CAD, significant LV hypertrophy, and HF have more restricted options than those with minimal or no structural heart disease. Several other important factors must be considered, including the risk for bradyarrhythmias, risk factors for excessive QT prolongation and torsades de pointes (eg, baseline QT prolongation, history of torsades de pointes during therapy with a QT interval–prolonging drug, potassium-wasting syndromes), and factors that influence drug disposition, such as patient age and renal or hepatic dysfunction. Because of its toxicity profile, amiodarone should only be used after consideration of risks and when other agents have failed or are contraindicated.

Table 13 summarizes antiarrhythmic drugs useful in the maintenance of sinus rhythm along with toxicity profiles. In general, antiarrhythmic drugs have the potential to precipitate or worsen bradycardia due to sinus node dysfunction or abnormal AV conduction. A history of syncope, sinus bradycardia, PR interval prolongation, and bundle-branch block raise concerns for a risk of bradyarrhythmia during antiarrhythmic drug therapy. Depending on the specific agent selected, a pacemaker may be required for patients with significant bradyarrhythmias.

In selecting a strategy of rhythm control with an antiarrhythmic drug, providing for adequate rate control in the event of AF recurrence should also be considered. Once antiarrhythmic drug therapy is initiated, patient symptoms may improve without complete AF suppression. The transition from frequent AF to infrequent, well-tolerated recurrence of AF is a reasonable outcome and does not necessarily indicate that the therapy should be discontinued. However, if attempts at rhythm control are abandoned (eg, after AF has been declared permanent), the antiarrhythmic drug should be discontinued.

Several systematic reviews have summarized the data on the efficacy and safety of antiarrhythmic drugs for treating AF. In a meta-analysis of 44 trials, antiarrhythmic drug therapy significantly reduced recurrence of AF (with a number needed to treat ranging from 2 to 9). All drugs may require discontinuation of therapy because of adverse effects (number needed to harm ranging from 9 to 27), and all but amiodarone and propafenone increased proarrhythmia in this analysis (number needed to harm ranging from 17 to 119). Vaughan Williams class IA drugs (quinidine and disopyramide, pooled data) were associated with increased mortality compared with controls, whereas no other antiarrhythmic drug showed a significant effect on mortality. Most of the trials in this meta-analysis had relatively short duration of follow-up and enrolled relatively healthy patients; therefore, it is difficult to extrapolate these data to other patient populations. Conclusions about other important clinical outcomes such as stroke and HF were not analyzed, and dronedarone was not included.

Antiarrhythmic drugs that prolong the QT interval, notably sotalol, dofetilide, and disopyramide (all of which block the rapidly activating delayed rectifier potassium current I_K), have a risk of causing torsades de pointes and should be avoided in patients at increased risk of this form of proarrhythmia. Amiodarone and dronedarone have rarely been associated with prolongation of the QT interval and torsades de pointes. General risk factors associated with increased risk of torsades de pointes include bradycardia, advanced age, hypokalemia, hypomagnesemia, female sex, baseline prolonged QT interval, congenital long-QT syndrome, concomitant use of other QT-prolonging therapies, HF, and possibly LV hypertrophy.

Structural heart disease has been associated with an increased risk of drug-induced proarrhythmia that may manifest as life-threatening ventricular arrhythmias. Manifestations of heart disease sufficient to warrant consideration include...
Table 13. Dosage and Safety Considerations for Maintenance of Sinus Rhythm in AF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Doses</th>
<th>Exclude/Use With Caution</th>
<th>Major Pharmacokinetic Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaughan Williams class IA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disopyramide</td>
<td>Immediate release: 100–200 mg once every 6 h</td>
<td>HF</td>
<td>Metabolized by CYP3A4: caution with inhibitors (eg, verapamil, diltiazem, ketoconazole, macrolide antibiotics, protease inhibitors, grapefruit juice) and inducers (eg, rifampin, phenobarbital, phenytoin)</td>
</tr>
<tr>
<td></td>
<td>Extended release: 200–400 mg once every 12 h</td>
<td>Prolonged QT interval, Prostatisism, glaucoma,</td>
<td>Inhibits CYP2D6: ↑concentrations of tricyclic antidepressants, metoprolol, antipsychotics; ↓efficacy of codeine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Avoid other QT interval–prolonging drugs</td>
<td>Inhibits P-glycoprotein: ↑digoxin concentration</td>
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<tr>
<td>Quinidine</td>
<td>• Immediate release: 324–648 mg every 8 h</td>
<td>Prolonged QT interval, Diarrhea</td>
<td></td>
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<tr>
<td></td>
<td>• 324–648 mg every 8 h</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Vaughan Williams class IC</td>
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<tr>
<td>Flecaïnide</td>
<td>• 50–200 mg once every 12 h</td>
<td>Sinus or AV node dysfunction, HF, CAD, Atrial flutter, Infranodal conduction disease, Brugada syndrome, Renal or liver disease</td>
<td>Metabolized by CYP2D6 (inhibitors include quinidine, fluoxetine, tricyclics; also genetically absent in 7%–10% of population)—poor metabolizers have ↑beta blockade</td>
</tr>
<tr>
<td></td>
<td>• 50–200 mg once every 12 h</td>
<td></td>
<td>Inhibits P-glycoprotein: ↑digoxin concentration</td>
</tr>
<tr>
<td></td>
<td>• 50–200 mg once every 12 h</td>
<td></td>
<td>Inhibits CYP2C9: ↑warfarin concentration (↑INR 25%)</td>
</tr>
<tr>
<td></td>
<td>• 50–200 mg once every 12 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propafenone</td>
<td>Immediate release: 150–300 mg once every 8 h</td>
<td>Sinus or AV node dysfunction</td>
<td>Metabolized by CYP2D6 (inhibitors include quinidine, fluoxetine, tricyclics; also genetically absent in 7%–10% of population) and renal excretion (dual impairment can ↑↑plasma concentration)</td>
</tr>
<tr>
<td></td>
<td>Extended release: 225–425 mg once every 12 h</td>
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<td>• 150–300 mg once every 8 h</td>
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<td>• 150–300 mg once every 8 h</td>
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<td></td>
<td>• 150–300 mg once every 8 h</td>
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<tr>
<td>Vaughan Williams class III</td>
<td></td>
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<tr>
<td>Amiodarone</td>
<td>Oral: 400–600 mg daily in divided doses for 2–4 wk; maintenance typically 100–200 mg QD</td>
<td>Sinus or AV node dysfunction, Infranodal conduction disease, Lung disease, Prolonged QT interval</td>
<td>Metabolizes most CYPs to cause drug interaction: ↑concentrations of warfarin (↑INR 0%–200%), statins, many other drugs</td>
</tr>
<tr>
<td></td>
<td>IV: 150 mg over 10 min; then 1 mg/min for 6 h; then 0.5 mg/min for 18 h or change to oral dosing; after 24 h, consider decreasing dose to 0.25 mg/min</td>
<td></td>
<td>Inhibits P-glycoprotein: ↑digoxin concentration</td>
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<tr>
<td>Dofetilide</td>
<td>125–500 mcg once every 12 h</td>
<td>Prolonged QT interval, Renal disease, Hypokalemia, Hypomagnesemia, Diuretic therapy, Avoid other QT interval–prolonging drugs</td>
<td>Metabolized by CYP3A: caution with inhibitors (eg, verapamil, diltiazem, ketoconazole, macrolide antibiotics, protease inhibitors, grapefruit juice) and inducers (eg, rifampin, phenobarbital, phenytoin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inhibits CYP3A, CYP2D6, P-glycoprotein: ↑concentrations of some statins, sirolimus, tacrolimus, beta blockers, digoxin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dronedarone</td>
<td>400 mg once every 12 h</td>
<td>Bradycardia, HF, Long-standing persistent AF/flutter, Liver disease, Prolonged QT interval</td>
<td></td>
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<tr>
<td>Sotalol</td>
<td>40–160 mg once every 12 h</td>
<td>Prolonged QT interval, Renal disease, Hypokalemia, Hypomagnesemia, Diuretic therapy, Avoid other QT interval–prolonging drugs</td>
<td>None (renal excretion)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sinus or AV nodal dysfunction, HF, Asthma</td>
<td></td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; AV, atrioventricular; CAD, coronary artery disease; HCTZ, hydrochlorothiazide; HF, heart failure; INR, international normalized ratio; IV, intravenous; and QD, once daily.

Adapted with permission from Roden et al.369
6.2.1.1. Specific Drug Therapy

Amiodarone is an iodinated compound that, along with its metabolites, blocks multiple ion channels (eg, I_Ca, I_Ks, I_Kur, I_Kchx, I_Ka,, I_Ks). It is a non-competitive beta-adrenergic antagonist. It has a long half-life of weeks and large volume of distribution into adipose tissue. Although suppression of sinus and AV nodal function can occur early within the first few days of oral therapy, the antiarrhythmic effect and QT prolongation can be delayed for days or weeks. A loading phase accelerates the onset of its antiarrhythmic activity, and administration in divided doses and with food minimizes the gastrointestinal symptoms associated with large doses (2600 mg) during the loading phase. Administration with food also significantly increases the rate and extent of amiodarone absorption. Use of oral amiodarone for AF is associated with the added benefit of effective rate control, frequently eliminating the need for other drugs to control the ventricular rate for AF recurrences. Drug interactions and toxicities, however, are sufficient to preclude its routine use as a rate-controlling agent.

Amiodarone is known to inhibit CYP3A, CYP2C9, P-glycoprotein, and, consequently, the elimination of multiple other medications. In patients also taking warfarin or digoxin, dose reduction in these drugs may be needed upon amiodarone initiation in anticipation of a rise in INR (that can be variable) and serum digoxin level. Doses of other medications for rate control should be reduced when the rate slows after initiation of amiodarone and stopped if the rate slows excessively.

Amiodarone is the most effective available antiarrhythmic drug for maintenance of sinus rhythm in patients with paroxysmal or persistent AF. In direct comparisons, it is more effective than dronedarone, sotalol, or propafenone. A mixed treatment comparison of amiodarone, dronedarone, flecainide, propafenone, and sotalol for the treatment of AF or atrial flutter found that amiodarone had the largest reduction of AF recurrence (OR: 0.22; 95% CI: 0.16 to 0.29) but was associated with the highest rate of patients experiencing ≥1 serious adverse event (OR: 2.41; 95% CI: 0.96 to 6.06) and treatment withdrawals due to adverse events (OR: 2.91; 95% CI: 1.66 to 5.11). Trends for increased mortality (OR: 2.17; 95% CI: 0.63 to 7.51) were found that were stronger when small studies randomizing <100 subjects per group were excluded from the analysis. Amiodarone therapy was associated with an increase in noncardiac mortality in patients with NYHA class III HF in SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial). The major cardiovascular side effect of amiodarone is bradycardia. Marked QT prolongation can occur, but it is very rarely associated with torsades de pointes. Extracardiac toxicities, including thyroid, liver, pulmonary, and ocular and skin discoloration, are a major problem with amiodarone, so it is not a first-choice agent (especially in younger patients) when other antiarrhythmic drugs are an option. The risk of many toxicities, including pulmonary toxicity, is dose related and can be fatal. Chronic oral doses of ≤200 mg daily may be effective and result in fewer side effects than higher-dose regimens. In patients with LV hypertrophy, HF, CAD, and/or previous MI, amiodarone is associated with a low risk of proarrhythmia, making it an appropriate initial choice to prevent recurrent AF in these clinical settings. Appropriate surveillance for lung, liver, and thyroid toxicity is warranted.

Flecainide and Propafenone are Vaughan Williams class IC drugs that may be considered for rhythm control in patients with AF without structural heart disease. Flecainide, along with other potent sodium channel–blocking drugs, increased mortality in patients with prior MI and therefore should be avoided in patients with ischemic heart disease. In addition, both drugs are negative inotropes and should be avoided in patients with LV dysfunction.

These medications can cause slowing of the atrial rate in atrial flutter, resulting in 1:1 AV conduction and an increased ventricular rate; therefore, concomitant AV nodal blocking medication is recommended. Drug-induced, use-dependent increases in PR and QRS durations of up to 25% compared with baseline can also occur during sinus rhythm. However, a greater increase in the QRS duration may be a marker for proarrhythmia risk. These agents should be used with caution in the presence of significant conduction system disease, including intraventricular conduction delay or bundle-branch block in the absence of a pacing system. Noncardiac side effects are uncommon and include dizziness and visual disturbance, and propafenone can cause a metallic taste. The parent compound has beta-blocker properties, and its metabolites are electrophysiologically active with weak beta-blocking activity. Propafenone is a substrate for CYP2D6, which is genetically absent in approximately 7% of patients (poor metabolizers) and is inhibited by quinidine, fluoxetine, and tricyclic antidepressants, among others. Thus, drug interactions and genetic susceptibility can cause abnormally increased plasma concentrations of propafenone, resulting in significant beta blockade.

Sotalol, an I_Ks inhibitor and beta blocker, is not effective for conversion of AF to sinus rhythm but may be used to prevent recurrent AF. Much like with other antiarrhythmic drugs, with the exception of amiodarone, the rates of maintaining sinus rhythm at 1 year for sotalol are 30% to 50%. Sotalol is renally cleared and should be used with caution or avoided in patients with CKD or unstable renal function. Sotalol causes drug-induced QT-interval prolongation, so it should be administered with caution or avoided when administered with other drugs known to prolong the QT interval. During follow-up, serum potassium and magnesium levels and renal function should be checked periodically. Trends toward increased mortality for sotalol (OR: 3.44; 95% CI: 1.02 to 11.39) were observed in a comparison study, and it is likely that proarrhythmia is a contributing mechanism. Some experts initiate sotalol in hospital with electrocardiographic monitoring to observe for QT prolongation and proarrhythmia in the absence of an implanted cardioverter-defibrillator.

Dofetilide is a potent and selective inhibitor of I_Ks that may be considered for rhythm control in patients who are at low risk for torsades de pointes induced by QT-interval prolongation. Dofetilide has minimal noncardiac side effects. In the SAIFIRE-D (Symptomatic Atrial Fibrillation Investigative Research on Dofetilide) trial, dofetilide (500 mcg twice daily)
exhibited 58% efficacy in maintaining sinus rhythm at 1 year after cardioversion, compared with only 25% in the placebo group.\textsuperscript{310} Torasdes de points occurred with an incidence of 0.8%. Dofetilide was discontinued because of excessive QT prolongation in 5% of patients. In the DIAMOND (Danish Investigations of Arrhythmia and Mortality On Dofetilide) study of patients with reduced LV function, sinus rhythm was maintained at 1 year in 79% of the dofetilide group compared with 42% of the placebo group.\textsuperscript{316} In the United States, for initiation or dose escalation of therapy, inpatient electrocardiographic monitoring is mandatory, as was the case in clinical trials. Under these circumstances, dofetilide does not increase mortality in HF and post-MI populations.\textsuperscript{373} It is renally cleared, dosed according to CrCl, and adjusted or discontinued depending on the degree of QT prolongation. It should not be administered concomitantly with multiple other drugs that influence dofetilide disposition (Table 13) or can prolong the QT interval.

**Dronedarone** may be considered for rhythm control in patients who do not have HF; dronedarone is a structural analogue of amiodarone but lacks the iodine moieties of amiodarone. It is associated with a lower incidence of adverse events than amiodarone but is also less efficacious.\textsuperscript{360} Its multiple electrophysiological actions include sympatholytic effects as well as blocking of calcium, sodium, and potassium currents. Dronedarone reduced the combined endpoint of death and cardiovascular complications (largely by reducing hospitalizations for AF) in patients with paroxysmal or persistent AF or atrial flutter and risk factors for thromboembolism.\textsuperscript{399}

Dronedarone increases mortality in patients with recently uncompromised HF and depressed LV function\textsuperscript{543} and is contraindicated in patients with NYHA class III or IV HF and in patients who have had an episode of decompensated HF in the past 4 weeks, especially if they have depressed LV function. In patients with permanent AF, dronedarone increases the combined endpoint of stroke, cardiovascular death, and hospitalization.\textsuperscript{282} Therefore, dronedarone is contraindicated in patients whose sinus rhythm is not restored.

The major cardiac adverse effects of dronedarone are bradycardia and QT prolongation. Torasdes de points is rare but has been reported. Like amiodarone, dronedarone inhibits its renal tubular secretion of creatinine, which can increase plasma creatinine levels. However, there is no reduction in the glomerular filtration rate. Dronedarone is metabolized by CYP3A4 and is a moderate inhibitor of CYP2D6 and P-glycoprotein. Consequently, it increases levels of digoxin and dabigatran and should not be administered with strong inhibitors of CYP3A4 (eg, ketoconazole and macrolide antibiotics), which may potentiate its effects. Dronedarone can be administered with verapamil or diltiazem, which are moderate CYP3A4 inhibitors, but low doses of these agents should be used initially and titrated according to response and tolerance. Dronedarone does not alter the INR when used with warfarin. Dronedarone has been associated with rare case reports of severe hepatotoxicity occurring within 6 months of initiation; therefore, hepatic serum enzymes should be monitored, especially during the first 6 months of treatment.

**Disopyramide** is a sodium channel–blocking drug with potent anticholinergic and negative inotropic effects that can be considered for rhythm control in patients with AF. Disopyramide can reduce recurrence of AF after direct-current cardioversion.\textsuperscript{374} Because of its prominent vagolytic pharmacological effects, disopyramide is useful in AF that occurs in the setting of high vagal tone ("vagally mediated AF"), such as sleep and in response to stimuli that elicit a vagal response, but there is little supporting evidence for this approach. Its negative inotropic effects may be desirable in patients with HCM associated with dynamic outflow tract obstruction.\textsuperscript{393} Otherwise, it is avoided in structural heart disease. Disopyramide can also prolong the QT interval.

**Quinidine** has a sodium channel–blocking effect at rapid heart rates and a potassium channel–blocking effect at slower heart rates, as well as vagolytic and alpha-adrenergic receptor–blocking effects, and was among the first antiarrhythmic drugs used to treat AF. It prolongs the QT interval, can cause torsades de pointes, and is used infrequently. Cumulative evidence from a systematic review suggests that quinidine and disopyramide may increase mortality slightly.\textsuperscript{365} Quinidine has no negative inotropic effects and can be used when there is advanced renal dysfunction. Quinidine requires close electrocardiographic monitoring at initiation and may be an alternative treatment for AF when other, newer antiarrhythmic drugs cannot be used.

**Beta blockers** are usually not considered effective for maintaining sinus rhythm in patients with AF. One placebo-controlled study of 394 patients with persistent AF found a lower risk of early recurrence after cardioversion and slower ventricular response with sustained-release metoprolol than with placebo.\textsuperscript{376} Combining an antiarrhythmic drug with a beta blocker may be helpful in some patients. These agents are useful to prevent AF in patients following cardiac surgery and during a high adrenergic state, such as exercise and thyrotoxicosis-related AF. At least theoretically, they can aggravate vagally mediated AF.

*See Online Data Supplement 12 for additional data on antiarrhythmic drug therapy.*

### 6.2.1.2. Outpatient Initiation of Antiarrhythmic Drug Therapy

Drug-related proarrhythmia is most common during the initiation phase of drug therapy. Serial ECGs are important to detect excessive QT prolongation (such as with dofetilide or sotalol), the appearance of "giant" U waves, or QRS prolongation >25% (such as with flecainide or propafenone), and should be performed near the time of peak drug concentration.\textsuperscript{377} Inpatient initiation or dose escalation of dofetilide in an electrocardiographic-monitored environment is required because of the risk of untoward QT-interval prolongation and arrhythmia provocation.\textsuperscript{332,336} Sotalol also results in QT prolongation and may cause proarrhythmia. Its initiation and dose escalation during hospitalization with electrocardiographic monitoring should be considered; the package insert has a corresponding black box warning. There is considerable experience, however, initiating sotalol in an outpatient setting. Some experts allow outpatient initiation when sotalol is started with the patient in sinus rhythm, provided that the QT interval and serum potassium level are normal and no other QT interval–prolonging medications are present, but require inpatient hospitalization when sotalol is initiated while a patient is in AF.\textsuperscript{316} Other experts always initiate sotalol in an inpatient-monitored setting.
Practice patterns vary widely both in terms of which patients are hospitalized for initiation of antiarrhythmic drug therapy and in length of hospitalization. The decision about whether to initiate other antiarrhythmic drugs in an inpatient or outpatient setting should be carefully individualized. Data supporting the outpatient initiation of antiarrhythmic drug therapy are best established for amiodarone and dronedarone (Table 13).

See Online Data Supplement 13 for additional data on antiarrhythmic drug therapy.

### 6.2.2. Upstream Therapy: Recommendations

#### Class IIa

1. An ACE inhibitor or angiotensin-receptor blocker (ARB) is reasonable for primary prevention of new-onset AF in patients with HF and LVEF < 30% (Level of Evidence: B)

#### Class IIb

1. Therapy with an ACE inhibitor or ARB may be considered for primary prevention of new-onset AF in the setting of hypertension (Level of Evidence: B)
2. Statin therapy may be reasonable for primary prevention of new-onset AF after coronary artery surgery (Level of Evidence: A)

#### Class III: No Benefit

1. Therapy with an ACE inhibitor, ARB, or statin is not beneficial for primary prevention of AF in patients without cardiovascular disease (Level of Evidence: B)

The goal of “upstream” therapy (ie, ACE inhibitors, ARBs, statins, and n-3 polyunsaturated fatty acids) is to modify the atrial substrate to reduce susceptibility to, or progression of, AF. Agents delivered as upstream drug therapy might have the ability to halt or delay the cellular processes leading to AF either before (primary prevention) or after (secondary prevention) the development of AF.

A number of prospective trials investigating ARBs and polyunsaturated fatty acids for prevention of recurrent AF have been disappointing. Although upstream therapies may be valuable strategies for primary prevention of cardiac changes leading to AF in selected patients, reversal of AF substrate has not been demonstrated, and such therapy is not recommended for the prevention of recurrence of AF in patients without another indication. In retrospective studies and studies in which AF was a prespecified secondary endpoint, ACE inhibitors or ARBs slightly reduce the development of AF in patients with HF and LV dysfunction and possibly those with hypertension and LV hypertrophy. Several systematic reviews of statin therapy to prevent AF have been performed. The administration of statins may reduce postoperative AF in patients undergoing coronary artery bypass graft surgery.

See Online Data Supplement 14 for additional data on upstream therapy.

### 6.3. AF Catheter Ablation to Maintain Sinus Rhythm: Recommendations

#### Class I

1. AF catheter ablation is useful for symptomatic paroxysmal AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication when a rhythm-control strategy is desired (Level of Evidence: A)
2. Before consideration of AF catheter ablation, assessment of the procedural risks and outcomes relevant to the individual patient is recommended (Level of Evidence: C)

#### Class IIa

1. AF catheter ablation is reasonable for some patients with symptomatic persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication (Level of Evidence: A)
2. In patients with recurrent symptomatic paroxysmal AF, catheter ablation is a reasonable initial rhythm-control strategy before therapeutic trials of antiarrhythmic drug therapy, after weighing the risks and outcomes of drug and ablation therapy (Level of Evidence: B)

#### Class IIb

1. AF catheter ablation may be considered for symptomatic long-standing (>12 months) persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication when a rhythm-control strategy is desired (Level of Evidence: B)
2. AF catheter ablation may be considered before initiation of antiarrhythmic drug therapy with a class I or III antiarrhythmic medication for symptomatic persistent AF when a rhythm-control strategy is desired (Level of Evidence: C)

#### Class III: Harm

1. AF catheter ablation should not be performed in patients who cannot be treated with anticoagulant therapy during and after the procedure (Level of Evidence: C)
2. AF catheter ablation to restore sinus rhythm should not be performed with the sole intent of obviating the need for anticoagulation (Level of Evidence: C)

The role of catheter ablation in the management of AF continues to evolve rapidly, with improvements in the efficacy and safety of the procedure. The efficacy of radiofrequency catheter ablation for maintaining sinus rhythm is superior to current antiarrhythmic drug therapy for maintenance of sinus rhythm in selected patient populations. A number of systematic reviews of the efficacy of AF catheter ablation versus antiarrhythmic drug therapy have been performed. Cryoballoon ablation is an alternative to point-by-point radiofrequency ablation to achieve pulmonary vein isolation. The evidence supporting the efficacy of catheter ablation is strongest for paroxysmal AF in younger patients with little to no structural heart...
disease and in procedures performed in highly experienced centers. Studies have demonstrated a reduction of AF-related symptoms in these contexts. Evidence is insufficient to determine whether AF catheter ablation reduces all-cause mortality, stroke, and HF. Ongoing clinical trials (CABANA [Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation] and EAST [Early Therapy of Atrial Fibrillation for Stroke Prevention Trial]) should provide new information for assessing whether AF catheter ablation is superior to standard therapy with either rate- or rhythm-control drugs for reducing total mortality and other secondary outcome measures and whether early application of a rhythm-control therapy involving ablation, antiarrhythmic drugs, or both can impact endpoints of stroke, cardiovascular death, or HF compared with usual care. These important trials will help address whether catheter ablation provides benefit beyond improvements in quality of life.

See Online Data Supplements 15 and 16 for additional data on maintaining sinus rhythm and AF catheter ablation.

6.3.1. Patient Selection

The decision whether to pursue catheter ablation depends on a large number of variables, including the type of AF (paroxysmal versus persistent versus long-standing persistent), degree of symptoms, presence of structural heart disease, candidacy for alternative options such as rate control or antiarrhythmic drug therapy, likelihood of complications, and patient preference. It is important to recognize that most patients enrolled in trials of AF catheter ablation have generally been younger, healthy persons with symptomatic paroxysmal AF refractory to 1 or more antiarrhythmic medications. The safety and efficacy of catheter ablation are less well established for other populations of patients, especially patients with long-standing persistent AF, very elderly patients, and patients with significant HF, including tachycardia-induced cardiomyopathy (Section 6.3). Figure 7 shows an approach to the integration of antiarrhythmic drugs and catheter ablation of AF in patients without and with structural heart disease.

Two RCTs compared radiofrequency catheter ablation with antiarrhythmic drug therapy as a first-line rhythm-control treatment. The RAAFT (Radiofrequency Ablation Versus Antiarrhythmic Drugs for Atrial Fibrillation Treatment)-2 trial compared the efficacy of AF catheter ablation with that of antiarrhythmic drug therapy as first-line therapy for rhythm control in 127 patients (88% with paroxysmal AF) with a higher 1-year freedom from AF (45% versus 28%; \( P = 0.02 \)). The MANTRA-PAF (Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation) trial compared AF catheter ablation with antiarrhythmic drug therapy as first-line therapy in 294 patients. At the 24-month follow-up, more patients in the ablation group were free from any AF or symptomatic AF, and quality of life was significantly better. However, total AF burden was not significantly different between the 2 groups, and major complications requiring intervention were more common in the ablation group. On the basis of these data, radiofrequency catheter ablation may be considered as first-line therapy in select patients before a trial of antiarrhythmic drug therapy when a rhythm-control strategy is desired.

6.3.2. Recurrence After Catheter Ablation

Recurrences of AF after catheter ablation are common during the first 3 months and do not preclude long-term success, although they are associated with an increased risk of procedural failure and rehospitalization. Therefore, when AF occurs early after catheter ablation, a pharmacological rhythm-control approach rather than early repeat ablation should be considered. Patients who have had AF catheter ablation and

![Figure 7. Strategies for rhythm control in patients with paroxysmal* and persistent AF. † "Catheter ablation is only recommended as first-line therapy for patients with paroxysmal AF (Class Ila recommendation). †† Drugs are listed alphabetically. ‡ Depending on patient preference when performed in experienced centers. § Not recommended with severe LVH (wall thickness >1.5 cm). || Should be used with caution in patients at risk for torsades de pointes ventricular tachycardia. ¶ Should be combined with AV nodal blocking agents. AF indicates atrial fibrillation; AV, atrioventricular; CAD, coronary artery disease; HF, heart failure; and LVH, left ventricular hypertrophy.](http://circ.ahajournals.org/)}
develop persistent AF within the 3 months following ablation may require cardioversion. Recurrent AF after 3 months is usually an indication of recovery of pulmonary vein conduction and may respond to repeat ablation or initiation of an antiarrhythmic drug. A number of centers have reported late AF recurrences >1 year after catheter ablation.

6.3.3. Anticoagulation Therapy Periablation
Because of the well-established risk of periprocedure stroke or TIA associated with AF catheter ablation, there is consensus that anticoagulation is indicated to prevent thromboembolism around the time of radiofrequency catheter ablation regardless of the patient’s baseline thromboembolic risk. Detailed consensus recommendations have been published about the approach to anticoagulation before, during, and after catheter ablation. Both intraprocedural heparin and oral anticoagulation are recommended for ≥2 months postprocedure. AF catheter ablation should not be performed in patients who cannot be treated with anticoagulant therapy during and after the procedure.

Several reports indicate that AF catheter ablation may be performed with fewer complications when oral warfarin anticoagulation is continued as an alternative to a bridging approach with UFH or LMWH. Several centers reported their experience with the use of direct thrombin and factor Xa inhibitors (mainly dabigatran) around the time of AF catheter ablation. Typically, dabigatran was held for 1 or 2 doses before the ablation procedure, in part reflecting the lack of a reversal agent. These reports suggest that the use of dabigatran is associated with a similar risk of bleeding and thromboembolic complications compared with uninterrupted warfarin; however, this is not a uniform finding. Continuation of anticoagulation ≥2 months after AF catheter ablation, if the procedure is perceived as successful, should be based on consideration of the patient’s thromboendarmic risk profile (Section 4.1), bleeding risk, and patient choice. Recurrence of AF after ablation is 3 to 7 times more likely to be asymptomatic compared with before ablation, and AF can recur late. Several large case series have reported a low risk of stroke after AF ablation. Although the stroke rate is low in these series, few patients at high risk of stroke were monitored after anticoagulation was stopped for a significant period of time.

6.3.4. Catheter Ablation in HF
A number of smaller clinical trials have evaluated the role of AF catheter ablation in selected patients with LV dysfunction and HF and demonstrate a reasonable rate of successful sinus rhythm maintenance with improvements in LVEF and symptoms. The degree to which LVEF improves varies according to patient characteristics. In cases where LV dysfunction is thought to be due to AF itself, AF catheter ablation and maintenance of sinus rhythm may result in a marked improvement. It may be difficult to determine in this population whether symptoms are related to AF or the underlying HF and whether AF itself has contributed to the decline in LVEF. Improved rate control or cardioversion with antiarrhythmic drug therapy may help determine the causality. Because of the extent of remodeling and underlying heart disease, recurrence rates and complication rates are higher in this population. A meta-analysis reported that the single-procedure efficacy of AF catheter ablation was lower in patients with systolic dysfunction, but a similar success rate could be achieved among patients with and without systolic dysfunction with repeat procedures. Patient selection biases likely influence reported outcomes. Taken as a whole, catheter ablation may be reasonable to treat symptomatic AF in selected patients with significant LV dysfunction and HF.

6.3.5. Complications Following AF Catheter Ablation
AF catheter ablation is associated with important risks of major complications. A 2010 international survey of radiofrequency catheter ablation procedures reported a 4.5% incidence of major complications, including a 1.3% rate of cardiac tamponade, a 0.94% rate of stroke or TIA, a 0.04% rate of atrial-esophageal fistula, and a 0.15% rate of death. A European observational multinational registry reported a complication rate of 7.7%, of which 1.7% were major complications. A report from a statewide inpatient database described a complication rate of 5% with a 9% readmission rate. Much of the data on rates of complications is derived from experienced centers or voluntary registries.

Table 14 lists the complications associated with radiofrequency catheter ablation for AF. A detailed summary of definitions and prevention of specific complications is covered elsewhere. Factors associated with complication rates include older age, female sex, and a CHADS2 score ≥2. Also, LA catheter ablation results in a small incidence of asymptomatic cerebral embolism detectable on cranial magnetic resonance imaging. Most of these lesions resolve or disappear over time. Further research is needed to better define the relationship between ablation strategy and risk and to determine methods to eliminate them.

6.4. Pacemakers and Implantable Cardioverter-Defibrillators for Prevention of AF
The primary role of pacemakers in the treatment of patients with AF is treatment of symptomatic bradycardia, which is often related to underlying sick sinus syndrome. Antiarrhythmic therapy may exacerbate sick sinus syndrome and require pacemaker implantation. For patients with sick sinus syndrome who need pacing, atrial or dual-chamber pacing significantly decreases the incidence of subsequent AF compared with RV pacing. Attempts to prevent AF episodes by proprietary overdrive atrial pacing algorithms that react to premature atrial complexes are inconsistent. Therefore, permanent pacing is not indicated for the prevention of AF in patients without other indications for pacemaker implantation. Atrial defibrillators to automatically cardiovert AF do not have clinical value; most patients find discharge energies >1 J uncomfortable, and early recurrence of AF following a shock is common. Implanted defibrillators are not indicated for rhythm control of AF.

6.5. Surgical Maze Procedures: Recommendations
Class IIa

1. An AF surgical ablation procedure is reasonable for selected patients with AF undergoing cardiac surgery for other indications. (Level of Evidence: C)
Class IIb

1. A stand-alone AF surgical ablation procedure may be reasonable for selected patients with highly symptomatic AF not well managed with other approaches.440 (Level of Evidence: B)

The surgical maze procedure was introduced in 1987. The initial 2 iterations were associated with high rates of pacemaker implantation and are no longer performed. The third version (Cox maze III) became the standard surgical procedure to restore sinus rhythm in patients with AF441 but is not widely performed because of surgeons’ reluctance to perform this complicated “cut and sew” atrial lines of ablation approach in association with valve or coronary artery bypass procedures or as a stand-alone procedure. The Cox maze intravenous operation is less invasive, using radiofrequency or cryoablation to replicate surgical lines of ablation.442

Data on long-term outcomes in patients undergoing stand-alone AF surgery are limited. Of 282 patients prospectively studied from 2002 to 2009 who underwent the Cox maze IV procedure, 42% had paroxysmal AF and 58% had either persistent or long-standing persistent AF.442 Ninety-five of 282 patients (34%) had a stand-alone procedure, and 187 of 282 patients (66%) had a concomitant AF procedure. Overall operative mortality was 2% (1% in stand-alone maze procedures), and freedom from atrial tachyarrhythmias was 89%, 93%, and 89% at 3, 6, and 12 months, respectively. Freedom from atrial tachyarrhythmias off all antiarrhythmic drugs was 63%, 79%, and 78% at 3, 6, and 12 months, respectively. In the period of the study subsequent to 2006, 24-hour Holter monitoring or pacemaker interrogation was performed in these patients. In this cohort, 92% were free of atrial tachyarrhythmias, and 78% were not taking antiarrhythmic drugs.442

Nine RCTs comparing patients who undergo concomitant AF surgery with patients who undergo mitral valve surgery alone suggest greater freedom from AF in treated patients443–451; however, in the composite body of evidence, there was no consistent surgical technique, patient populations in the trial were quite varied, a consistent endpoint defining procedural success was lacking, and long-term clinical endpoints were often missing as well.

The Society of Thoracic Surgeons Adult Cardiac Surgery Database from 2005 to 2010 recorded 91,801 AF surgical ablations, of which 4893 (5.3%) were stand-alone procedures.452 Propensity matching of 1708 patients with and without cardio pulmonary bypass showed no difference in mortality risk between groups, but the “off bypass group” had fewer

<table>
<thead>
<tr>
<th>Complication</th>
<th>Symptoms/Signs</th>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>Air embolism</td>
<td>Acute ischemia, cardiac arrest, AV block, hypotension</td>
<td>Supplemental oxygen, fluids, CPR, or pacing if indicated</td>
</tr>
<tr>
<td>Atrial-esophageal fistula</td>
<td>Usually 1–4 wk after ablation, dysphagia, unexplained fever, chills, sepsis, neurological events (septic emboli)</td>
<td>CT or MRI of esophagus, avoiding endoscopy, immediate surgical correction</td>
</tr>
<tr>
<td>Cardiac tamponade/perforation</td>
<td>Abrupt or gradual fall in BP</td>
<td>Pericardiocentesis, emergent surgical drainage if pericardiocentesis fails</td>
</tr>
<tr>
<td>Phrenic nerve injury resulting in diaphragmatic paralysis</td>
<td>Shortness of breath, elevated hemidiaphragm</td>
<td>None; usually resolves spontaneously</td>
</tr>
<tr>
<td>Iatrogenic atrial flutter</td>
<td>Tachycardia</td>
<td>Cardioversion, antiarrhythmic drugs, or repeat ablation</td>
</tr>
<tr>
<td>Gastric motility disorder</td>
<td>Nausea, vomiting, bloating, abdominal pain</td>
<td>Depends on severity of symptoms</td>
</tr>
<tr>
<td>Mitral valve injury requiring surgery</td>
<td>Entrainment of catheter</td>
<td>Advance sheath with gentle catheter retraction, surgical removal</td>
</tr>
<tr>
<td>MI</td>
<td>Chest pain, ST changes, hypotension</td>
<td>Standard therapy</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>Chest pain, typical quality</td>
<td>NSAIDs, colchicine, steroids</td>
</tr>
<tr>
<td>Pulmonary vein stenosis</td>
<td>Shortness of breath, cough, hemoptysis</td>
<td>PV dilation/stent or no therapy</td>
</tr>
<tr>
<td>Radiation injury</td>
<td>Pain and reddening at radiation site; can present late</td>
<td>Treat as burn injury</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>Neurological deficit</td>
<td>Consider lysis therapy</td>
</tr>
<tr>
<td>Vascular access complications</td>
<td>Pain or pulsatile mass at groin</td>
<td>Observation, compression, thrombin injection, possible surgery</td>
</tr>
<tr>
<td>• Femoral pseudoaneurysm</td>
<td>Pain, bruit at groin site</td>
<td>Observation, compression, possible surgery</td>
</tr>
<tr>
<td>• Arteriovenous fistula</td>
<td>Pain, swelling</td>
<td>Compression</td>
</tr>
<tr>
<td>• Hematoma</td>
<td>None; usually resolves spontaneously</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; AV, atrioventricular; BP, blood pressure; CPR, cardiopulmonary resuscitation; CT, computed tomography; MI, myocardial infarction; MRI, magnetic resonance imaging; N/A, not applicable; NSAIDs, nonsteroidal anti-inflammatory drugs; PV, pulmonary valve; and TIA, transient ischemic attack.
Table 15. Summary of Recommendations for Specific Patient Groups and AF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
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<tbody>
<tr>
<td><strong>Hypertrophic cardiomyopathy</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Anticoagulation is indicated in HCM with AF independent of the CHA2DS2-VASc score</td>
<td>I</td>
<td>B</td>
<td>50, 457</td>
</tr>
<tr>
<td>Antiarrhythmic drugs can be useful to prevent recurrent AF in HCM. Amiodarone or disopyramide combined with a beta blocker or nondihydropyridine calcium channel antagonist are reasonable</td>
<td>Ila</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>AF catheter ablation can be beneficial for HCM to facilitate a rhythm-control strategy when antiarrhythmics fail or are not tolerated</td>
<td>Ila</td>
<td>B</td>
<td>458–461</td>
</tr>
<tr>
<td>Sotalol, dofetilide, and dronedarone may be considered for a rhythm-control strategy in HCM</td>
<td>IIb</td>
<td>C</td>
<td>11</td>
</tr>
<tr>
<td><strong>AF complicating ACS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urgent cardioversion of new-onset AF in the setting of ACS is recommended for patients with hemodynamic compromise, ongoing ischemia, or inadequate rate control</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>IV beta blockers are recommended to slow RVR with ACS and no HF, hemodynamic instability, bronchospasm</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>With ACS and AF with CHA2DS2-VASc score ≥2, anticoagulation with warfarin is recommended unless contraindicated</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Amiodarone or digoxin may be considered to slow RVR with ACS and AF and severe LV dysfunction and HF or hemodynamic instability</td>
<td>IIb</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Nondihydropyridine calcium antagonists might be considered to slow RVR with ACS and AF only in the absence of significant HF or hemodynamic instability</td>
<td>IIb</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Hyperthyroidism</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blockers are recommended to control ventricular rate with AF complicating thyrotoxicosis unless contraindicated</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>When beta blockers cannot be used, a nondihydropyridine calcium channel antagonist is recommended to control ventricular rate</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Pulmonary diseases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A nondihydropyridine calcium channel antagonist is recommended to control ventricular rate with AF and COPD</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Cardioversion should be attempted for patients with pulmonary disease who become hemodynamically unstable with new-onset AF</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>WPW and pre-excitation syndromes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioversion is recommended for patients with AF, WPW syndrome, and RVR who are hemodynamically compromised</td>
<td>I</td>
<td>C</td>
<td>64</td>
</tr>
<tr>
<td>IV procainamide or ibutilide to restore sinus rhythm or slow ventricular rate is recommended for patients with pre-excited AF and RVR who are not hemodynamically compromised</td>
<td>I</td>
<td>C</td>
<td>64</td>
</tr>
<tr>
<td>Catheter ablation of the accessory pathway is recommended in symptomatic patients with pre-excited AF, especially if the accessory pathway has a short refractory period</td>
<td>I</td>
<td>C</td>
<td>64</td>
</tr>
<tr>
<td>IV amiodarone, adenosine, digoxin, or nondihydropyridine calcium channel antagonists in patients with WPW syndrome who have pre-excited AF is potentially harmful</td>
<td>III: Harm</td>
<td>B</td>
<td>493–495</td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A beta blocker or nondihydropyridine calcium channel antagonist is recommended for persistent or permanent AF in patients with HFpEF</td>
<td>I</td>
<td>B</td>
<td>269</td>
</tr>
<tr>
<td>In the absence of preexcitation, an IV beta blocker (or a nondihydropyridine calcium channel antagonist with HFpEF) is recommended to slow ventricular response to AF in the acute setting, with caution in patients with overt congestion, hypotension, or HFpEF</td>
<td>I</td>
<td>B</td>
<td>502–505</td>
</tr>
<tr>
<td>In the absence of pre-excitation, IV digoxin or amiodarone is recommended to control heart rate acutely</td>
<td>I</td>
<td>B</td>
<td>277, 503, 506, 507</td>
</tr>
<tr>
<td>Assess heart rate during exercise and adjust pharmacological treatment in symptomatic patients during activity</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Digoxin is effective to control resting heart rate with HFpEF</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>A combination of digoxin and beta blocker (or a nondihydropyridine calcium channel antagonist with HFpEF) is reasonable to control resting and exercise heart rate with AF</td>
<td>Ila</td>
<td>B</td>
<td>267, 503</td>
</tr>
<tr>
<td>It is reasonable to perform AV node ablation with ventricular pacing to control heart rate when pharmacological therapy is insufficient or not tolerated</td>
<td>Ila</td>
<td>B</td>
<td>269, 508, 509</td>
</tr>
<tr>
<td>IV amiodarone can be useful to control heart rate with AF when other measures are unsuccessful or contraindicated</td>
<td>Ila</td>
<td>C</td>
<td>N/A</td>
</tr>
</tbody>
</table>

(Continued)
reoperations for bleeding, shorter hospital stays, and less prolonged ventilation. Minimally invasive stand-alone operations, bilateral pulmonary vein isolation, intraoperative confirmation of mapping, ablation of ganglionic plexi, and exclusion of the LAA procedures have been developed. Of 114 patients undergoing bilateral minithoracotomy surgical ablation of AF, 10% (11 patients) died within the perioperative period, and the overall complication rate was 10%.443 At the 6-month follow-up, 2 patients (1.8%) died within the perioperative period, and the overall complication rate was 10%.443

### Table 15. Continued

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>With AF and RVR causing or suspected of causing tachycardia-induced cardiomyopathy, it is reasonable to achieve rate control by AV nodal blockade or a rhythm-control strategy</td>
<td>IIa</td>
<td>B</td>
<td>51, 307, 510</td>
</tr>
<tr>
<td>In patients with chronic HF who remain symptomatic from AF despite a rate-control strategy, it is reasonable to use a rhythm-control strategy</td>
<td>IIa</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Amiodarone may be considered when resting and exercise heart rate cannot be controlled with a beta blocker (or a nondihydropyridine calcium channel antagonist with HFpEF) or digoxin, alone or in combination</td>
<td>IIb</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>AV node ablation may be considered when rate cannot be controlled and tachycardia-mediated cardiomyopathy is suspected</td>
<td>IIb</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>AV node ablation should not be performed without a pharmacological trial to control ventricular rate</td>
<td>III: Harm</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>For rate control, IV nondihydropyridine calcium channel antagonists, IV beta blockers, and dronedarone should not be given with decompensated HF</td>
<td>III: Harm</td>
<td>C</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Familial (genetic) AF**

For patients with AF and multigenerational family members with AF, referral to a tertiary care center for genetic counseling and testing may be considered.

### Postoperative cardiac and thoracic surgery

- A beta blocker is recommended to treat postoperative AF unless contraindicated
- A nondihydropyridine calcium channel blocker is recommended when a beta blocker is inadequate to achieve rate control with postoperative AF
- Preoperative amiodarone reduces AF with cardiac surgery and is reasonable as prophylactic therapy for patients at high risk of postoperative AF
- It is reasonable to restore sinus rhythm pharmacologically with ibutilide or direct-current cardioversion with postoperative AF
- It is reasonable to administer antithrombotic medications for postoperative AF
- It is reasonable to administer antiarrhythmic medications to maintain sinus rhythm with recurrent or refractory postoperative AF
- It is reasonable to administer antithrombotic medications for postoperative AF with cardioversion if AF does not revert spontaneously to sinus rhythm during follow-up
- Prophylactic sotalol may be considered for patients with AF risk after cardiac surgery
- Calchicine may be considered postoperatively to reduce AF after cardiac surgery

ACS indicates acute coronary syndromes; AF, atrial fibrillation; AV, atrioventricular; CHA2DS2-VASc, Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, Prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65 to 74 years, Sex category; COPD, chronic obstructive pulmonary disease; COR, Class of Recommendation; HCM, hypertrophic cardiomyopathy; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; IV, intravenous; LV, left ventricular; N/A, not applicable; RVR, rapid ventricular response; and WPW, Wolff-Parkinson-White.

### 7. Specific Patient Groups and AF

See Table 15 for a summary of recommendations for this section and Online Data Supplement 17 for additional data on specific patient groups and AF.

#### 7.1. Athletes

Paroxysmal or persistent AF is common in athletes and may be autonomic mediated or triggered by other supraventricular tachycardias.454 Contributing conditions such as hypertension and CAD should be considered, particularly for older athletes, and a transthoracic echocardiogram is helpful to evaluate for structural heart disease. Evaluation of the rate...
of ventricular response during an episode of AF is warranted and may require ambulatory electrocardiographic monitoring and/or exercise testing to a level of exertion similar to that of the intended sport. Other therapies such as radiofrequency catheter ablation or a “pill-in-the-pocket” approach can be considered in athletes. Specifics of these therapies are considered in Section 6.1.3.455

7.2. Elderly
The prevalence of AF increases with age, and approximately 35% of patients with AF are ≥80 years of age.30,31 The elderly are a heterogeneous group with potential for multiple comorbidities (Table 3). It is critical to consider the implications of comorbidities to ensure that the patient’s overall goals of care are factored into management decisions. For the older patient with AF, symptoms may be minimal and somewhat atypical. The risk of stroke is increased in the elderly. For this reason, the CHA2DS2-V ASc risk scoring system identifies 65 to 74 years of age as a minor risk factor for stroke and ≥75 years of age as a major risk factor for stroke (Section 4.1).

Because AF is often associated with minimal or no symptoms in this population and the clearance of antiarrhythmic medications is diminished, sensitivity to proarrhythmic effects, including bradycardias, is often increased. Therefore, a rate-control strategy is often preferred,30 and direct-current cardioversion is less often warranted.456 Typically, rate control can be achieved with beta blockers or nondihydropyridine calcium channel antagonists. Care must be taken in these patients because they are often more susceptible to orthostatic hypotension or bradycardias and when AF is paroxysmal and sinus node dysfunction is more common. Comorbidities should also be considered. Digoxin can be useful for rate control in the relatively sedentary individual, but there are concerns about its risks (Section 5.1.3).

7.3. Hypertrophic Cardiomyopathy: Recommendations

Class I

1. Anticoagulation is indicated in patients with HCM with AF independent of the CHA2DS2-VASc score.50,467 (Level of Evidence: B)

Class IIa

1. Antiarrhythmic medications can be useful to prevent recurrent AF in patients with HCM. Amiodarone or disopyramide combined with a beta blocker or nondihydropyridine calcium channel antagonists are reasonable for therapy. (Level of Evidence: C)
2. AF catheter ablation can be beneficial in patients with HCM in whom a rhythm-control strategy is desired when antiarrhythmic drugs fail or are not tolerated.458–461 (Level of Evidence: B)

Class IIb

1. Sotalol, dofetilide, and dronedarone may be considered for a rhythm-control strategy in patients with HCM.11 (Level of Evidence: C)

Patients with HCM are considered separately because their unique pathology distinguishes them from other patients with LV hypertrophy. HCM is defined on the basis of standard criteria such as the echocardiographic identification of a hypertrophied, nondilated LV in the absence of another cardiac or systemic disease capable of producing the magnitude of hypertrophy evident.462 AF is relatively common in HCM, increases with age, and is often poorly tolerated symptomatically.30 The incidence of AF is estimated at 2% per year in patients with HCM, and approximately two thirds of patients with both HCM and AF are paroxysmal.30 AF is associated with increased mortality in patients with HCM (3% in patients with AF versus 1% in sinus rhythm per year)463 and is primarily due to HF. The HF risk associated with AF in patients with HCM is worse in patients with outflow obstruction and those who develop AF before 50 years of age.50

There is an important risk of stroke and systemic embolism in patients with HCM and AF.50,464,465 In a study of 480 patients with HCM, the OR for stroke in those with AF was 17.7.30 Although no randomized studies of anticoagulant therapy have been reported, the incidence of thromboembolism in patients with HCM and AF is high, and anticoagulation is indicated for these patients independent of their CHA2DS2-VASc (or CHADS2) scores. Anticoagulation with direct thrombin or factor Xa inhibitors may represent another option to reduce the risk of thromboembolic events, but data for patients with HCM are not available.50,177,467

Given the poor tolerance of AF in patients with HCM, a rhythm-control strategy is preferred. However, for those patients for whom a rate-control strategy is chosen, a nondihydropyridine calcium channel blocker, a beta blocker, or a combination of the 2 drugs is preferable. Digoxin, a positive inotrope, may increase the outflow gradient in HCM patients and should be avoided. There have been no systematic studies of the treatment of AF in patients with HCM, but various antiarrhythmic agents have been used, including disopyramide, propafenone, amiodarone, sotalol, dofetilide, and dronedarone. An implantable cardioverter-defibrillator may provide added safety with QT interval–prolonging drugs. Amiodarone or disopyramide in combination with ventricular rate-controlling agents is generally preferred.11,466

Success and complication rates for AF catheter ablation appear to be similar for HCM and other forms of heart disease, but reported outcomes are likely influenced by selection bias.11,458,460 The surgical maze procedure for AF shows some success467; however, the role of a surgical maze procedure for patients undergoing other open chest surgical procedures (ie, septal myectomy) is unresolved.11,467

7.4. AF Complicating ACS: Recommendations

Class I

1. Urgent direct-current cardioversion of new-onset AF in the setting of ACS is recommended for patients with hemodynamic compromise, ongoing ischemia, or inadequate rate control. (Level of Evidence: C)
2. Intravenous beta blockers are recommended to slow a rapid ventricular response to AF in patients with ACS who do not display HF, hemodynamic instability, or bronchospasm. (Level of Evidence: C)
For patients with ACS and AF with a CHA2DS2-VASc score of 2 or greater, anticoagulation with warfarin is recommended unless contraindicated. *(Level of Evidence: C)*

### Class IIb

1. Administration of amiodarone or digoxin may be considered to slow a rapid ventricular response in patients with ACS and AF associated with severe LV dysfunction and HF or hemodynamic instability. *(Level of Evidence: C)*

2. Administration of nondihydropyridine calcium antagonists might be considered to slow a rapid ventricular response in patients with ACS and AF only in the absence of significant HF or hemodynamic instability. *(Level of Evidence: C)*

The incidence of AF in patients with ACS ranges from 10% to 21% and increases with patient age and severity of MI. FDA approved drugs and cardioversion often fail to achieve sustained sinus rhythm. Antiarrhythmic drugs and cardioversion often fail to achieve sustained sinus rhythm while thyrotoxicosis persists; therefore, efforts to restore normal sinus rhythm may be deferred until the patient is euthyroid. Beta blockers are effective in controlling the ventricular rate in this situation, and treatment with beta blockers is particularly important in cases of thyroid storm; nondihydropyridine calcium channel antagonists are recommended for rate control and may facilitate conversion to normal sinus rhythm. Digoxin may be considered in those with severe LV dysfunction and HF or hemodynamic instability. Systemic anticoagulation is indicated in those with large anterior infarcts and in survivors of ACS who develop persistent AF. Treatment with ACE inhibitors appears to reduce the incidence of AF in patients with LV dysfunction after ACS.

### 7.5. Hyperthyroidism: Recommendations

#### Class I

1. Beta blockers are recommended to control ventricular rate in patients with AF complicating thyrotoxicosis unless contraindicated. *(Level of Evidence: C)*

2. In circumstances in which a beta blocker cannot be used, a nondihydropyridine calcium channel antagonist is recommended to control the ventricular rate. *(Level of Evidence: C)*

AF is the most common arrhythmia in patients with hyperthyroidism (5% to 15% of patients) and is more frequent among those >60 years of age. Complications of AF in hyperthyroidism include HF and thromboembolism, although the correlation with thromboembolic disease is controversial. Treatment is directed primarily toward restoring a euthyroid state, which is usually associated with a spontaneous reversion of AF to sinus rhythm. Antithyroid drugs and cardioversion often fail to achieve sustained sinus rhythm while thyrotoxicosis persists; therefore, efforts to restore normal sinus rhythm may be deferred until the patient is euthyroid. Beta blockers are effective in controlling the ventricular rate in this situation, and treatment with beta blockers is particularly important in cases of thyroid storm; nondihydropyridine calcium channel antagonists are recommended for rate control. Although several studies reported thromboembolism in patients with thyrotoxicosis and AF, evidence suggests that embolic risk was not necessarily increased independent of other stroke risk factors. Anticoagulation for the patient with thyrotoxicosis and AF should be guided by CHA2DS2-VASc risk factors (Sections 4.1 and 4.1.1).

Hyperthyroidism and thyrotoxicosis can infrequently result from long-term amiodarone use. In the event of iatrogenic hyperthyroidism during treatment with amiodarone, the drug should be discontinued. The risks and benefits of treating patients with AF with a known history of thyroid disease with amiodarone should be carefully weighed before initiation of therapy, and patients should be monitored closely.

### 7.6. Acute Noncardiac Illness

A number of acute noncardiac conditions are associated with AF (eg, hypertension, postoperative state, pulmonary embolism, viral infections). Management of the underlying condition and correction of contributing factors as first-line treatment is common to all of these scenarios, and for many of these patients AF will spontaneously terminate.
with correction of the underlying condition. However, during acute illness, patients may require rate control with cardioversion, AV nodal blockers, and/or antiarrhythmic drugs if AF is poorly tolerated or rate control is not feasible. The specific rate- or rhythm-control agent(s) will depend on the underlying medical condition. Of note is that an elevated catecholamine state is common to many of these clinical circumstances, and unless contraindicated, a beta blocker is the preferred initial drug. The role of anticoagulation is less clear and likely disease specific and needs to be addressed on the basis of risk profile and duration of AF.

### 7.7. Pulmonary Disease: Recommendations

**Class I**

1. A nondihydropyridine calcium channel antagonist is recommended to control the ventricular rate in patients with AF and chronic obstructive pulmonary disease. *(Level of Evidence: C)*

2. Direct-current cardioversion should be attempted in patients with pulmonary disease who become hemodynamically unstable as a consequence of new-onset AF. *(Level of Evidence: C)*

Supraventricular arrhythmias, including AF, are common in patients with chronic obstructive pulmonary disease. AF should be distinguished from multifocal atrial tachycardia, which is unlikely to respond to electrical cardioversion but will often slow with treatment of the underlying disease and in response to nondihydropyridine calcium channel blockers. Treatment of the underlying lung disease and correction of hypoxia and acid-base imbalance are of primary importance in this situation and represent first-line therapy. Antiarrhythmic drug therapy and cardioversion may be ineffective against AF until respiratory decompensation has been corrected. Theophylline and beta-adrenergic agonists can precipitate AF and make control of the ventricular response rate difficult. Non–beta-1-selective blockers, sotalol, propafenone, and adenosine are contraindicated in patients with bronchospasm. However, beta blockers, sotalol, or propafenone may be considered in patients with obstructive lung disease who develop AF and do not have bronchospasm. Rate control can usually be achieved safely with nondihydropyridine calcium channel antagonists or possibly amiodarone. Digoxin can be used with calcium channel blockers, particularly in those with preserved LVEF. In patients refractory to drug therapy, AV nodal ablation and ventricular pacing may be necessary to control the ventricular rate. Anticoagulation, although not specifically studied in patients with AF due to pulmonary disease, is discussed in Section 4.2 for risk-based antithrombotic therapy.

### 7.8. WPW and Pre-Excitation Syndromes: Recommendations

**Class I**

1. Prompt direct-current cardioversion is recommended for patients with AF, WPW syndrome, and rapid ventricular response who are hemodynamically compromised. *(Level of Evidence: C)*

2. Intravenous procainamide or ibutilide to restore sinus rhythm or slow the ventricular rate is recommended for patients with pre-excited AF and rapid ventricular response who are not hemodynamically compromised. *(Level of Evidence: C)*

3. Catheter ablation of the accessory pathway is recommended in symptomatic patients with pre-excited AF, especially if the accessory pathway has a short refractory period that allows rapid antegrade conduction. *(Level of Evidence: C)*

**Class III: Harm**

1. Administration of intravenous amiodarone, adenosine, digoxin (oral or intravenous), or nondihydropyridine calcium channel antagonists (oral or intravenous) in patients with WPW syndrome who have pre-excited AF is potentially harmful because these drugs accelerate the ventricular rate. *(Level of Evidence: B)*

AF is of specific concern in patients with WPW syndrome because of the potential for degeneration to ventricular fibrillation related to rapidly conducting anterograde accessory pathways. The risk of developing AF over 10 years in patients with WPW syndrome is estimated at 15%, although the mechanism of increased AF risk is poorly understood. Approximately 25% of patients with WPW syndrome have accessory pathways with short anterograde refractory periods (<250 msec), which are associated with a risk of rapid ventricular rates and ventricular fibrillation. Patients with multiple accessory pathways are also at greater risk of ventricular fibrillation. The safety and efficacy of catheter ablation of the accessory pathway is established; however, ablation of the accessory pathway does not always prevent AF, especially in older patients, and additional pharmacological or ablative therapy may be required. Once the accessory pathway has been eliminated, the process of selecting pharmacological therapy is the same as for patients without pre-excitation.

Specifics of antiarrhythmic therapies are described in Section 6. During AF, the ventricular rate is determined by competing conduction over the AV node and the accessory pathway(s). As with any unstable arrhythmia, cardioversion is recommended for hemodynamic instability. Agents that slow AV nodal conduction without prolonging accessory pathway refractoriness can accelerate the ventricular rate and precipitate hemodynamic collapse and ventricular fibrillation in high-risk patients. Intravenous administration of ibutilide or procainamide may slow the rate of conduction over the accessory pathway, slow the ventricular rate, or may convert AF to sinus rhythm; it is recommended for hemodynamically stable patients in the setting of AF with conduction over an accessory pathway. Verapamil, diltiazem, adenosine, digoxin (oral or intravenous), and intravenous amiodarone can precipitate ventricular fibrillation and should not be used. Similarly, use of lidocaine in pre-excited AF is considered potentially harmful. Oral amiodarone can slow or block accessory pathway conduction during chronic oral therapy. Although beta blockers theoretically pose a similar potential risk, the data are sparse regarding administration of these agents in rapid AF in patients with WPW syndrome; nevertheless, they should be used with caution.
7.9. Heart Failure: Recommendations

Class I

1. Control of resting heart rate using either a beta blocker or nondihydropyridine calcium channel antagonist is recommended for patients with persistent or permanent AF and compensated HF with preserved ejection fraction (HFpEF).286 (Level of Evidence: B)

2. In the absence of pre-excitation, intravenous beta-blocker administration (or a nondihydropyridine calcium channel antagonist in patients with HFpEF) is recommended to slow the ventricular response to AF in the acute setting, with caution needed in patients with overt congestion, hypotension, or HF with reduced LVEF.292-300 (Level of Evidence: B)

3. In the absence of pre-excitation, intravenous digoxin or amiodarone is recommended to control heart rate acutely in patients with HF.277,503,506,507 (Level of Evidence: C)

4. Assessment of heart rate control during exercise and adjustment of pharmacological treatment to keep the rate in the physiological range is useful in symptomatic patients during activity. (Level of Evidence: C)

5. Digoxin is effective to control resting heart rate in patients with HF with reduced EF. (Level of Evidence: C)

Class IIa

1. A combination of digoxin and a beta blocker (or a nondihydropyridine calcium channel antagonist for patients with HFpEF) is reasonable to control resting and exercise heart rate in patients with AF.247,303 (Level of Evidence: B)

2. It is reasonable to perform AV node ablation with ventricular pacing to control heart rate when pharmacological therapy is insufficient or not tolerated.269,508,509 (Level of Evidence: B)

3. Intravenous amiodarone can be useful to control heart rate in patients with AF when other measures are unsuccessful or contraindicated. (Level of Evidence: C)

4. For patients with AF and rapid ventricular response causing or suspected of causing tachycardia-induced cardiomyopathy, it is reasonable to achieve rate control by either AV nodal blockade or a rhythm-control strategy.31,307,316 (Level of Evidence: B)

5. For patients with chronic HF who remain symptomatic from AF despite a rate-control strategy, it is reasonable to use a rhythm-control strategy. (Level of Evidence: C)

Class IIb

1. Oral amiodarone may be considered when resting and exercise heart rate cannot be adequately controlled using a beta blocker (or a nondihydropyridine calcium channel antagonist in patients with HFpEF) or digoxin, alone or in combination. (Level of Evidence: C)

2. AV node ablation may be considered when the rate cannot be controlled and tachycardia-mediated cardiomyopathy is suspected. (Level of Evidence: C)

Class III: Harm

1. AV node ablation should not be performed without a pharmacological trial to achieve ventricular rate control. (Level of Evidence: C)

2. For rate control, intravenous nondihydropyridine calcium channel antagonists, intravenous beta blockers, and dronedarone should not be administered to patients with decompensated HF. (Level of Evidence: C)

Patients with HF are more likely than the general population to develop AF,39 and there is a direct relationship between the NYHA class and prevalence of AF in patients with HF, progressing from 4% in those who are NYHA class I to 40% in those who are NYHA class IV.511 AF is a strong independent risk factor for subsequent development of HF as well.38,512 In addition to those with HF and depressed EF, patients with HF due to diastolic dysfunction with HFpEF are also at greater risk for AF.513 HF and AF can interact to perpetuate and exacerbate each other through mechanisms such as rate-dependent worsening of cardiac function, fibrosis, and activation of neurohumoral vasoconstrictors. AF can worsen symptoms in patients with HF and conversely, worsened HF can promote a rapid ventricular response in AF.

As with other patient populations, the main goals of therapy for those with AF and HF are prevention of thromboembolism and control of symptoms. Most patients with AF and HF can be expected to be candidates for systemic anticoagulation unless contraindicated (Section 4). General principles of management include correction of underlying causes of AF and HF as well as optimization of HF management. As in other patient populations, the issue of rate control versus rhythm control has been investigated. For patients who develop HF as a result of AF, a rhythm-control strategy should be pursued. AF with a rapid ventricular response is one of the few potentially reversible causes of HF. Therefore, a patient who presents with newly detected HF in the presence of AF with a rapid ventricular response should be presumed to have a rate-related cardiomyopathy until proved otherwise. In this situation, 2 strategies can be considered. One is rate control of the patient’s AF to see if HF and EF improve. The other is to attempt to restore and maintain sinus rhythm. In this situation, it is common practice to initiate amiodarone and then arrange for cardioversion a month later. Amiodarone has the advantage of being both an effective rate-control medication and the most effective antiarrhythmic medication with a low risk of proarrhythmia.

In patients with HF who develop AF, a rhythm-control strategy is not superior to a rate-control strategy.314 If rhythm control is chosen, AF catheter ablation in patients with HF may lead to an improvement in LV function and quality of life but is less likely to be effective than in patients with intact cardiac function.47,317

Because of their favorable effect on morbidity and mortality in patients with systolic HF, beta blockers are the preferred agents for achieving rate control unless otherwise
contraindicated. Digoxin may be an effective adjunct to a beta blocker. Nondihydropyridine calcium antagonists, such as diltiazem, should be used with caution in those with depressed EF because of their negative inotropic effect. For those with HF and preserved EF, nondihydropyridine calcium antagonists can be effective for achieving rate control but may be more effective when used in combination with digoxin. For those patients for whom a rate-control strategy is chosen, AV node ablation and cardiac resynchronization therapy device placement can be useful when rate control cannot be achieved either because of drug inefficacy or intolerance.515–520

7.10. Familial (Genetic) AF: Recommendation

Class IIb

1. For patients with AF and multigenerational family members with AF, referral to a tertiary care center for genetic counseling and testing may be considered. (Level of Evidence: C)

AF is heritable, and having an affected family member is associated with a 40% increased risk of the arrhythmia.155,521–524 Premature AF, defined as a first-degree relative with onset of AF before the age of 66, is associated with a doubling in risk of AF.155 Thus, it is common, particularly among younger, healthier persons with AF, to observe families with AF. In the last 10 years, many mutations have been identified in individuals and families with AF.525 The implicated genes include a wide range of ion channels, signaling molecules, and related proteins; however, the role of these mutations in more common forms of AF appears limited. Population-based or genomewide association studies identified ≥29 distinct genetic loci for AF.156–159 Furthermore, combinations of AF-associated single nucleotide polymorphisms may identify individuals at high risk for arrhythmia.536,537 However, the role of these common genetic variants in risk stratification,155,528,529 assessment of disease progression, and determination of clinical outcomes137,530,531 is limited. Routine genetic testing related to AF is not indicated.532

7.11. Postoperative Cardiac and Thoracic Surgery: Recommendations

Class I

1. Treating patients who develop AF after cardiac surgery with a beta blocker is recommended unless contraindicated.533–536 (Level of Evidence: A)

2. A nondihydropyridine calcium channel blocker is recommended when a beta blocker is inadequate to achieve rate control in patients with postoperative AF.537 (Level of Evidence: B)

Class IIa

1. Preoperative administration of amiodarone reduces the incidence of AF in patients undergoing cardiac surgery and is reasonable as prophylactic therapy for patients at high risk for postoperative AF.538–540 (Level of Evidence: A)

2. It is reasonable to restore sinus rhythm pharmacologically with ibutilide or direct-current cardioversion in patients who develop postoperative AF, as advised for nonsurgical patients.541 (Level of Evidence: B)

3. It is reasonable to administer antiarrhythmic medications in an attempt to maintain sinus rhythm in patients with recurrent or refractory postoperative AF, as advised for other patients who develop AF.537 (Level of Evidence: B)

4. It is reasonable to administer antithrombotic medication in patients who develop postoperative AF, as advised for nonsurgical patients.542 (Level of Evidence: B)

5. It is reasonable to manage well-tolerated, new-onset postoperative AF with rate control and anticoagulation with cardioversion if AF does not revert spontaneously to sinus rhythm during follow-up. (Level of Evidence: C)

Class IIb

1. Prophylactic administration of sotalol may be considered for patients at risk of developing AF after cardiac surgery.536,543 (Level of Evidence: B)

2. Administration of colchicine may be considered for patients postoperatively to reduce AF after cardiac surgery.544 (Level of Evidence: B)

Postoperative AF occurs in 25% to 50% of patients after open heart surgery. Increased age is the most consistent risk factor.545 With the projected increase in the number of elderly patients undergoing cardiac operations, the incidence of postoperative AF is likely to increase. Postoperative AF is associated with stroke,546 increased cost,547 and mortality.548 Beta blockers, nondihydropyridine calcium channel blockers, and amiodarone are useful as treatments in patients with postoperative AF and may be initiated preoperatively in some patients.591,544

In a meta-analysis of patients undergoing coronary revascularization, those who received preoperative statin therapy had less AF than those not treated with statins.391 No published data exist for patients undergoing valvular or other heart surgery.

The COPPS (Colchicine for the Prevention of the Postpericardiotomy Syndrome) substudy examined the efficacy and safety of colchicine for AF prevention.544 In this multicenter trial, patients were randomized to colchicine with standard therapy or standard therapy alone. The primary endpoint was incidence of AF at 1 month postoperatively. Patients receiving colchicine had a reduced incidence of AF (12% versus 22% at 30 days postoperatively). The colchicine group also had a shorter length of hospital stay.

8. Evidence Gaps and Future Research Directions

The past decade has seen substantial progress in the understanding of mechanisms of AF, clinical implementation of ablation for maintaining sinus rhythm, and new drugs for stroke prevention. Further studies are needed to better inform clinicians about the risks and benefits of therapeutic options for an individual patient. Continued research is needed into the mechanisms that initiate and sustain AF. It is hoped that better understanding of these tissue and cellular mechanisms will lead to more defined approaches to treating and
abolishing AF. This includes new methodological approaches for AF ablation that would favorably impact survival, thrombembolism, and quality of life across different patient profiles. New pharmacological therapies are needed, including antiarrhythmic drugs that have atrial selectivity and drugs that target fibrosis, which will hopefully reach clinical evaluation. The successful introduction of new anticoagulants is encouraging, and further investigations will better inform clinical practices for optimizing beneficial applications and minimizing the risks of these agents, particularly in the elderly, in the presence of comorbidities and in the perioperative period. Further investigations must be performed to better understand the links between the presence of AF, AF burden, and stroke risk, and to better define the relationship between AF and dementia. The roles of emerging surgical and procedural therapies to reduce stroke will be defined. Great promise lies in prevention. Future strategies for reversing the growing epidemic of AF will come from basic science and genetic, epidemiological, and clinical studies.

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**References**


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continuous intravenous diltiazem infusion for 24-hour heart rate control


Key Words: AHA Scientific Statements • atrial fibrillation • cardiovascular physiology/pathophysiology • cardiovascular surgery: transplantation, ventricular assistance, cardiomyopathy • epidemiology • full revision • health policy and outcome research • other atrial fibrillation
Appendix 1. Author Relationships With Industry and Other Entities (Relevant)—2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

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†No financial benefit.

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§Dr. Sacco’s relationship with Boehringer Ingelheim was added just after final balloting of the recommendations and before organizational review, so it was not relevant during the writing or voting stages of the guideline’s development.

ACC indicates American College of Cardiology; AHA, American Heart Association; DSMB, data safety monitoring board; and HRS, Heart Rhythm Society.
### Appendix 2. Reviewer Relationships With Industry and Other Entities (Relevant)—2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

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| Anitra Romfh | Content Reviewer—ACC Adult Congenital and Pediatric Cardiology Section Leadership Council | Children’s Hospital Boston—Cardiologist | None | None | None | None | None | None | None |</p>
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ACC indicates American College of Cardiology; AHA, American Heart Association; AIG, Association of International Governors; DSMB, data safety monitoring board; EP, electrophysiology; HF, heart failure; HHS, Health and Human Services; HRS, Heart Rhythm Society; ICD, implantable cardioverter-defibrillator; PharmD, Doctor of Pharmacy; PI, principal investigator; STOP-AF, Sustained Treatment Of Paroxysmal Atrial Fibrillation; STS, Society of Thoracic Surgeons; UCLA, University of California, Los Angeles; USUHS, Uniformed Services University of the Health Sciences; UT, University of Texas; VA, Veterans Affairs; and VCU, Virginia Commonwealth University.

### Appendix 3. Abbreviations

- **ACE** = angiotensin-converting enzyme
- **ACS** = acute coronary syndrome
- **AF** = atrial fibrillation
- **ARB** = angiotensin-receptor blocker
- **AV** = atrioventricular
- **bpm** = beats per minute
- **CAD** = coronary artery disease
- **CKD** = chronic kidney disease
- **CrCl** = creatinine clearance
- **ECG** = electrocardiogram/electrocardiographic
- **EF** = ejection fraction
- **HCM** = hypertrophic cardiomyopathy
- **HF** = heart failure
- **HFpEF** = heart failure with preserved ejection fraction
- **INR** = international normalized ratio
- **LA** = left atrial/atrium
- **LAA** = left atrial appendage
- **LMWH** = low-molecular-weight heparin
- **LV** = left ventricular
- **LVEF** = left ventricular ejection fraction
- **RCT** = randomized controlled trial
- **RV** = right ventricular
- **TEE** = transesophageal echocardiography
- **TIA** = transient ischemic attack
- **TTR** = time in therapeutic range
- **UFH** = unfractionated heparin
- **WPW** = Wolff-Parkinson-White
Appendix 4. Initial Clinical Evaluation in Patients With AF

Minimum Evaluation

1. History and physical examination, to define
   - Presence and nature of symptoms associated with AF
   - Clinical type of AF (paroxysmal, persistent, or permanent)
   - Onset of first symptomatic attack or date of discovery of AF
   - Frequency, duration, precipitating factors, and modes of initiation or termination of AF
   - Response to any pharmacological agents that have been administered
   - Presence of any underlying heart disease or reversible conditions (eg, hyperthyroidism or alcohol consumption)

2. ECG, to identify
   - Rhythm (verify AF)
   - LVH
   - P-wave duration and morphology or fibrillatory waves
   - Pre-excitation
   - Bundle-branch block
   - Prior MI
   - Other atrial arrhythmias
   - To measure and follow R-R, QRS, and QT intervals in conjunction with antiarrhythmic drug therapy

3. TTE, to identify
   - VHD
   - LA and RA size
   - LV and RV size and function
   - Peak RV pressure (pulmonary hypertension)
   - LV hypertrophy
   - LA thrombus (low sensitivity)
   - Pericardial disease

4. Blood tests of thyroid, renal, and hepatic function
   - For a first episode of AF
   - When ventricular rate is difficult to control

Additional Testing (1 or several tests may be necessary)

1. 6-min walk test
   - If adequacy of rate control is in question

2. Exercise testing
   - If adequacy of rate control is in question
   - To reproduce exercise-induced AF
   - To exclude ischemia before treatment of selected patients with a type IC* antiarrhythmic drug

3. Holter or event monitoring
   - If diagnosis of type of arrhythmia is in question
   - As a means of evaluating rate control

4. TEE
   - To identify LA thrombus (in LAA)
   - To guide cardioversion

5. Electrophysiological study
   - To clarify the mechanism of wide-QRS-complex tachycardia
   - To identify a predisposing arrhythmia such as atrial flutter or paroxysmal supraventricular tachycardia
   - To seek sites for curative AF ablation or AV conduction block/modification

6. Chest radiograph, to evaluate
   - Lung parenchyma, when clinical findings suggest an abnormality
   - Pulmonary vasculature, when clinical findings suggest an abnormality

*Type IC refers to the Vaughan Williams classification of antiarrhythmic drugs.
AF indicates atrial fibrillation; AV, atrioventricular; ECG, electrocardiogram; LA, left atrial; LAA, left atrial appendage; LV, left ventricular; LVH, left ventricular hypertrophy; MI, myocardial infarction; RA, right atrial; RV, right ventricular; TEE, transesophageal echocardiography; TTE, transthoracic echocardiogram; and VHD, valvular heart disease.

Adapted with permission from Fuster et al.4

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http://circ.ahajournals.org/content/130/23/e199

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/content/130/23/e272.full.pdf

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2014/03/25/CIR.0000000000000041.DC1
http://circ.ahajournals.org/content/suppl/2014/03/25/CIR.0000000000000041.DC2

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1. On page e211, in Table 6, in the penultimate row, the Class III: No Benefit recommendation 1 read, “Direct thrombin dabigatran and factor Xa inhibitor rivaroxaban are not recommended in patients with AF and end-stage CKD or on hemodialysis because of a lack of evidence from clinical trials regarding the balance of risks and benefits.” It has been changed to read, “Direct thrombin dabigatran and factor Xa inhibitor rivaroxaban are not recommended in patients with AF and end-stage CKD or on dialysis because of a lack of evidence from clinical trials regarding the balance of risks and benefits.”

2. On page e212, in the second column, the fourth paragraph, the Class III: No Benefit recommendation 1 read, “The direct thrombin inhibitor dabigatran and the factor Xa inhibitor rivaroxaban are not recommended in patients with AF and end-stage CKD or on hemodialysis because of the lack of evidence from clinical trials regarding the balance of risks and benefits.” It has been changed to read, “The direct thrombin inhibitor dabigatran and the factor Xa inhibitor rivaroxaban are not recommended in patients with AF and end-stage CKD or on dialysis because of the lack of evidence from clinical trials regarding the balance of risks and benefits.”

3. On page e213, in the second column, the third paragraph, the first sentence read, “Bleeding risk scores to quantify hemorrhage risk include HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly), RIETE (Computerized Registry of Patients With Venous Thromboembolism), HEMORR2HAGES (Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Rebleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk, and Stroke), and ATRIA…” It has been changed to read, “Bleeding risk scores to quantify hemorrhage risk include HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly), RIETE (Computerized Registry of Patients With Venous Thromboembolism), and ATRIA…”

4. On page e216, in the second column, the third paragraph, the first sentence read, “Dabigatran was the first new oral anticoagulant approved by the US Food and Drug Administration (FDA) for prevention of stroke in patients with AF and is a direct thrombin inhibitor.” It has been changed to read, “Dabigatran is the first new oral anticoagulant approved by the US Food and Drug Administration (FDA) to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF and is a direct thrombin inhibitor.”

5. On page e217, in Figure 5, in the row for “ARISTOTLE,” the entry in the “Event Rate” column read, “1.80 (1.41–1.80).” It has been changed to read, “1.60 (1.41–1.80).”

6. On page e217, in the first column, the third paragraph, the first sentence read, “...(CHADS, score 0 to 1 in 31% of subjects, 2 in 33%, and >2 in 32%).” It has been changed to read, “...(CHADS, score 0 to 1 in 31.8% of subjects, 2 in 35.6%, and >2 in 32.5%).”

7. On page e217, in the second column, the last paragraph, the first and second sentences read, “Rivaroxaban is the second new oral anticoagulant approved by the FDA and is a direct factor Xa inhibitor (Figure 4). It can be administered as a single daily dose with a large meal to ensure adequate absorption.” They have been changed to read, “Rivaroxaban is the second new oral anticoagulant approved by the FDA for reduction of risk of stroke and systemic embolism in patients with nonvalvular AF and is a direct factor Xa inhibitor (Figure 4). It should be administered as a single daily dose with the evening meal to ensure adequate absorption.”

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8. On page e218, in the first column, the second paragraph, the first sentence read, “Apixaban is the third new oral anticoagulant approved by the FDA and is another direct factor Xa inhibitor (Figure 4).” It has been changed to read, “Apixaban is the third new oral anticoagulant approved by the FDA for reduction of risk of stroke and systemic embolism with nonvalvular AF and is another direct factor Xa inhibitor (Figure 4).”

9. On page e219, in Table 8, in row 1, the entry in the fourth column “Rivaroxaban” read, “20 mg HS.” It has been changed to read, “20 mg QD with the evening meal.”

10. On page e219, in Table 8, in row 2, the entry in the third column “Dabigatran” read, “150 mg BID or 75 mg BID (CrCl >30 mL/min).” It has been changed to read, “150 mg BID (CrCl >30 mL/min).”

11. On page e219, in Table 8, in row 2, the entry in the fourth column “Rivaroxaban” read, “15 mg HS.” It has been changed to read, “15 mg QD with the evening meal.”

12. On page e219, in Table 8, in row 3, the entry in the fourth column “Rivaroxaban” read, “15 mg HS.” It has been changed to read, “15 mg QD with the evening meal.”

13. On page e219, in Table 8, the footnote list read, “…§Modeling studies suggest that dabigatran 75 mg BID might be safe for patients with CrCl 15–30 mL/min, but this has not been validated in a prospective cohort. Some countries outside the United States use 110 mg BID. || Dose-adjusted warfarin has been used, but observational data on safety and efficacy are conflicting…” It has been changed to read, “…§Dose-adjusted warfarin has been used, but observational data on safety and efficacy are conflicting. || Modeling studies suggest that dabigatran 75 mg BID might be safe for patients with CrCl 15–30 mL/min, but this has not been validated in a prospective cohort. Some countries outside the United States use 110 mg BID.” Symbols in the Table were adjusted accordingly.

14. On page e219, in Table 8, the footnote abbreviation list read, “…CrCl, creatinine clearance; HS, once daily in evening with food; and INR, international normalized ratio.” It has been changed to read, “…CrCl, creatinine clearance; FDA, Food and Drug Administration; INR, international normalized ratio; and QD, once daily.”

15. On page e219, in the second column, in the second paragraph, the third through the sixth sentences read, “Absorbed dabigatran etexilate is “pumped” back into the intestinal tract; therefore, proton pump inhibitors may reduce absorption of dabigatran. Rivaroxaban and apixaban are contraindicated with drugs that inhibit cytochrome P450 3A4 (CYP3A4), such as azole antifungal agents, ritonavir, and clarithromycin.” They have been changed to read, “Absorbed dabigatran etexilate is “pumped” back into the intestinal tract. Dabigatran also can cause gastrointestinal symptoms. Coprescription with a proton pump inhibitor may mildly reduce dabigatran peak concentrations; however, dose adjustment is not warranted. Rivaroxaban and apixaban are contraindicated with drugs that are combined P-glycoprotein and strong P450 3A4 (CYP3A4) inducers.”

16. On page e223, in Table 10, in the first column, the last line, an asterisk (*) was inserted after “Amiodarone,” and the following was added to the footnotes, “*Multiple dosing schemes exist for the use of amiodarone.”

17. On page e229, in Table 12, in the first column, the first line, an asterisk (*) was inserted after “Amiodarone,” and the following was added to the footnotes, “*Multiple dosing schemes exist for the use of amiodarone.”

18. On page e231, in Table 13, in the second row “Dofetilide” under the “Vaughan Williams class III” heading, in the “Exclude/Use With Caution” column, “Hypomagnesemia” was added to the bulleted list.

19. On page e231, in Table 13, in the second row “Dofetilide” under the “Vaughan Williams class III” heading, in the “Major Pharmacokinetic Drug Interactions” column, the text read, “Metabolized by CYP3A: verapamil…” It has been changed to read, “Primary renal elimination involving glomerular filtration and active tubular secretion: verapamil…”

20. On page e231, in Table 13, in the fourth row “Sotalol” under the “Vaughan Williams class III” heading, in the “Exclude/Use With Caution” column, Hypomagnesemia was added to the bulleted list.

21. On page e204, in Table 2, on pages e204, e228, and e235 in the text, and page e245 in the Reference Section, Reference 7 was removed and replaced with references 7a and 7b.

Reference 7 read,
References 7a and 7b read,


22. On page e250, in the Reference Section, Reference 239 was replaced with a new reference. Reference 239 read,


Reference 239 now reads,


These corrections have been made to the print version and to the current online version of the article, which is available at http://circ.ahajournals.org/content/130/23/e199.full.
2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation—ONLINE AUTHOR LISTING OF COMPREHENSIVE RELATIONSHIPS WITH INDUSTRY AND OTHERS (April 2012)

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*Indicates significant relationship.
†No financial benefit.
‡Dr. Sacco’s relationship with Boehringer Ingelheim was added just after final balloting of the recommendations and prior to organizational review, so it was not relevant during the writing or voting stages of the guideline’s development.

AHA indicates American Heart Association; CIHR, Canadian Institutes for Health Research; CME, continuing medical education; DSMB, Data Safety Monitoring Board; IHD, ischemic heart disease; and PI, principal investigator; and SCD, sudden cardiac death.
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AF indicates atrial fibrillation.

### Data Supplement 2. Pathophysiologic Mechanisms Generating the AF Substrate (Section 2)

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<td>Extracardiac factors</td>
<td>See Section 2.2</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation.
<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Study Type/Size</th>
<th>Study Intervention</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR: &amp; 95% CI:</th>
<th>Adverse Events</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>To compare 2 fixed doses of dabigatran with open-label use of warfarin in pts with AF at increased risk of stroke</td>
<td>RCT, open-label, blinded doses of dabigatran (18,113)</td>
<td>Dabigatran 110 mg (6,015) Dabigatran 150 mg (6,076) Warfarin (6,021)</td>
<td>AF and ≥1 of the following: prior stroke or TIA; LVEF&lt;40% , NYHA class II or higher HF Sx, age ≥75 y or an age of 65-74 y plus DM, HTN, or CAD Mean CHADS2 of 2.1</td>
<td>Dabigatran in 2 fixed doses – oral prodrug, direct competitive inhibitor of thrombin Warfarin INR 2-3, mean TTR 64%</td>
<td>Stroke or SE Major Hemorrhage</td>
<td>Stroke</td>
<td>Dabigatran 10 mg 1.53%/y Dabigatran 150 mg 1.11%/y Warfarin 1.69%/y</td>
<td>Dyspepsia</td>
<td>Open-label Median duration of FU 2 y</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>110 mg</td>
<td>1.12%/y</td>
<td>Warfarin</td>
<td>1.02%/y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>150 mg</td>
<td>1.51%/y</td>
<td>Warfarin</td>
<td>1.02%/y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>1.02%/y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ROCKET-AF

Patel MR, et al., 2011 (150)

To compare QD oral rivaroxaban with dose-adjusted warfarin for the prevention of stroke and SE in pts with NVAF who were at moderate to high risk of stroke

RCT, double-dummy, double-blinded (14,264)

Rivaroxaban (7,131)
Warfarin (7,133)

NVAF at moderate to high risk of stroke: Hx of stroke, TIA, or SE or ≥2 of the following (HF or LVEF<35% , HTN, age >75 y, DM (CHADS2 score of≥2)

Mean CHADS2 score of 3.5

Severe valvular disease, transient AF caused by a reversible disorder, hemorrhage risk related criteria; severe, disabling stroke within 3 mo or any stroke within 14 d, TIA within 3 d; indication for anticoagulant Tx

Rivaroxaban Factor Xa inhibitor, 20 mg QD or 15 mg QD for those with CrCl of 39-40 mL/min
Warfarin INR 2-3, mean TTR 55%

Any stroke or SE
Per-protocol as treated Rivaroxaban 1.7%/y Warfarin 2.2%/y
Intention to Treat Rivaroxaban 2.1%/y Warfarin 2.4%/y

Major and non-major clinically relevant bleeding
Rivaroxaban 3.3/100 pt-years Warfarin 3.6/100 pt-years
ICH Rivaroxaban 0.5/100 pt-years Warfarin 0.7/100 pt-years
Major GI Rivaroxaban 3.15% Warfarin 2.16%

Stroke, SE, or VD
Rivaroxaban 3.11/100 pt-years Warfarin 3.64/100 pt-years
HR: 0.86; 95% CI: 0.74-0.99; p=0.034
Per-Protocol, as treated HR: 0.79; 95% CI: 0.66-0.96; p<0.001 for noninferiority
Intention to treat HR: 0.88; 95% CI: 0.75-1.03; p<0.001 for noninferiority p=0.12 for superiority
N/A

Median duration of follow-up was 707 d
Lower TTR in warfarin group
1° analysis was prespecified as a per-protocol analysis
High-event rate after discontinuation of Tx
<table>
<thead>
<tr>
<th>Study</th>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Arm 1</th>
<th>Arm 2</th>
<th>AF or Stroke Risk Factor</th>
<th>Treatment</th>
<th>Major Bleeding Events</th>
<th>Stroke, SE, Major Bleeding or Death from Any Cause</th>
<th>HR</th>
<th>95% CI</th>
<th>p Value</th>
<th>No. of Patients</th>
<th>Median Duration of FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARISTOTLE</td>
<td>Granger CB, et al., 2011</td>
<td>(151)</td>
<td>RCT, double-dummy, double-blinded (18,201)</td>
<td>Apixaban (9,120)</td>
<td>Warfarin (9,081)</td>
<td>AF and ≥1 stroke risk factor (age &gt;75 y; previous stroke, TIA or SE; symptomatic HF within the prior 3 mo or LVEF ≤40%; DM; or HTN) Mean CHADS2 score of 2.1</td>
<td>Apixaban Factor Xa inhibitor 5 mg BID or 2.5 mg BID among pts with ≥2 of the following (≥80 y, body weight ≤60 kg, or serum Cr level of ≥1.5 mg/dL)</td>
<td>Apixaban 2.13%/y</td>
<td>Warfarin 3.09%/y</td>
<td>Apixaban 1.27%/y</td>
<td>Warfarin 1.6%/y</td>
<td>HR: 0.79; 95% CI: 0.66-0.95; p&lt;0.001 for noninferiority, p=0.01 for superiority</td>
<td>No difference</td>
<td>Median duration of FU 1.8 y</td>
</tr>
<tr>
<td>AVERROES</td>
<td>Connolly SJ, et al., 2011</td>
<td>(152)</td>
<td>RCT double-blind, double-dummy (5,559)</td>
<td>Apixaban (2,808)</td>
<td>ASA (2,791)</td>
<td>≥50 y and AF and ≥1 of the following stroke risk factors: prior stroke or TIA, ≥75 y, HTN, DM, HF, LVEF ≤35%, or PAD. Pts could not be receiving VKAs</td>
<td>Apixaban Factor Xa inhibitor 5 mg BID or 2.5 mg BID among pts with ≥2 of the following (age ≤80 y, body weight ≤60 kg, or serum Cr level of ≥1.5 mg/dL)</td>
<td>Apixaban 1.4%/y</td>
<td>ASA 1.2%</td>
<td>Apixaban 1.6%/y</td>
<td>ASA 3.7%/y</td>
<td>HR: 0.45; 95% CI: 0.32-0.62; p&lt;0.001</td>
<td>No difference</td>
<td>N/A</td>
</tr>
</tbody>
</table>
because it had already been demonstrated to be unsuitable or because it was expected to be unsuitable.

Mean CHADS2 of 2.0

within the previous 10 d, severe renal insufficiency (a sCr>2.5 mg/dL) or a calculated CrCl<25 mL/min

81-325 mg/dL

Apixaban 0.4% ASA 0.4%

1° indicates primary; AF, atrial fibrillation; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in AF; ASA, aspirin; AVERROES, Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; BID, twice daily; CAD, coronary artery disease; CHADS2, Congestive heart failure, Hypertension, Age 75 years, Diabetes mellitus, Stroke; ; CP, codeine phosphate; Cr, creatinine; CrCl, creatinine clearance; DM, diabetes mellitus; FU, follow-up; GI, gastrointestinal; HF, heart failure; HR, hazard ratio; HTN, hypertension; Hx, history; ICH, intracranial hemorrhage; INR, international normalized ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; N/A, not applicable; PAD, peripheral arterial disease; PE, pulmonary embolism; N/A, not applicable; NVAF, nonvalvular atrial fibrillation; NYHA, New York Heart Association; OAC, oral anticoagulation; pts, patient; QD, once daily; RCT, randomized controlled trial; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial; RR, relative risk; sCr, serum creatinine; SE, systemic embolism; Sx, symptom; TIA, transient ischemic attack; TTR, time in therapeutic range; Tx, therapy; UD, valvular disease; and VKA, vitamin K antagonist.

Data Supplement 4. Warfarin vs. Control (Section 4.2)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/ Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR: &amp; 95% CI:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aguilar MI, et al., 2005 (153) 16034869</td>
<td>To characterize the efficacy and safety of oral anticoagulants for the 1° prevention of stroke in pts with chronic AF</td>
<td>Cochrane Collaboration Systematic Review (AFASAK I, BAATAF, CAFA, SPAF I, SPINAF)</td>
<td>2,313 pts Warfarin 1,154 PC 1,159</td>
<td>AF (intermittent or sustained)</td>
<td>Prior stroke or TIA, mitral stenosis or prosthetic cardiac valves</td>
<td>Oral VKAs (warfarin) mean INR 2.0-2.6</td>
<td>All Stroke (ischemic or ICH) ICH, Major extracranial bleeds Warfarin 27 PC 71 ICH, Warfarin 5, PC 2 Extradural bleeds, Warfarin</td>
</tr>
</tbody>
</table>
Data Supplement 5. Warfarin vs. Antiplatelet Therapy (Section 4.2)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/ Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR: &amp; 95% CI:</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aguilar MI, et al., 2007 (154) 17636831</td>
<td>To characterize the relative effect of long-term oral anticoagulant Tx compared with antiplatelet Tx in pts with AF and no Hx of stroke or TIA</td>
<td>Cochrane Collaboration Systematic Review (ACTIVE-W, AFASAK I, AFASAK II, ATHENS, NASPEAF, PATAF, SPAF Ila, SPAF IIb)</td>
<td>9,598 pts OAC 4,815 Antiplatelet 4,783</td>
<td>AF (intermittent or sustained) Prior stroke or TIA, mitral stenosis or prosthetic cardiac valves</td>
<td>Adjusted dose warfarin or other coumarins; antiplatelet therapies</td>
<td>All Stroke (ischemic or ICH) OAC 132/4,815 Antiplatelet 190/4,783</td>
<td>Stroke, MI, or VD</td>
<td>All Stroke OR: 0.68; 95% CI: 0.54-0.85; p=0.00069 Ischemic stroke OR: 0.53; 95% CI: 0.41-0.69 ICH OR: 1.98; 95% CI: 1.20-3.28 Major Extracranial bleeds OR: 1.98; 95% CI: 1.20-3.28 N/A</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Participants</td>
<td>Primary Outcomes</td>
<td>Treated</td>
<td>Comparator</td>
<td>Other Details</td>
<td></td>
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</tr>
<tr>
<td>Saxena R, et al., 2011 (155) 15494992</td>
<td>Cochrane Collaboration Systematic Review (EAF, SIFA)</td>
<td>1,371 pts, warfarin 679, antiplatelet 692</td>
<td>AF and prior minor stroke or TIA</td>
<td>Rheumatic VD</td>
<td>Oral VKAs (warfarin) mean INR&gt;2.0; Antiplatelets 300 mg ASA; indobufen 200 mg BID</td>
<td>All major vascular events (VD, recurrent stroke, MI, or SE)</td>
<td>Any ICH; major extracranial bleed</td>
<td>All fatal or nonfatal recurrent strokes</td>
</tr>
<tr>
<td>Mant J, et al., 2007 BAFTA (156) 17693178</td>
<td>RCT</td>
<td>973 pts, ASA 485, warfarin 488</td>
<td>Age ≥75 y, AF or flutter by EKG within 2 y from 1st care practices</td>
<td>Rheumatic heart disease, a major nontraumatic hemorrhage within 5 y, ICH, documented peptic ulcer disease within the previous year, esophageal varices,</td>
<td>ASA 75 mg QD; Warfarin target INR 2.5, range 2-3</td>
<td>Fatal or nonfatal disabling stroke (ischemic or hemorrhagic), other ICH, or clinically significant arterial embolism</td>
<td>Warfarin 24 (1.8%/y)</td>
<td>Hemorrhage</td>
</tr>
</tbody>
</table>
Data Supplement 6. Beta Blockers (Sections 5.1.1)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/ Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR: &amp; 95% CI</th>
<th>Adverse Events</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrams J, et al., 1985 (157)</td>
<td>Evaluation of the efficacy and safety of esmolol in comparing to propranolol for the acute control of SVT</td>
<td>Randomized prospective, multicenter double-blind</td>
<td>IV esmolol vs. IV propranolol</td>
<td>Pts over age 18 y with ventricular rates &gt;120 bpm 2° to AF, atrial flutter, SVT, atrial tachycardia, idioptic sinus tachycardia and AV reentrant tachycardias</td>
<td>WPW syndrome, hypotension, sick sinus syndrome, AV conduction delay decompensate d HF or noncardiac precipitated arrhythmias</td>
<td>Esmolol vs. propranolol</td>
<td>Composite endpoint of either ≥20% reduction from average baseline heart rate, reduction in heart rate to &lt;100 bpm, or conversion to NSR</td>
<td>N/A</td>
<td>No difference Hypotensi on (esmolol 45% vs. propranolol 18%) Small sample size Only 66% of pts had AF</td>
</tr>
<tr>
<td>Farshir R, et al., 1999 (158)</td>
<td>Comparison of the effects of 5 standard drug</td>
<td>Prospective, open-label crossover outpatient</td>
<td>N/A</td>
<td>Chronic AF pts who had a duration of ≥1 y LVEF&lt;0.35, WPW syndrome, sick sinus</td>
<td>Comparison of the effects of 5 standard drug</td>
<td>Comparison of 24 h mean ventricular rates Peak ventricular response at 5 m of exercise:</td>
<td>p&lt;0.01 for comparison of atenolol or propranolol and</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
regimens: digoxin, diltiazem, atenolol, digoxin plus diltiazem, and digoxin + atenolol on the mean 24-h heart rate

1° indicates primary; 2°, secondary; AF, atrial fibrillation; AV, atrioventricular; HF, heart failure; HR, hazard ratio; IV, intravenous; LVEF, left ventricular ejection fraction; N/A, not applicable; NSR, normal sinus rhythm; pts, patients; SVT, supraventricular tachycardia; Tx, therapy; and WPW, Wolff-Parkinson-White.

### Data Supplement 7. Nondihydropyridine Calcium Channel Blockers (Sections 5.1.2)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR: &amp; 95% CI:</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ellenbogen KA, et al., 1991 (159) 1894861</td>
<td>To demonstrate the safety and efficacy of a continuous IV diltiazem infusion for 24 h heart rate control</td>
<td>Randomized, double-blind, parallel, PC-controlled</td>
<td>IV diltiazem vs. PC</td>
<td>Pts &gt;18 y with AF or atrial flutter with duration &gt;24 h and HR&gt;120 bpm</td>
<td>Severe CHF, sinus node dysfunction, 2nd or 3rd degree AV block, WPW syndrome or hypotension</td>
<td>IV diltiazem vs. PC</td>
<td>Therapeutic response (ventricular response &lt;100 bpm, ≥20% decrease in heart rate from baseline or conversion to NSR) 74% vs. 0%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Steinberg JS, et al., 1987 (160) 3805530</td>
<td>To determine the efficacy of diltiazem to control ventricular response at rest, during exercise, and during daily activities</td>
<td>Prospective, open-label</td>
<td>Oral diltiazem</td>
<td>Pts with chronic AF with a VR&gt;100 bpm at 3 min of a standardized exercise test</td>
<td>UA, acute MI, WPW syndrome, hypotension, renal or hepatic failure, sick sinus syndrome without a pacemaker</td>
<td>Oral diltiazem</td>
<td>Ventricular response: Rest: 69±10 vs. 96±17 Exercise: 116±26 vs. 155±28</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>
To compare the clinical efficacy of IV diltiazem, digoxin, and amiodarone for acute VR in symptomatic AF

**Study Name, Author, Year**  
Siu CW, 2009 et al., (161)  

**Study Aim**  
To compare the clinical efficacy of IV diltiazem, digoxin, and amiodarone for acute VR in symptomatic AF

**Study Type/ Size (N)**  
Randomized, prospective, open-label

**Intervention vs. Comparator (n)**  
IV diltiazem vs. IV amiodarone vs. IV digoxin

**Patient Population**  
Hospitalized pts with symptomatic AF<48 h with ventricular response >120 bpm

**Study Intervention**  
Ventricular response >200 bpm, pre-excitation syndrome, hypotension, CHF, implanted pacemaker/defibrillator, recent MI, UA or stroke

**Endpoints**  
VR control (<90 bpm) within 24 h: ventricular response <90 bpm sustained for ≥4 h

**P Values, OR: HR: RR: & 95% CI:**  
Diltiazem 90% vs. amiodarone 74% vs. digoxin 74%  
p<0.47

**Inclusion Criteria**  
AF indicates atrial fibrillation; AV, atrioventricular; CHF, congestive heart failure; IV, intravenous; MI, myocardial infarction; N/A, not applicable; NSR, normal sinus rhythm; PC, placebo; pts, patients; RR, relative risk; UA, unstable angina; VR, ventricular rate; and WPW, Wolff-Parkinson-White.

### Data Supplement 8. Digoxin (Sections 5.1.3)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/ Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR: &amp; 95% CI:</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IV Digoxin in Acute AF (162) 9129897</strong></td>
<td>To examine the effects of IV digoxin in acute AF</td>
<td>Randomized, prospective, multicenter, double-blind PC-controlled</td>
<td>IV digoxin vs. PC</td>
<td>Pts &gt;18 y with AF≤7d</td>
<td>Ongoing Tx with digoxin or antiarrhythmics, sick sinus syndrome or 2nd /3rd degree AV block without a pacemaker, WPW syndrome, heart rate &lt;60 or &gt;170 bpm, ongoing ischemia or recent MI</td>
<td>IV digoxin vs. PC</td>
<td>Conversion to sinus rhythm at 16 h</td>
<td>Digoxin 46% vs. PC 51%</td>
</tr>
<tr>
<td><strong>AFFIRM Olshansky B, et al., 2004 (163) 15063430</strong></td>
<td>To examine whether digoxin use was associated with adverse</td>
<td>Post hoc analysis</td>
<td>Nonrandomized comparison of digoxin vs. no digoxin</td>
<td>Pts with AF considered at high risk for stroke</td>
<td>N/A</td>
<td>Post hoc analysis including propensity analysis</td>
<td>Estimated HR of 1.41 for all-cause mortality for digoxin</td>
<td>Estimated HR of 1.61 for arrhythmic mortality</td>
</tr>
</tbody>
</table>
AF indicates atrial fibrillation; AFFIRM, Atrial Fibrillation Follow-up Investigation of Rhythm Management; AV, atrioventricular; HR, hazard ratio; IV, intravenous; MI, myocardial infarction; N/A, not applicable; PC, placebo; pts, patients; RR, relative risk; Tx, therapy; and WPW, Wolff-Parkinson-White.

### Data Supplement 9. Other Pharmacological Agents for Rate Control (Sections 5.1.4)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/ Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Primary Endpoint &amp; Results</th>
<th>Safety Endpoint &amp; Results</th>
<th>Secondary Endpoint &amp; Results</th>
<th>P Values, OR: HR: RR: &amp; 95% CI:</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delle Karth G, et al., 2001 (164) 11395591</td>
<td>To compare the efficacy of IV diltiazem bolus/infusion vs. IV amiodarone bolus vs. IV amiodarone bolus/infusion for immediate (4 h) and 24-h rate control during AF</td>
<td>Randomized prospective, controlled</td>
<td>IV diltiazem bolus/infusion vs. IV amiodarone bolus vs. IV amiodarone bolus/infusion for immediate (4 h) and 24-h rate control during AF</td>
<td>Critically ill pts with recent-onset AF with ventricular rate &gt;120 bpm</td>
<td>N/A</td>
<td>N/A</td>
<td>IV diltiazem bolus/infusion vs. IV amiodarone bolus vs. IV amiodarone bolus/infusion for immediate (4 h) and 24-h rate control during AF</td>
<td>Sustained heart rate reduction ≥30% within 4 h</td>
<td>70% vs. 55% vs. 75%</td>
<td>Bradycardia or hypotension</td>
<td>35% vs. 0% vs. 5%</td>
</tr>
<tr>
<td>Connolly SJ, et al., 2011 (165) 22082198</td>
<td>Assess impact of dronedarone on major vascular events in high-risk permanent AF</td>
<td>Randomized prospective, multicenter, double-blind, PC-controlled trial (3,236)</td>
<td>Dronedarone 400 mg po BID vs. PC</td>
<td>Permanent AF / flutter, age ≥65 y with ≥1 risk factor: CAD, CVA or TIA, CHF, LVEF≤50, PAD or age ≥75 y with HTN and DM</td>
<td>Paroxysmal or persistent AF, ICD, heart rate &lt;50 bpm, QT interval corrected &gt;500 ms</td>
<td>Dronedarone vs. PC</td>
<td>Composite of stroke, MI, SE, or CV death</td>
<td>Composite of unplanned hospitalization for CV event/ death</td>
<td>N/A</td>
<td>N/A</td>
<td>HR: 2.29; 95% CI: 1.34-3.94 Stroke HR: 2.32; 95% CI: 1.11-4.88 Unplanned hospitalization for CV event HR: 1.81; 95% CI: 1.44-2.70</td>
</tr>
</tbody>
</table>

1º indicates primary; 2º, secondary; AF, atrial fibrillation; BID, twice daily; CAD, coronary artery disease; CHF, congestive heart failure; CV, cardiovascular; CVA, cerebrovascular accident; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; ICD, implantable cardioverter defibrillator; IV, intravenous; LVEF, left ventricular ejection fraction; MI, myocardial infarction; N/A, not applicable; NS, not significant; PAD, peripheral artery disease; PC, placebo; po, orally; pts, patients; RR, relative risk; SE systemic embolism; and TIA, transient ischemic attack.

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## Data Supplement 10. AV Junction Ablation (Sections 5.2)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/ Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Endpoints Primary Endpoint &amp; Results</th>
<th>P Values, OR: HR: RR: &amp; 95% CI:</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ozcan C, et al., 2001 (166) 11287974</td>
<td>Assess effect of radio-frequency ablation of the AV node and implantation of a permanent pacemaker on long-term survival in pts with AF refractory to drug Tx</td>
<td>Observational single site</td>
<td>Comparison to 2 control populations</td>
<td>All pts who underwent AV nodal ablation and pacemaker implantation for medically refractory AF between 1990 and 1998</td>
<td>N/A</td>
<td>AV nodal ablation pacemaker compared to 2 control groups</td>
<td>No difference in survival between ablation/pacemaker group and control group treated with drugs Excess observed death in ablation/pacemaker group relative to age/sex matched population</td>
<td>N/A</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; AV, atrioventricular; N/A, not applicable; pts, patients; RR, relative risk; and Tx, therapy.

## Data Supplement 11. Broad Considerations in Rate Control (Sections 5.3.1)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/ Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Study Intervention</th>
<th>Endpoints</th>
<th>P Values, OR: HR: RR: &amp; 95% CI:</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Gelder IC, et al., 2010 (167) 20231232</td>
<td>Lenient rate control is noninferior to strict rate control in permanent AF</td>
<td>Randomized, prospective, multicenter, open label N=614</td>
<td>Lenient rate control (resting heart rate &lt;110) vs. strict rate control (resting heart rate &lt;80)</td>
<td>Age &lt;80 y, permanent AF, oral anticoagulant or ASA Tx</td>
<td>N/A</td>
<td>Composite of CV death and morbidity at 12.9% vs. 14.9%</td>
<td>Death, components of 1° endpoint, Sx, and functional status 1° endpoint, 3 y, HR: 0.84; 95% CI: 0.58-1.21</td>
<td>HF (3.8% vs. 4.1%); HR: 0.97; 95% CI: 0.48-1.96 Stroke 1.6% vs. 3.9%; HR: 0.35; 95% CI: 0.13-0.92 CV death 2.9% vs. 3.9%, HR: 0.79; 95% CI: 0.38-1.65</td>
</tr>
</tbody>
</table>

1° indicates primary; AF, atrial fibrillation; ASA, aspirin; CV, cardiovascular; HF, heart failure; HR, hazard ratio; N/A, not applicable; pts, patients; RACE, Rate Control Efficacy in Permanent Atrial Fibrillation; RR, relative risk; Sx, symptom; and Tx, therapy.
### Data Supplement 12. Antiarrhythmic Drug Therapy (Section 6.2.1)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/ Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Patient Population</th>
<th>Endpoints</th>
<th>Adverse Events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADONIS, Singh BN, et al., 2007 (168) <strong>17804843</strong></td>
<td>To assess the efficacy of dronedarone in maintenance of SR in pts with AF</td>
<td>RCT, double-blind (625)</td>
<td>Dronedarone 400 mg BID (417) vs. PC (208)</td>
<td>Age ≥21 y ≥1 episode AF in previous 3 mo</td>
<td>Time to the 1st recurrence of AF or atrial flutter</td>
<td>N/A</td>
<td>Dronedarone was more effective than PC in maintaining SR and in reducing ventricular rate during recurrent AF</td>
</tr>
<tr>
<td>AFFIRM Substudy, 2003 (169) <strong>12849654</strong></td>
<td>To evaluate the efficacy of antiarrhythmic drugs for AF</td>
<td>RCT, open-label (410)</td>
<td>Amiodarone 200 mg/d vs. class I drug vs. sotalol</td>
<td>Substudy of pts randomized to rhythm control</td>
<td>Probability of SR at 1 y alive, on Tx drug, and in SR</td>
<td>AEs leading to drug discontinuation 12.3% amiodarone 11.1% sotalol 28.1% class I agent</td>
<td>Amiodarone more effective than sotalol or class I agent for SR without cardioversion</td>
</tr>
<tr>
<td>Aliot E, et al., 1996 (170) <strong>8607394</strong></td>
<td>To assess the safety and efficacy of flecainide vs. propafenone in PAF or atrial flutter</td>
<td>RCT, open-label (97)</td>
<td>Flecainide 100-200 mg/d (48) vs. Propafenone 600 mg/d (49)</td>
<td>Inclusion: &gt;18 y with symptomatic PAF or atrial flutter</td>
<td>Probability of SR at 1 y 0.619 flecainide 0.469 propafenone (p=0.79)</td>
<td>8.5% flecainide group had neurologic side effects 16.7% propafenone group GI side effects</td>
<td>Flecainide and propafenone similar efficacy (although small sample size and open-label design) Nonsignificant trend toward higher side-effects with propafenone</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Intervention</td>
<td>Inclusion</td>
<td>Outcomes</td>
<td>Conclusion</td>
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<tr>
<td><strong>ANDROMEDA</strong>, Kober L, et al., 2008 (171) 18565860</td>
<td>To evaluate the efficacy of dronedarone in HF pts</td>
<td>RCT, double-blind (627)</td>
<td>Dronedarone (310) PC (317)</td>
<td>Age &gt;18 y, hospitalized for HF, LVEF&lt;35%, NYHA class III or IV (Did not require AF Dx, Hx of AF 37-40%)</td>
<td>Death from any cause or HF hospitalization 17.1% dronedarone 12.6% PC HR: 1.38; 95% CI: 0.92-2.09; p=0.12</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td><strong>ASAP</strong>, Page RL, et al., 2003 (172) 12615792</td>
<td>To assess the frequency of asymptomatic AF in pts treated with azimilide</td>
<td>RCT, double-blind (1,380)</td>
<td>Azimilide 35-125 mg/d (891) PC (489)</td>
<td>Inclusion: Symptomatic AF in SR at time of randomization Exclusion: Rest angina or UA, class IV CHF, Hx of torsade de pointes, QTc &gt;440 ms, resting SR&lt;50 bpm</td>
<td>Time to 1st documented asymptomatic AF – no significant difference 40% reduction in asymptomatic AF episodes in the 100 mg or 125 mg azimilide group vs. PC (p=0.03)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td><strong>ATHENA</strong>, Hohnloser SH, et al., 2009 (173) 19213680</td>
<td>N/A</td>
<td>RCT, double-blind (4,628)</td>
<td>Dronedarone 400 mg BID (2,301) PC (2,327)</td>
<td>Inclusion: AF (paroxysmal or persistent) and ≥1 of these: &gt;70 y, HTN, DM, LVEF&lt;40%, LAD&gt;50 mm, Hx of TIA/stroke/embolism</td>
<td>1° – 1st hospitalization due to CV event or death 31.9% dronedarone 39.4% PC HR: 0.76; p&lt;0.001</td>
<td>Death due to any cause CV death CV hospitalization</td>
<td></td>
</tr>
<tr>
<td><strong>Bellandi F, et al., 2001 (174) 11564387</strong></td>
<td>To evaluate the long-term efficacy and safety of propafenone and sotalol for maintaining SR</td>
<td>RCT, double-blind (194)</td>
<td>Propafenone HCL 900 mg/d (102) Sotalol HCL 240 mg/d (106) PC (92)</td>
<td>≥18 y, recurrent AF (≥4 episodes previous 12 mo) and episode of AF at enrollment &lt;48 h</td>
<td>Proportion of pts remaining in SR at 1 y FU 63% propafenone 73% sotalol 35% PC (p=0.001)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td><strong>Benditt DG, et al., 1999 (175) 10496434</strong></td>
<td>To evaluate the efficacy of sotalol for maintaining of SR</td>
<td>RCT, double-blind (253)</td>
<td>Sotalol 80 mg BID (59) Sotalol 120 mg BID (63) Sotalol 160 mg PC (63)</td>
<td>Inclusion: symptomatic AF or atrial flutter and SR at time of randomization Dose reduction in presence of renal dysfunction</td>
<td>Time to first recurrent symptomatic AF or atrial flutter after steady state (intention to treat) 27 d PC</td>
<td>Proportion of pts free of AF 12 mo 28% PC 30% sotalol 80 mg 40% sotalol 120</td>
<td>Bradycardia and fatigue most common AEs No cases of torsade de pointes in this study Outpatient initiation in 27%</td>
</tr>
</tbody>
</table>

Dronedarone is associated with increased mortality in pts with severe HF and reduced LVEF related to worsening of HF.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Outcome Measures</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>At 1 y</th>
<th>AE Pre-Tx</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byrne-Quinn E, et al., 1970 (176) 4911757</td>
<td>RCT, double-blind (65)</td>
<td>Percentage of pts at FU in SR</td>
<td>Age &gt;18 y and sustained AF&gt;72 h</td>
<td>QT&gt;450 ms, sinus rate &lt;50, other QT prolonging drugs, renal failure (CrCl&lt;40 mL/min), Hx of HF, uncorrected hypokalemia, asymptomatic AF, sick sinus syndrome without pacer, MI&lt;2 mo, syncope, TIA/stroke</td>
<td>24.3% PC 57% quinidine</td>
<td>N/A</td>
<td>1 death presumed related to quinidine</td>
</tr>
<tr>
<td>Carunchio A, et al., 1995 (177) 7642012</td>
<td>RCT, open-label (66)</td>
<td>Arrhythmia free survival at 12 mo</td>
<td>Age &gt;18 y and sustained AF&gt;72 h</td>
<td>QT&gt;450 ms, sinus rate &lt;50, other QT prolonging drugs, renal failure (CrCl&lt;40 mL/min), Hx of HF, uncorrected hypokalemia, asymptomatic AF, sick sinus syndrome without pacer, MI&lt;2 mo, syncope, TIA/stroke</td>
<td>70% flecainide 60% sotalol 27% PC</td>
<td>N/A</td>
<td>Flecainide and sotalol have similar efficacy in prevention of recurrence of AF</td>
</tr>
<tr>
<td>Channer KS, et al., 2004 (178) 14720531</td>
<td>RCT, double-blind (161)</td>
<td>Percentage in SR at 1 y</td>
<td>Age &gt;18 y and sustained AF&gt;72 h</td>
<td>QT&gt;450 ms, sinus rate &lt;50, other QT prolonging drugs, renal failure (CrCl&lt;40 mL/min), Hx of HF, uncorrected hypokalemia, asymptomatic AF, sick sinus syndrome without pacer, MI&lt;2 mo, syncope, TIA/stroke</td>
<td>49% long-term amiodarone 33% short-term (8 wk after DCCV) amiodarone 5% PC</td>
<td>N/A</td>
<td>Given the long-term AEs with amiodarone, 8 wk of adjuvant Tx suggested as option by authors</td>
</tr>
<tr>
<td>Study</td>
<td>Authors</td>
<td>Design</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>Outcomes</td>
<td>Conclusions</td>
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<tr>
<td>CTAF, Roy D, et al., 2000 (179)</td>
<td>Low dose amiodarone would be more efficacious in preventing recurrent AF than sotalol or propafenone</td>
<td>RCT (403)</td>
<td>Symptomatic AF within previous 6 mo but not persistent AF&gt;6mo</td>
<td></td>
<td>Recurrence of AF during FU (mean 16 mo) 35% amiodarone 63% sotalol or propafenone (p&lt;0.001)</td>
<td>N/A</td>
<td>AEs requiring drug discontinuation 18% amiodarone vs. 11% sotalol or propafenone group (p=0.06)</td>
</tr>
<tr>
<td>DAFNE, Touboul P, et al., 2003 (180)</td>
<td>To determine the most appropriate dose of dronedarone for prevention of AF after DCCV</td>
<td>RCT, double-blind (199)</td>
<td></td>
<td>Inclusion: age 21–85 y, pts with persistent AF (&gt;72 h and &lt;12 mo) scheduled for DCCV</td>
<td>Time to first documented AF recurrence at 6 mo 60 d for dronedarone 400 mg BID 5.3 d for PC (p=0.001)</td>
<td>Spontaneous conversion of AF with dronedarone 5.8 to 14.8% pts</td>
<td>Premature discontinuation 22.6% 1600 mg, 3.9% 800 mg</td>
</tr>
<tr>
<td>DIAMOND, Pedersen OD, et al., 2001 (181)</td>
<td>To evaluate the efficacy of dofetilide to maintain SR in pt with LV dysfunction</td>
<td>RCT, double-blind (506)</td>
<td>Probability of maintaining SR at 1 y 79% dofetilide 42% with PC (p&lt;0.001)</td>
<td>Inclusion: Persistent AF associated with either HF or recent acute MI Dose reduction for renal insufficiency Exclusion: HR: &lt;50 bpm, QTc&gt;460 ms (500 ms with BBB), K&lt;3.6 or &gt;5.5, CrCl&lt;20 mL/min</td>
<td>No effect on all-cause mortality Dofetilide associated with reduced rate of rehospitalization</td>
<td>Torsade de pointes occurred in 4 dofetilide pts (1.6%)</td>
<td>N/A</td>
</tr>
<tr>
<td>DIONYSOS, Le Heuzey JY, et al., 2010 (182)</td>
<td>To evaluate the efficacy and safety of amiodarone and dronedarone in pts with persistent AF</td>
<td>RCT, double-blind (504)</td>
<td>Recurrence of AF (including unsuccessful CV) or premature study discontinuation at 12 mo 75.1% dronedarone, 58.8% amiodarone, HR: 1.59; 95% CI: 1.28-1.98; p&lt;0.0001</td>
<td>Inclusion: age ≥21 y with documented AF for &gt;72 h for whom CV and AAD were indicated and oral anticoagulation</td>
<td>Drug discontinuation less frequent with dronedarone (10.4 vs. 13.3%). MSE was 39.3% and 44.5% with dronedarone and amiodarone, respectively, at 12 mo (HR: 0.80;</td>
<td>N/A</td>
<td>Dronedarone was less effective than amiodarone in decreasing AF recurrence, but had a better safety profile</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Objective</td>
<td>Design, Labeling</td>
<td>Treatment 1</td>
<td>Treatment 2</td>
<td>AF Recurrence (%)</td>
<td>Event Rate</td>
<td>Duration of AF Recurrence</td>
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<tr>
<td>Dogan A, et al., 2004 (183)</td>
<td>To evaluate the efficacy of propafenone for maintenance of SR after cardioversion</td>
<td>RCT, Single-blind</td>
<td>Propafenone</td>
<td>PC</td>
<td>450 mg/d (58)</td>
<td>Recent onset or persistent AF</td>
<td>Percentage of AF recurrences at 15 mo</td>
</tr>
<tr>
<td>EURIDIS, Singh BN, et al., 2007 (168)</td>
<td>To assess the efficacy of dronedarone in maintenance of SR in pts with AF</td>
<td>RCT, double-blind</td>
<td>Dronedarone</td>
<td>PC</td>
<td>400 mg BID (411)</td>
<td>≥1 episode AF in previous 3 mo, Age ≥2y</td>
<td>Time to the 1st recurrence of AF or atrial flutter 96 d dronedarone 41 d in the PC</td>
</tr>
<tr>
<td>FAPIS, Chimienti M, et al., 1996 (184)</td>
<td>To compare the safety of flecainide to propafenone for Tx of PAF</td>
<td>RCT, open-label</td>
<td>Flecainide</td>
<td>Propafenone</td>
<td>Acetate 200 mg/d (97)</td>
<td>Paroxysmal AF without structural heart disease</td>
<td>Probability of remaining free of AEs at 12 mo 77% flecainide 75% propafenone 1 VT in propafenone group 2 accelerated ventricular response with flecainide</td>
</tr>
<tr>
<td>GEFACA, Galperin J, et al., 2001 (185)</td>
<td>To evaluate the efficacy of amiodarone for restoration and maintenance of SR</td>
<td>RCT, double-blind</td>
<td>Amiodarone</td>
<td>PC</td>
<td>200 mg/d (47)</td>
<td>Persistent AF&gt;2 mo duration</td>
<td>Recurrent AF in 37% amiodarone and 80% PC group Spontaneous conversion 34% with amiodarone and 0% PC</td>
</tr>
</tbody>
</table>
| Kalusche D, et al., 1994 (186) 7846939 | To compare the efficacy of sotalol to a fixed combination of quinidine and verapamil | RCT, open-label (82) | Quinidine sulfate 1000 mg/d  
Sotalol HCL 240-400 mg/d | N/A | SR at 6 and 12 mo  
75.7% and 67.3%  
quinidine/verapamil  
63.4 and 49.9%  
sotalol  
p=NS | N/A | 5 pts quinidine/verapamil discontinued due to noncardiac AEs, 3 pts in sotalol discontinued due to bradycardia  
No proarrhythmia noted | N/A |
| Kochiadakis GE, et al., 2004 (187) 15589019 | Compare the efficacy and safety of sotalol and propafenone for prevention of recurrent AF | RCT, single-blind (254) | Propafenone HCL 240 mg/d (86)  
Sotalol HCL 320 mg/d (85)  
PC (83) | Symptomatic AF, successful chemical or DCCV if persistent | Percentage recurrence AF during FU  
69/85 sotalol  
45/86 propafenone  
73/83 PC (p<0.001) | N/A | N/A | Long-term results show superiority of propafenone (question methods of comparison) |
| Kuhlmann, et al., 2000 (188) 10898425 | To evaluate the efficacy of metoprolol XL to reduce AF recurrence after cardioversion | RCT, double-blind (394) | Metoprolol XL 100 mg/d (197)  
PC (197) | Inclusion: Persistent AF with successful cardioversion (DC or chemical)  
Exclusion: Concomitant Tx with any class I or class 3 AAD, beta blocker or CCB | Percentage of pts with recurrent AF during FU (up to 6 mo)  
48.7% metoprolol XL  
59.9% PC (p=0.005) | Mean HR was lower with recurrent AF in pts on metoprolol (107 vs. 98;  
p=0.015) | SAEs similar with metoprolol or PC | Metoprolol XL prevents recurrent AF after cardioversion  
Short duration of FU |
| Naccarelli GV, et al., 1996 (189) 8607392 | To compare the efficacy of flecainide to quinidine for PAF | RCT, open-label (239) | Flecainide acetate 200-300 mg/d (122)  
Quinidine sulfate 1000-1500 mg/d (117) | Symptomatic PAF | Percentage of pts with reported episodes of symptomatic AF  
72% flecainide  
74.3% quinidine (p=0.54) | Combined endpoint efficacy and tolerability at 1 y 70%  
flecainide vs. 55.4% quinidine (p<0.007) | N/A | Flecainide and quinidine have similar efficacy but flecainide is better tolerated |
| PAFAC, Fetsch T, et al., 2004 (190) 15302102 | To compare the efficacy of quinidine and sotalol to PC for maintenance of SR in pt with persistent AF | RCT, double-blind (848) | Quinidine sulfate 480 mg/d  
Sotalol HCL 320 mg/d | Persistent AF lasting >7 d (mean duration: 15 mo)  
N=848, male: 66%, age (mean, SD): 63, ±9,  
structural heart disease: NS, left anterior descending: 45 mm, LVEF: 60% | At 12 mo:  
Mortality  
Pro-arrhythmia  
AEs  
AF recurrence | N/A | N/A | N/A |
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Objective</th>
<th>Study Design</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Age</th>
<th>Risk Factors</th>
<th>Coprimary Outcomes</th>
<th>Unplanned CV Hospitalization or Death</th>
<th>Hospitalization for HF</th>
<th>Most Common AEs</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>PALLAS, Connolly SJ, et al., 2011 (165) 22082198</td>
<td>To assess whether dronedarone would reduce major vascular events in high-risk permanent AF</td>
<td>RCT, double-blind (3236)</td>
<td>Dronedarone 400 mg BID</td>
<td>PC</td>
<td>Age &gt;65 y with permanent AF or atrial flutter with no plan to restore SR and high risk feature: CAD, previous stroke or TIA, HF class II or III Sx, LVEF&lt;40%, PAD or age &gt;75 y, HTN &amp; DM</td>
<td>Stroke, MI, SE, or CV death, 43 pts receiving dronedarone and 19 receiving PC (HR: 2.29; 95% CI: 1.34-3.94; p=0.002) Unplanned CV hospitalization or death, 127 pts receiving dronedarone and 67 pts receiving PC (HR: 1.95; 95% CI: 1.45-2.62; p&lt;0.001)</td>
<td>ALT&gt;3x upper limit normal range occurred in 22 of 1,481 (1.5%) pts receiving dronedarone and in 7 of 1,546 (0.5%) receiving PC</td>
<td>Dronedarone increased rates of HF, stroke, and death from CV causes in pts with permanent AF who were at risk for major vascular events.</td>
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<tr>
<td>Piccini JP, et al., 2009 (191) 19744618</td>
<td>To evaluate randomized trials of amiodarone and dronedarone for safety and efficacy in AF</td>
<td>Meta-analysis</td>
<td>4 trials of amiodarone vs. PC</td>
<td>PC</td>
<td>Randomized PC-controlled trials of amiodarone and dronedarone for maintenance of SR in pts with AF</td>
<td>OR: 0.12 amiodarone vs. PC (95% CI: 0.08-0.19) OR: 0.79 dronedarone vs. PC (95% CI: 0.33-1.87)</td>
<td>Amiodarone trend towards increased mortality Amiodarone greater number AEs than dronedarone</td>
<td>Dronedarone is less effective than amiodarone but has fewer AEs</td>
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<tr>
<td>Study</td>
<td>Study design</td>
<td>Treatment</td>
<td>Inclusion</td>
<td>Exclusion</td>
<td>Outcome measures</td>
<td>AE reporting 1</td>
<td>AE reporting 2</td>
<td>AE reporting 3</td>
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<tr>
<td>Plewan A, et al., 2001 (192)</td>
<td>RCT, open-label (128)</td>
<td>Sotalol 160 mg/d Bisoprolol fumarate 5 mg/d</td>
<td>Persistent AF (mean duration: 9 mo). N=128 Male: 62%. Age (mean, SD): 59, ±10 Structural heart disease: 72%. LAD: 48 mm. LVEF: 41%</td>
<td>At 8 mo: Mortality Pro-arrhythmia AEs AF recurrence</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>PRODIS, Crijns HJ, et al., 1996 (193)</td>
<td>RCT, double-blind (56)</td>
<td>Disopyramide phosphate 750 mg/d Propafenone HCL 900 mg/d</td>
<td>Persistent AF (mean duration: 5 mo). N=56 Male: 68%. Age (mean, SD): 60, ±11 Structural heart disease: 65%. LAD: 46 mm. LVEF: NS</td>
<td>At 6 mo: Mortality Pro-arrhythmia AEs AF recurrence</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>RAFT, Pritchett EL, et al., 2003 (194)</td>
<td>RCT, double-blind (523)</td>
<td>Propafenone hydrochloride 450-850 mg/d (397) PC (126)</td>
<td>Inclusion: Symptomatic AF (type not specified) SR at time of randomization Exclusion: Permanent AF, NYHA class III or IV HF, cardiac surgery &lt;6 mo, MI&lt;12 mo, WPW syndrome, 2nd or 3rd degree AV block, QRS&gt;160 ms, HR&lt;50 bpm, Hx of VF, VT or ICD</td>
<td>At 9 mo: Mortality Pro-arrhythmia AEs AF recurrence</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Reimold SC, et al., 1993 (195)</td>
<td>RCT, open-label (100)</td>
<td>Propafenone HCL 675 mg/d (50) Sotalol HCL 320 mg/d (50)</td>
<td>Pts with AF with previous AAD failure</td>
<td>Percentage with SR at 3, 6, and 12 mo 46%, 41%, 30% propafenone 49%, 46% sotalol</td>
<td>N/A</td>
<td>N/A</td>
<td>Propafenone and sotalol similar efficacy</td>
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<td>Richiardi E, et al., 1992 (196)</td>
<td>RCT, open-label (200)</td>
<td>Propafenone 900 mg/d Quinidine 1000 mg/d</td>
<td>≥3 AF episodes in past 6 mo Exclusion: LA size &gt;55 mm, hepatic or renal insufficiency, MI&lt;30 d, pregnant, decompensated HF, thyroid dysfunction</td>
<td>SR at 6 mo 60% propafenone 56% quinidine SR at 1 y 48% propafenone 42% quinidine</td>
<td>p=NS</td>
<td>N/A</td>
<td>10% side effects propafenone 24% side-effects quinidine (p=0.02)</td>
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<tr>
<td>SAFE-T, Singh BN, et al.</td>
<td>RCT, double-blind</td>
<td>Amiodarone 300 mg/d</td>
<td>Inclusion: Persistent AF&gt;72 h including at time of</td>
<td>Pharmacological Conversion to SR Sustained SR improved QOL NS difference in AEs among the 3 groups</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Inclusion</td>
<td>Exclusion</td>
<td>Randomization/Exclusion</td>
<td>Outcomes</td>
<td>Safety</td>
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<tr>
<td><strong>Amiodarone and Sotalol in Converting AF and Maintenance of SR</strong>&lt;br&gt;22.1% amiodarone&lt;br&gt;24.2% sotalol&lt;br&gt;0.8% PC&lt;br&gt;Median Time to Recurrence AF (intention to treat)&lt;br&gt;487 d amiodarone&lt;br&gt;74 d sotalol&lt;br&gt;6 d PC&lt;br&gt;p&lt;0.001&lt;br&gt;27.1% amiodarone&lt;br&gt;24.2% sotalol&lt;br&gt;0.8% PC</td>
<td>RCT, double-blind (665)&lt;br&gt;PC</td>
<td>Age 18-85 y with AF or atrial flutter 2-26 wk duration&lt;br&gt;Exclusion: Paroxysmal AF or atrial flutter, NYHA class III or IV HF, CrCl&lt;60 mL/min, intolerance to beta blockers, Hx of long QT syndrome</td>
<td></td>
<td>randomization &amp; on oral anticoagulation&lt;br&gt;Exclusion: Sinus node dysfunction, QRS&gt;180 ms, QT interval&gt;400 ms (QT&gt;500 ms with BBB), sinus rate&lt;50 bpm, Hx of renal or hepatic disease, use of verapamil, diltiazem, QT prolonging drugs</td>
<td>Pharmacological Conversion Rate&lt;br&gt;6.1% 125 mcg BID&lt;br&gt;9.8% 250 mcg BID&lt;br&gt;29.9% 500 mcg BID&lt;br&gt;1.2% PC&lt;br&gt;p=0.015 250 mcg and p&lt;0.001 500 mcg (vs. PC)</td>
<td>2 cases of torsade de pointes during initiation phase (0.8%)&lt;br&gt;1 sudden death (proarrhythmic) on Day 8 (0.4%)</td>
<td>In-hospital initiation and dosage adjustment based on QTc and CrCl to minimize proarrhythmic risk</td>
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<td><strong>SAFIRE-D, Singh S, et al., 2000 (198)</strong>&lt;br&gt;11067793</td>
<td>To determine the efficacy and safety of dofetilide in converting AF or atrial flutter to SR and maintaining SR for 1 y&lt;br&gt;4.8% PC&lt;br&gt;Median Time to Recurrence AF (intention to treat)&lt;br&gt;74 d amiodarone&lt;br&gt;6 d PC&lt;br&gt;p&lt;0.001&lt;br&gt;27.1% amiodarone&lt;br&gt;24.2% sotalol&lt;br&gt;0.8% PC</td>
<td>RCT, double-blind (250)&lt;br&gt;PC</td>
<td></td>
<td>Pharmacological Conversion Rate&lt;br&gt;6.1% 125 mcg BID&lt;br&gt;9.8% 250 mcg BID&lt;br&gt;29.9% 500 mcg BID&lt;br&gt;1.2% PC&lt;br&gt;p=0.015 250 mcg and p&lt;0.001 500 mcg (vs. PC)</td>
<td>Probability of SR at 1 y&lt;br&gt;0.40 125 mcg BID&lt;br&gt;0.37 250 mcg BID&lt;br&gt;0.58 500 mcg BID&lt;br&gt;0.25 PC&lt;br&gt;N/A</td>
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<td><strong>SOPAT, Patten M, et al., 2004 (199)</strong>&lt;br&gt;15321697</td>
<td>To assess the effectiveness of 2 AAD on frequency of AF&lt;br&gt;6.1% PC&lt;br&gt;Time to 1st recurrence of symptomatic PAF or premature discontinuation&lt;br&gt;105.7 d PC&lt;br&gt;150.4 d high-dose quinidine/verapamil&lt;br&gt;148.9 d low-dose quinidine/verapamil&lt;br&gt;1 death and 1 VT event related to high-dose quinidine/verapamil&lt;br&gt;2 syncopal events related to sotalol&lt;br&gt;Quinidine/verapamil fixed combination similar efficacy to sotalol but with risk of SAEs</td>
<td>RCT, double-blind (1033)&lt;br&gt;PC</td>
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<td><strong>Stroobandt R, et al., 1997 (200)</strong></td>
<td>To assess the efficacy of propafenone at maintaining sinus rhythm</td>
<td>RCT, double-blind (102)</td>
<td>Propafenone HCL 150 mg TID (77) PC (25)</td>
<td>Age ≥18 y with AF, enrolled in maintenance phase after attempt at pharmacological conversion with IV propafenone (and if unsuccessful DCCV)</td>
<td>Proportion of pts free from recurrent symptomatic AF at 6 mo 67% propafenone 35% PC (p&lt;0.001)</td>
<td>N/A</td>
<td>NS difference in AEs</td>
<td>Evidence for the efficacy of propafenone in maintaining sinus rhythm after cardioversion. Short duration of FU (6 mo)</td>
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<tr>
<td><strong>SVA-3, Pritchett EL, et al., 2000 (201)</strong></td>
<td>To assess the effectiveness of azimilide in reducing symptomatic AF or atrial flutter</td>
<td>RCT, double-blind (384)</td>
<td>Azimilide 50 mg, 100 mg, or 125 mg PC</td>
<td>Inclusion: Age ≥18 y, Symptomatic AF at time of randomization Exclusion: Rest angina or UA, class IV CHF, Hx of torsade de pointes, QTc&gt;440 ms, resting SR&lt;50 bpm</td>
<td>Time to 1st symptomatic AF recurrence Azimilide 100 mg/125 mg QD vs. PC, HR: 1.58; p=0.005</td>
<td>N/A</td>
<td>2 sudden deaths in azimilide groups and 1 case of torsade de pointes</td>
<td>Initiated in outpatient setting</td>
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<tr>
<td><strong>Villani R, et al., 1992 (202)</strong></td>
<td>To compare the efficacy of amiodarone to disopyramide</td>
<td>RCT, open-label (76)</td>
<td>Amiodarone 200 mg/d (41) Disopyramide phosphate 500 mg/d (35)</td>
<td>Recurrence of AF at end of FU 57% disopyramide (13 mo) 32% amidarone (14 mo)</td>
<td>N/A</td>
<td>Disopyramide discontinued due to AE 14% &lt;1 wk and another 14% by end of trial 8.5% developed hyperthyroidism</td>
<td>Amiodarone is more effective than disopyramide for prevention of recurrent AF</td>
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**AAD** indicates antiarrhythmic drug; **ADONIS**, American-Australian-African Trial With Dronedarone in Patients With Atrial Fibrillation or Atrial Flutter for the Maintenance of Sinus Rhythm; **AE**, adverse event; **AF**, atrial fibrillation; **AFFIRM**, Atrial Fibrillation Follow-up Investigation of Rhythm Management; **ALT**, alanine aminotransferase; **ANDROMEDA**, European Trial of Dronedarone in Moderate to Severe Congestive Heart Failure; **ASAP**, ASA and Plavix; **ATHENA**, A Trial With Dronedarone to Prevent Hospitalization or Death in Patients With Atrial Fibrillation; **AV**, atrioventricular; **BBB**, bundle-branch block; **BID**, twice daily; **CABG**, coronary artery bypass graft; **CCB**, calcium channel blocker; **CHF**, congestive heart failure; **COPD**, chronic obstructive pulmonary disorder; **CrCl**, creatinine clearance; **CTA**, Canadian Trial of Atrial Fibrillation; **CV**, cardiovascular; **DAFNE**, Dronedarone Atrial Fibrillation Study after Electrical Cardioversion; **DC**, direct current; **DCCV**, direct current cardioversion; **DIAMOND**, Danish Investigators of Arrhythmia and Mortality on Dofetilide; **DIONYSOS**, Efficacy & Safety of Dronedarone Versus Amiodarone for the Maintenance of Sinus Rhythm in Patients With Atrial Fibrillation; **DM**, diabetes mellitus; **Dx**, diagnosis; **FAPIS**, Flecainide and Propafenone Italian Study; **FU**, follow-up; **GEFACA**, Grupo de Estudio de Fibrilacion Auricular Con Amiodarona; **GI**, gastrointestinal; **HCL**, hydrochloride; **HF**, heart failure; **HR**, hazard ratio; **HTN**, hypertension; **Hx**, history; **ICD**, implantable cardioverter defibrillator; **K**, potassium; **LA**, left atrial; **LAD**, left atrial dimension; **LV**, left ventricular; **LVEF**, left ventricular ejection fraction; **MI**, myocardial infarction; **MSE**, main safety endpoint; **N/A**, not applicable; **NS**, not significant; **NYHA**, New York Heart Association; **OR**, odds ratio; **PAF**, paroxysmal atrial fibrillation; **PALLAS**, Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy; **PC**, placebo; **pts**, patients; **QD**,...
once daily; QID, four times a day; QOL, quality of life; RAFT, Rythmol Atrial Fibrillation Trial; RCT, randomized controlled trial; RR, relative risk; SAFE-T, Sotalol Amiodarone Atrial Fibrillation Efficacy Trial; SAFIRE-D, Symptomatic Atrial Fibrillation Investigative Research on Dofetilide; SD, standard deviation; SOPAT, Suppression of Paroxysmal Atrial Tachyarrhythmias; SR, sinus rhythm; SVA, Supraventricular Arrhythmia Program; TIA, transient ischemic attack; TID, three times a day; Tx, therapy; UA, unstable angina; VF, ventricular fibrillation; VT, ventricular tachycardia; and WPW, Wolff-Parkinson-White.

### Data Supplement 13. Outpatient Initiation of Antiarrhythmic Drug Therapy (Section 6.2.1.2)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Type</th>
<th>Intervention (n)</th>
<th>Rhythm at Time of Initiation</th>
<th>Place of Initiation</th>
<th>Patient Population</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benditt D, et al., 1999 (175) <strong>10496434</strong></td>
<td>Prospective dose finding study</td>
<td>Sotalol 80 BID (59) Sotalol 120 BID (63) Sotalol 160 BID (62) PC (69)</td>
<td>SR</td>
<td>50 pts - outpatient 134 pts - inpatient</td>
<td>Structural heart disease 57% Exclusion: Hx of torsade de pointes, CHF, QT&gt;450 ms, hypokalemia hypomagnesemia, bradycardia</td>
<td>No cases of VT/VF/torsade QT&gt;520 ms in 7 pts (4 in 120 mg BID and 3 in 160 mg BID) Premature discontinuation due to AEs 25% inpatients, but 6% of outpatients (bradycardia predominantly)</td>
</tr>
<tr>
<td>Chung MK, et al., 1998 (203) <strong>9669266</strong></td>
<td>Retrospective</td>
<td>Sotalol</td>
<td>Not documented</td>
<td>Inpatient</td>
<td>120 inpatients admitted for sotalol initiation Structural heart disease (80%)</td>
<td>7 (5.8%) new or increased ventricular arrhythmias, 2 with torsades de pointes (d 6 in pt with pacemaker and hypokalemia and d 4 in pts with ICD) 20 (16.7%) with significant bradycardia 8 (6.7%) excessive QT prolongation</td>
</tr>
<tr>
<td>SAFE-T, Singh BN, et al., 2005 (197) <strong>15872201</strong></td>
<td>Prospective RCT</td>
<td>Total 665 Amiodarone 267 Sotalol 261 Placebo 137</td>
<td>AF</td>
<td>Outpatient</td>
<td>Initiated sotalol or amiodarone in the outpatient setting during AF Excluded CHF class III or IV, Hx of long QT, CrCl&lt;60</td>
<td>1 case torsade in sotalol group (nonfatal, time of occurrence not specified) 13 deaths/267 (6 sudden) amiodarone group 15 deaths/261 (8 sudden) sotalol group 3 deaths/137 (2 sudden) PC group (no significant difference)</td>
</tr>
<tr>
<td>Zimetbaum PJ, et al., 1999 (204) <strong>10072241</strong></td>
<td>Prospective</td>
<td>172 Amiodarone 66 (38%) Flecaainide 45 (26%) Sotalol 20 (12%) Disopyramide 16 (9%) Propafenone 11 (6%) Quinidine 8 (5%) Procainamide 6 (4%)</td>
<td>SR</td>
<td>Outpatient</td>
<td>Pts with AF in sinus at time of initiation started on oral antiarrhythmic medication Received 1 or 2 doses of AAD in hospital or clinic and monitored for ≤8 h and then 10 d continuous loop event recorder Exclusion: QTc&gt;550 ms, NYHA class III or IV CHF, or pacemaker</td>
<td>6 symptomatic AEs (none before d 4) Class Ic 3 atrial flutter with 1:1 d 6 or 7 1 symptomatic brady d 4 Sotalol 1 symptomatic bradycardia d 7 1 QT prolongation 370-520 ms d 4</td>
</tr>
<tr>
<td>Study Name, Author, Year</td>
<td>Study Aim</td>
<td>Study Type/ Size (N)</td>
<td>Intervention vs. Comparator (n)</td>
<td>Patient Population</td>
<td>Endpoints</td>
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<tr>
<td>Hauser TH, et al., 2003 (205) 12804730</td>
<td>Prospective</td>
<td>409 Amiodarone 212 (51.8%) Class Ic 127 (31.1%) Propafenone 64 (15.6%) Flecainide 63 (15.4%) Sotalol 37 (9.0%) Class IA 33 (8.1%) Quinidine 8 (2%) Disopyramide 16 (3.9%) Procainamide 9 (2.2%)</td>
<td>SR</td>
<td>Outpatient</td>
<td>Pts with AF in sinus at time of initiation started on oral AAD with daily 30 s recording or with Sx</td>
<td>Amiodarone 2 Death (sudden) d 7 and d 9 3 Bradycardia requiring pacemaker d 6, 7, and 8 9 Bradycardia requiring dose reduction</td>
</tr>
<tr>
<td>CTAF, Roy D, et al., 2000 (179) 10738049</td>
<td>Prospective open-label RCT</td>
<td>403 Amiodarone 201 Sotalol 101 Propafenone 101</td>
<td>Sinus≈60%</td>
<td>Outpatient</td>
<td>Exclusion: QTc&gt;480, bradycardia &lt;50 bpm</td>
<td>Arrhythmic deaths – 3 amiodarone group (2 had been off the drug &gt;1 y) and 1 in sotalol/propafenone group</td>
</tr>
<tr>
<td>Kochiadakis GE, et al., 2004 (187) 15589019</td>
<td>N/A</td>
<td>254 Sotalol 85 Propafenone 86 PC 83</td>
<td>Sinus</td>
<td>Inpatient</td>
<td>N/A</td>
<td>No torsades noted Sotalol - 3 bradycardia during loading phase Propafenone – 1 bradycardia; 1 QRS widening</td>
</tr>
</tbody>
</table>

AAD indicates antiarrhythmic drug; AE, adverse event; AF, atrial fibrillation; BID, twice daily; CHF, congestive heart failure; CrCl, creatinine clearance; CTAF, Canadian Trial of Atrial Fibrillation; Hx, history; ICD, implantable cardioverter-defibrillator; IV, intravenous; NYHA, New York Heart Association; pts, patients; RCT, randomized controlled trial; RR, relative risk; SAFE-T, Sotalol Amiodarone Atrial Fibrillation Efficacy Trial; SR, sinus rhythm; Sx, symptom; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Data Supplement 14. Upstream Therapy (Section 6.2.2)
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Primary Endpoint</th>
<th>Secondary Endpoints</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANTIPAF, Goette A, et al., 2012 (206)</td>
<td>Prospective, PC-controlled RCT</td>
<td>Olmesartan 40 mg QD (214) PC (211)</td>
<td>Pts with PAF and no other indication for ACE inhibitor or ARB Tx</td>
<td>No difference in the 1st endpoint of AF burden (p=0.770)</td>
<td>No difference in QOL, time to 1st AF recurrence, time to persistent AF and hospitalizations</td>
<td>In pts with AF (2° prevention) but without structural disease, 1 y of ARB does not appear to decrease AF burden</td>
</tr>
<tr>
<td>GISSI-AF, 2009 (207)</td>
<td>Prospective, PC-controlled, RCT</td>
<td>Valsartan (722) PC (720)</td>
<td>AF and underlying CV disease, diabetes, or left atrial enlargement</td>
<td>Co-primary endpoints: Time to first recurrence of AF, 295 d valsartan, 271 d PC</td>
<td>Proportion of pts who had &gt;1 recurrence of AF&gt;12 mo, 26.9% valsartan, 27.9% PC OR: 0.95; p=0.66</td>
<td>N/A Tx with valsartan not associated with reduced AF</td>
</tr>
<tr>
<td>Healey JS, et al., 2005 (208)</td>
<td>Systematic review of all RCT evaluating the benefit of trials of ACE inhibitor and ARBs in prevention of AF</td>
<td>Meta-analysis</td>
<td>N/A</td>
<td>11 studies included with 56,308 pts</td>
<td>ACE inhibitor and ARB reduced incidence of AF (RR: 0.28; p=0.0002) Reduction in AF greatest in pts with HF (RR: 0.44; p=0.007) No significant reduction in pts with HTN (RR: 0.12; p=0.4) although 1 study 29% reduction in pts with LVH (RR: 0.29)</td>
<td>N/A ACE inhibitor and ARBs appear to be effective in prevention of AF probably limited to pts with systolic LV dysfunction or HTN LVH</td>
</tr>
<tr>
<td>J-RHYTHM II, Yamashita T, et al., 2011 (208, 209)</td>
<td>Open label, RCT</td>
<td>Candesartan Amlodipine</td>
<td>Pts with PAF (2° prevention) and HTN</td>
<td>N/A</td>
<td>N/A Tx of HTN by candesartan was not superior to amlodipine for reduction in AF frequency</td>
<td></td>
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<tr>
<td>Schneider MP, et al., 2010 (210)</td>
<td>Meta-analysis</td>
<td>N/A</td>
<td>23 studies included with 87,048 pts</td>
<td>N/A</td>
<td>N/A N/A</td>
<td></td>
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</tbody>
</table>

1° indicates primary; 2°, secondary; ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ANTIPAF, Angiotensin II-Antagonist in Paroxysmal Atrial Fibrillation; ARB, angiotensin-receptor blockers; CV, cardiovascular; GISSI-AF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Atrial Fibrillation; HF, heart failure; HTN, hypertension; J-RHYTHM, Japanese Rhythm Management Trial for Atrial Fibrillation; LV, left ventricular; LVH, left ventricular hypertrophy; N/A, not applicable; OR, odds ratio; PAF, paroxysmal atrial fibrillation; PC, placebo; pts, patients; QD, once daily; QOL, quality of life; RCT, randomized controlled trial; RR, relative risk; and Tx, therapy.
## Data Supplement 15. AF Catheter Ablation to Maintain Sinus Rhythm (Section 6.3)

<table>
<thead>
<tr>
<th>Study Name, Author, Year</th>
<th>Study Aim</th>
<th>Study Type/ Size (N)</th>
<th>Intervention vs. Comparator (n)</th>
<th>Type of AF</th>
<th>Ablation Technique</th>
<th>Endpoints</th>
<th>AF Free at 1 y</th>
<th>Crossover Rate to RFA</th>
<th>Adverse Events</th>
<th>Study Limitations</th>
</tr>
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<tbody>
<tr>
<td>Krittayaphong R, et al., 2003 (211) 12866763</td>
<td>To compare the efficacy of amiodarone to RFA for maintenance of SR</td>
<td>RCT (30)</td>
<td>RFA</td>
<td>Paroxysmal and persistent</td>
<td>Circumferential PVI with anatomic isolation</td>
<td>Freedom from AF at 12 mo</td>
<td>79%</td>
<td>40%</td>
<td>0.018</td>
<td>Not stated</td>
</tr>
<tr>
<td>RAAFT, Wazni OM, et al., 2005 (212) 15928285</td>
<td>To determine whether PVI is feasible as 1st line Tx for symptomatic AF</td>
<td>RCT (70)</td>
<td>RFA (33)</td>
<td>Paroxysmal</td>
<td>Segmental PVI with electrical isolation</td>
<td>Freedom from AF at 12 mo (Any recurrence of symptomatic AF or asymptomatic AF&gt;15 s)</td>
<td>87%</td>
<td>37%</td>
<td>p&lt;0.001</td>
<td>49%</td>
</tr>
<tr>
<td>CACAF, Stabile G, et al., 2005 (213) 16214831</td>
<td>Compare RFA to AAD for prevention of AF in pts who failed AAD</td>
<td>RCT (137)</td>
<td>RFA (68)</td>
<td>Paroxysmal and persistent</td>
<td>Circumferential PVI with anatomic isolation</td>
<td>Freedom from AF at 12 mo</td>
<td>56%</td>
<td>9%</td>
<td>p&lt;0.001</td>
<td>57%</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Study Design</td>
<td>Intervention 1</td>
<td>Intervention 2</td>
<td>PVI Method</td>
<td>Freedom from AF</td>
<td>P1</td>
<td>P2</td>
<td>Comments</td>
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<td>Oral H, et al., 2006 (214)</td>
<td>Persistent AF</td>
<td>RCT (146)</td>
<td>RFA (77)</td>
<td>Control (69)</td>
<td>Circumferential PVI with anatomic isolation</td>
<td>Monthly freedom from AF off AAD</td>
<td>70%</td>
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<td>RFA 74% (intention to treat), p=0.05</td>
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<td></td>
<td>70%</td>
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<td>Control 58% (on-Tx analysis), p=0.05</td>
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<td>74%</td>
<td></td>
<td>RFA 70% (on-Tx analysis), p&lt;0.001</td>
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<td></td>
<td>4%</td>
<td></td>
<td>Control 58% (on-Tx analysis), p=0.05</td>
<td></td>
</tr>
<tr>
<td>APAF Pappone C, et al., 2006 (128)</td>
<td>Paroxysmal AF</td>
<td>RCT (198)</td>
<td>RFA (99)</td>
<td>AAD (99)</td>
<td>Circumferential PVI with anatomic isolation</td>
<td>Freedom from AF at 12 mo</td>
<td>86%</td>
<td>22%</td>
<td>p&lt;0.001</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>89%</td>
<td>23%</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>A4 Jais P, et al., 2008 (215)</td>
<td>Paroxysmal AF</td>
<td>RCT (112)</td>
<td>RFA (53)</td>
<td>AAD (59)</td>
<td>Circumferential PVI with electrical isolation</td>
<td>Freedom from AF at 12 mo</td>
<td>89%</td>
<td>23%</td>
<td>p&lt;0.001</td>
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<td></td>
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<td></td>
<td></td>
<td>80%</td>
<td>43%</td>
<td>p=0.001</td>
<td></td>
</tr>
<tr>
<td>Forleo GB, et al., 2009 (216)</td>
<td>Paroxysmal AF</td>
<td>RCT (70)</td>
<td>RFA (35)</td>
<td>AAD (35)</td>
<td>Circumferential PVI with electrical isolation</td>
<td>N/A</td>
<td>80%</td>
<td>43%</td>
<td>Not stated</td>
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</table>

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<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnoses</th>
<th>Controls</th>
<th>Study Design</th>
<th>Patients</th>
<th>Procedure</th>
<th>Outcomes 1</th>
<th>Outcomes 2</th>
<th>p-Value</th>
<th>Follow-up</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermocool Wilber DJ, et al., 2010 (217) 20103757</td>
<td>Diabetes, paroxysmal AF</td>
<td>AAD</td>
<td>RCT (167)</td>
<td>RFA (106)</td>
<td>PVI with electrical isolation</td>
<td>Freedom from protocol-defined Tx failure (documented symptomatic AF, repeat ablation &gt;80 days after initial, changes in drug regimen post blanking, absence of entrance block)</td>
<td>66%</td>
<td>16%</td>
<td>&lt;0.001</td>
<td>59% 4.9% RFA more effective than medical Tx alone in preventing recurrent Sx of paroxysmal AF in pts who have already failed Tx with 1 AAD</td>
</tr>
<tr>
<td>STOP-AF Packer DL, et al., 2013 (218) 23500312</td>
<td>Paroxysmal AF (98%) and Persistent</td>
<td>AAD</td>
<td>RCT (245)</td>
<td>Cryoballoon ablation (163) AAD (flecainide, propafenone, sotalol) (82)</td>
<td>PVI with electrical isolation</td>
<td>Freedom from CTF (no detected AF, no AF interventions, no use of non-study drugs) 3-mo blanking period</td>
<td>70%</td>
<td>7.3%</td>
<td>&lt;0.001</td>
<td>79% All events: cryoablation 12.3%, AAD 14.6% Procedure event rate 6.3% Phrenic nerve paralysis 11.2% (29) with 86.2% (25) resolved at 12 mo</td>
</tr>
<tr>
<td>RAAFT2 Morillo C, et al., 2014 (219)</td>
<td>Paroxysmal (98%) and Persistent</td>
<td>AAD</td>
<td>RCT (127)</td>
<td>RFA (66) AAD (61)</td>
<td>PVI with electrical isolation</td>
<td>AF, atrial flutter, or atrial tachycardia &gt;30 s at 24 months</td>
<td>45%</td>
<td>28%</td>
<td>=0.02</td>
<td>47% 9% RFA after additional ablation</td>
</tr>
<tr>
<td>MANTRA-PAF</td>
<td>Symptomatic</td>
<td>AAD</td>
<td>RCT (294)</td>
<td>RFA (146)</td>
<td>PVI with electrical isolation</td>
<td>Cumulative</td>
<td>13%</td>
<td>19%</td>
<td>=0.10</td>
<td>36% RFA group – 1 No difference</td>
</tr>
<tr>
<td>Study Name, Author, Year</td>
<td>Study Aim</td>
<td>Study Size (N)</td>
<td>Patient Population</td>
<td>Study Intervention</td>
<td>Endpoints</td>
<td>Follow-Up</td>
<td>Adverse Events</td>
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<tr>
<td>Bonnano C, et al., 2010 (221) 19834326</td>
<td>Systematic review of RCT of RFA vs. AAD</td>
<td>8 studies (844 pts)</td>
<td>N/A</td>
<td>N/A</td>
<td>Freedom from AF after a single procedure</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Calkins H, et al., 2009 (222) 19808490</td>
<td>Systematic review of radiofrequency ablation for AF</td>
<td>63 studies included (8789 pts)</td>
<td>Mean age 55.5 y</td>
<td>N/A</td>
<td>Single-procedure success rate of ablation off AAD Tx was 57% (95% CI: 50% to 64%)</td>
<td>Major complication rate 4.9%</td>
<td>Stroke/TIA 0.5% Mortality 0.7% Cardiac tamponade 0.8% PV stenosis 1.6% LA/esophageal fistula 0.0%</td>
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<tr>
<td>Parkash R, et al., 2011 (223) 21332861</td>
<td>Systematic review of RCT to assess optimal technique for RFA of AF</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Freedom from AF after a single procedure</td>
<td>Wide-area PVI appeared to offer the most benefit for both paroxysmal (6 studies, RR: 0.78; 95% CI: 0.63-0.97) and persistent AF (3 studies, RR: 0.64; 95% CI: 0.43-0.94)</td>
<td>N/A</td>
<td></td>
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</tr>
<tr>
<td>Piccini JP, et al., 2009 (224) 20009077</td>
<td>Meta-analysis of all RCTs comparing PVI and medical Tx for the</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Freedom from recurrent AF at 12 mo PVI was associated with markedly increased odds of freedom</td>
<td>N/A</td>
<td>Among those randomly assigned to PVI, 17% required a repeat PVI ablation before 12 mo. The</td>
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</table>
Data Supplement 17. Specific Patient Groups (Section 7)

<table>
<thead>
<tr>
<th>Study</th>
<th>Aim of study</th>
<th>Study Size</th>
<th>Patient Population / Inclusion &amp; Exclusion Criteria</th>
<th>Endpoint(s)</th>
<th>Statistical Analysis Reported</th>
<th>CI and/or OR/RR/ Other P values</th>
<th>OR/HR/RR/ Other P values</th>
<th>Study Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roy D, et al., 2008 (225)</td>
<td>To investigate maintenance of SR (rhythm control) with ventricular rate control in pts with LVEF≤35% and Sx of CHF, and a Hx of AF</td>
<td>1,376 (682 in rhythm-control group and 694 in rate-control group)</td>
<td>Inclusion criteria: LVEF≤35% (measured by nuclear imaging, echocardiography, or cardiac angiography, with testing performed ≤6 mo before enrollment); Hx of CHF (defined as symptomatic NYHA class II or IV within the previous 6 mo, asymptomatic condition that pt had been hospitalized for HF during the previous 6 mo, or LVEF≤25%; Hx of AF (with EKG documentation), defined as 1 episode lasting for ≥6 h or requiring cardioversion within the previous 6 mo or an episode lasting for ≥10 min within the previous 6 mo and previous electrical cardioversion for AF; and eligibility for long-term Tx in either of the 2 study groups</td>
<td>1° outcome was time to death from CV causes</td>
<td>None of the 2° outcomes differed significantly between the Tx groups</td>
<td>95% CI: 0.86-1.30; p=0.53</td>
<td>95% CI: 0.80-1.17; p=0.73</td>
<td>95% CI: 0.40-1.35; p=0.32</td>
</tr>
<tr>
<td>AFFIRM, Olshansky B, et al., (163)</td>
<td>To evaluate and compare several drug classes for long-term ventricular rate control</td>
<td>2027</td>
<td>Inclusion criteria: (All criteria must have been met). Episode of AF documented on EKG or rhythm strip within last 6 wk, ≥65 y or &lt;65 y + ≥1 clinical risk factor for stroke (systemic HTN, DM, CHF, TIA, prior cerebral vascular accident, left atrium ≥50 mm by echocardiogram, fractional shortening &lt;25% by echocardiogram (unless paced or LBBB present), or LVEF&lt;0.40 by radionuclide ventriculogram, contrast angiography, or quantitative echocardiography), duration of AF episodes in last 6 mo must total ≥6 h, unless electrical and/or pharmacologic cardioversion was performed prior to 6 h, duration of continuous AF must be &lt;6 mo, unless normal SR can be restored and maintained ≥24 h, in opinion of clinical investigator, pt (based on clinical and laboratory evaluation before randomization) must be eligible for both Tx groups, based on pt Hx, pt must be eligible for ≥2 AADs (or 2 dose levels of amiodarone) and ≥2 rate-controlling drugs</td>
<td>Overall rate control was met in 70% of pts given beta blockers as the 1st drug (with or without digoxin), vs. 54% with CCBs (with or without digoxin), and 58% with digoxin alone</td>
<td>N/A</td>
<td>N/A</td>
<td>In pts with AF, rate control is possible in the majority of pts. In the AFFIRM FU study, beta blockers were most effective. The authors noted frequent medication changes and drug combinations were needed</td>
<td></td>
</tr>
<tr>
<td>ANDROME DA, Kober L, et al., 2008 (171) 18565860</td>
<td>To evaluate the efficacy of dronedarone in reducing hospitalization due to CHF in pts with symptomatic HF</td>
<td>627</td>
<td>Inclusion criteria: Pts ≥18 y hospitalized with new or worsening HF and who had ≥1 episode of SOB on minimal exertion or at rest (NYHA III or IV) or paroxysmal nocturnal dyspnea within the month before admission. Exclusion criteria: LV wall motion index of &gt;1.2 (approximating an EF of &gt;35%), acute MI within 7 d prior to screening, a heart rate &lt;50 bpm, PR interval &gt;0.28 s, sinoatrial block or 2nd or 3rd degree AV block not treated with a pacemaker, Hx of Torsades de pointes, corrected QT interval &gt;500 ms, a serum potassium level &lt;3.5 mmol/L, use of class I or III AADs, drugs known to cause Torsades de pointes, or potent inhibitors of the P450 CYP3A4 cytochrome system, other serious disease, acute myocarditis, constrictive pericarditis, planned or recent (within the preceding mo) cardiac surgery or angioplasty, clinically significant obstructive heart disease, acute pulmonary edema within 12 h before randomization, pregnancy or lactation, expected poor compliance, or participation in another clinical trial.</td>
<td>The 1st endpoint was the composite of death from any cause or hospitalization for HF.</td>
<td>After inclusion of 627 pts, the trial was prematurely terminated for safety reasons. A median FU of 2-mo death occurred in 8.1% of dronedarone group and 3.8% of PC group. After additional 6 mo, 42 pts in dronedarone group (13.5%) and 39 pts in PC group (12.3%) died. The 1st endpoint did not differ significantly between the 2 groups; there were 53 events in the dronedarone group (17.1%) and 40 events in the PC group (12.6%). p=0.03; 95% CI: 1.07-4.25 p=0.60; 95% CI: 0.73-1.74 p=0.12; 95% CI: 0.92-2.09.</td>
<td>Dronedarone increased early mortality in pts recently hospitalized with symptomatic HF and depressed LV function. 96% of deaths were attributed to CV causes, predominantly progressive HF and arrhythmias.</td>
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</table>
RACE II
Van Gelder IC, et al., 2010 (167)

To investigate if lenient rate control is not inferior to strict control for preventing CV morbidity and mortality in pts with permanent AF

| 614 | Inclusion criteria: Permanent AF up to 12 mo, age ≤80 y, mean resting heart rate >80 bpm, and current use of oral anticoagulation Tx (or ASA, if no risk factors for thromboembolic complications present) Exclusion Criteria: Paroxysmal AF; contraindications for either strict or lenient rate control (e.g., previous adverse effects on negative chronotrophic drugs); unstable HF defined as NYHA IV HF or HF necessitating hospital admission <3 mo before inclusion; cardiac surgery <3 mo; any stroke; current or foreseen pacemaker, ICD, and/or cardiac resynchronization Tx; signs of sick sinus syndrome or AV conduction disturbances (i.e., symptomatic bradycardia or asystole >3 s or escape rate <40 bpm in awake Sx-free pts; untreated hyperthyroidism or <3 mo euthyroidism; inability to walk or bike | Composite of death from CV causes, hospitalization for HF, and stroke, SE, bleeding and life-threatening arrhythmic events. FU duration 2 y, with a maximum of 3 y | 1° outcome incidence at 3 y was 12.9% in the lenient-control group and 14.9% in the strict-control group. Absolute difference with respect to the lenient-control group of -2.0 percentage points. More pts in the lenient-control group met the heart rate target or targets (304 [97.7%] vs. 203 [67.0%] in the strict-control group) Frequencies of Sx and AEs were similar in the 2 groups | Absolute risk difference, -2.0% Absolute risk difference, CI: -7.6-3.5; p<0.001 90% CI: 0.58-1.21; p=0.001 p<0.001 |

Gaita F, et al., 2007 (226)

Assess usefulness and safety of transcatheter ablation of AF in pts with HCM

| 26 | Pts with HCM with paroxysmal (n=13) or permanent (n=13) AF refractory to antiarrhythmic Tx Characteristics: age 58±11 y, time from AF onset 7.3±6.2 y, left atrial volume 170±48 mL, 19±10 mo clinical FU | Pulmonary vein isolation at RFCA plus linear lesions | 64% overall success rate 10 of these 16 success pts were off AAD Tx at final evaluation 77% success rate in PAF compared with 50% in the subgroup with permanent AF | N/A |

Lenient rate control is as effective as strict rate control and easier to achieve in pts with permanent AF
| Kilicaslan F, et al., 2006 (227) 16500298 | The purpose of this study was to report the results and outcome of PV antrum isolation in pts with AF and HOCM | 27 | 27 pts with AF and HOCM who underwent PV antrum isolation between February 2002 and May 2004. Mean age 55±10 y, Mean AF duration was 5.4±3.6 y, AF was paroxysmal in 14 (52%), persistent in 9 (33%), and permanent in 4 (15%). Mean FU of 341±237 d | Maintenance of sinus rhythm after PV antrum isolation | 13 pts (48%) had AF recurrence | N/A | N/A | AF recurrence after the 1st PV antrum isolation is higher in pts with HOCM. However, after repeated ablation procedures, long-term cure can be achieved in a sizable number of pts. PV antrum isolation is a feasible therapeutic option in pts with AF and HOCM |

| Bunch TJ, et al., 2008 (228) 18479329 | Assess efficacy of RFCA for drug-refractory AF in HCM | 32 | Consecutive pts (25 male, age 51±11 y) with HCM underwent PV isolation (n=8) or wide area circumferential ablation with additional linear ablation (=25) for drug-refractory AF. Paroxysmal AF=21 (64%) pts had paroxysmal AF. Persistent/permanent AF=12 (36%) had persistent/permanent AF. Duration AF=6.2±5.2 y, Average EF=0.63±0.12, Average left atrial volume index was 70±24 mL/m², FU of 1.5±1.2 y | Survival with AF elimination and AF control | N/A | 1-y survival with AF elimination was 62% (95% CI: 0.66-0.84) and with AF control was 75% (95% CI: 0.66-0.84) | N/A | AF control was less likely in pts with a persistent/chronic AF, larger left atrial volumes, and more advanced diastolic disease. Additional linear ablation may improve outcomes in pts with severe left atrial enlargement and more advanced diastolic dysfunction. 2 pts had a periprocedural TIA, 1 PV stenosis, and 1 died after mitral valve replacement from prosthetic valve thrombosis. QOL scores improved from baseline at 3 and 12 mo |
Assess the outcome of a multicentre HCM cohort following RFCA for symptomatic AF refractory to medical Tx

<table>
<thead>
<tr>
<th>Di Donna P, et al., 2010 (229) 20173211</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age 54±13 y;</strong></td>
</tr>
<tr>
<td>Time from AF onset 5.7±5.5 y</td>
</tr>
<tr>
<td>Paroxysmal AF=35; (57%)</td>
</tr>
<tr>
<td>Recent persistent AF=15; (25%)</td>
</tr>
<tr>
<td>Long-standing persistent AF=11; (18%)</td>
</tr>
<tr>
<td>Ablation scheme: pulmonary vein isolation plus linear lesions</td>
</tr>
<tr>
<td>32 of 61 pts, 32 (52%) required redo procedures.</td>
</tr>
<tr>
<td>Antiarrhythmic Tx was maintained in 22 (54%)</td>
</tr>
<tr>
<td>FU: 29±16 mo</td>
</tr>
<tr>
<td>41 (67%) NSR at FU</td>
</tr>
</tbody>
</table>

1° indicates primary; 2, secondary; AAD, antiarrhythmic drug; AE, adverse event; AF, atrial fibrillation; AFFIRM, Atrial Fibrillation Follow-up Investigation of Rhythm Management; ANDROMEDA, European Trial of Dronedarone in Moderate to Severe Congestive Heart Failure; ASA, aspirin; AV, atrioventricular; AVB, atrioventricular block; CAD, coronary artery disease; CCB, calcium channel blocker; CHF, congestive heart failure; CV, cardiovascular; DM, diabetes mellitus; EF, ejection fraction; EKG, electrocardiogram; FU, follow-up; HCM, hypertrophic cardiomyopathy; HF, heart failure; HOCM, hypertrophic obstructive cardiomyopathy; HR, hazard ratio; HTN, hypertension; Hx, history; ICD, implantable cardioverter defibrillator; IV, intravenous; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; N/A, not applicable; NSR, normal sinus rhythm; NYHA, New York Heart Association; pts, patients; PV, pulmonary vein; QOL, quality of life; RACE, Rate Control Efficacy in Permanent Atrial Fibrillation; RFCA, radio frequency catheter ablation; RR, relative risk; SOB, shortness of breath; SR, sinus rhythm; Sx, symptom; TIA, transient ischemic attack; and Tx, therapy.
References


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