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# 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

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# 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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This document was approved by the American College of Cardiology Board of Trustees, the American Heart Association Science Advisory and Coordinating Committee, and the Heart Rhythm Society Board of Trustees in March 2014.

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## Table of Contents

## 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 procedure, 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 (1). The Class 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 for which sparse data are available, 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 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* (GDMT) to represent optimal medical therapy as defined by ACC/AHA guideline (primarily Class I)-recommended therapies. This new term, GDMT, is used herein and throughout subsequent guidelines.

Because the ACC/AHA practice guidelines address patient populations (and clinicians) residing in North America, drugs that are not currently available in North America 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 care. 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.

In December 2009, the ACC and AHA implemented a new RWI policy that requires the writing committee chair plus a minimum of 50% of the writing committee to have no relevant RWI (Appendix 1 includes the ACC/AHA definition of *relevance*). The Task Force and all writing committee members review their respective RWI disclosures during each conference call and/or meeting of the writing committee, and members provide updates to their RWI as changes occur. All guideline recommendations require a confidential vote by the writing committee and require approval by a consensus of the voting members. Members may not draft or vote on any recommendations pertaining to their RWI. Members who recused themselves from voting are indicated in the list of writing committee members, and specific section recusals are noted in Appendix 1. Authors' and peer reviewers' RWI pertinent to this guideline are disclosed in Appendixes 1 and 2. In addition, to ensure complete transparency, writing committee members' comprehensive disclosure information—including RWI not pertinent to this document—is available as an online supplement (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000041/-/DC1). Comprehensive disclosure information for the Task Force is also available online at http://www.cardiosource.org/en/ACC/About-ACC/Who-We-Are/Leadership/Guidelines-and-Documents-Task-Forces.aspx. The ACC and AHA exclusively sponsor the work of the writing committee, without commercial support. Writing committee members volunteered their time for this activity. Guidelines are official policy of both the ACC and AHA.

In an effort to maintain relevance at the point of care for clinicians, the Task Force continues to oversee an ongoing process improvement initiative. As a result, in response to pilot projects, several changes to these guidelines will be apparent, including limited narrative text, a focus on summary and evidence tables (with references linked to abstracts in PubMed), and more liberal use of summary recommendation tables (with references that support LOE) to serve as a quick reference.

In April 2011, the Institute of Medicine released 2 reports: *Finding What Works in Health Care: Standards for Systematic Reviews* and *Clinical Practice Guidelines We Can Trust* (2, 3). It is noteworthy that the Institute of Medicine cited ACC/AHA practice guidelines as being compliant with many of the proposed standards. A thorough review of these reports and of our current methodology is under way, with further enhancements anticipated.

The recommendations in this guideline are considered current until they are superseded by a focused update, the full-text guideline is revised or until a published addendum declares it out of date and no longer official ACC/AHA policy.

*Jeffrey L. Anderson, MD, FACC, FAHA*
*Chair, ACC/AHA Task Force on Practice Guidelines*

**Table 1.** Applying Classification of Recommendations and Level of Evidence

SIZE OF TREATMENT EFFECT

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT

| | **CLASS I**<br>*Benefit >>> Risk*<br>Procedure/Treatment **SHOULD** be performed/ administered | **CLASS IIa**<br>*Benefit >> Risk*<br>*Additional studies with focused objectives needed*<br>**IT IS REASONABLE** to perform procedure/administer treatment | **CLASS IIb**<br>*Benefit ≥ Risk*<br>*Additional studies with broad objectives needed; additional registry data would be helpful*<br>Procedure/Treatment **MAY BE CONSIDERED** | **CLASS III** *No Benefit* or **CLASS III** *Harm*<br>Procedure/Test — Treatment<br>COR III: No benefit — Not Helpful — No Proven Benefit<br>COR III: Harm — Excess Cost w/o Benefit or Harmful — Harmful to Patients |
|---|---|---|---|---|
| **LEVEL A**<br>Multiple populations evaluated*<br>Data derived from multiple randomized clinical trials or meta-analyses | ■ Recommendation that procedure or treatment is useful/effective<br>■ Sufficient evidence from multiple randomized trials or meta-analyses | ■ Recommendation in favor of treatment or procedure being useful/effective<br>■ Some conflicting evidence from multiple randomized trials or meta-analyses | ■ Recommendation's usefulness/efficacy less well established<br>■ Greater conflicting evidence from multiple randomized trials or meta-analyses | ■ Recommendation that procedure or treatment is not useful/effective and may be harmful<br>■ Sufficient evidence from multiple randomized trials or meta-analyses |
| **LEVEL B**<br>Limited populations evaluated*<br>Data derived from a single randomized trial or nonrandomized studies | ■ Recommendation that procedure or treatment is useful/effective<br>■ Evidence from single randomized trial or nonrandomized studies | ■ Recommendation in favor of treatment or procedure being useful/effective<br>■ Some conflicting evidence from single randomized trial or nonrandomized studies | ■ Recommendation's usefulness/efficacy less well established<br>■ Greater conflicting evidence from single randomized trial or nonrandomized studies | ■ Recommendation that procedure or treatment is not useful/effective and may be harmful<br>■ Evidence from single randomized trial or nonrandomized studies |
| **LEVEL C**<br>Very limited populations evaluated*<br>Only consensus opinion of experts, case studies, or standard of care | ■ Recommendation that procedure or treatment is useful/effective<br>■ Only expert opinion, case studies, or standard of care | ■ Recommendation in favor of treatment or procedure being useful/effective<br>■ Only diverging expert opinion, case studies, or standard of care | ■ Recommendation's usefulness/efficacy less well established<br>■ Only diverging expert opinion, case studies, or standard of care | ■ Recommendation that procedure or treatment is not useful/effective and may be harmful<br>■ Only expert opinion, case studies, or standard of care |
| Suggested phrases for writing recommendations | should<br>is recommended<br>is indicated<br>is useful/effective/beneficial | is reasonable<br>can be useful/effective/beneficial<br>is probably recommended or indicated | may/might be considered<br>may/might be reasonable<br>usefulness/effectiveness is unknown/unclear/uncertain or not well established | COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective<br>COR III: Harm: potentially harmful; causes harm; associated with excess morbid-ity/mortality; should not be performed/ administered/ other |
| Comparative effectiveness phrases† | treatment/strategy A is recommended/indicated in preference to treatment B<br>treatment A should be chosen over treatment B | treatment/strategy A is probably recommended/indicated in preference to treatment B<br>it is reasonable to choose treatment A 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/efficacy 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, focusing on 2006 to the present, was conducted through October 2012, and selected other references through February 2014. Searches were extended to studies, reviews, and other evidence that were conducted in human subjects, published in English, and accessible via 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, atrioventricular 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 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, 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 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 has 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, the AHA, and the Heart Rhythm Society, as well as 1 reviewer from the Society of Thoracic Surgeons, and 43 individual content reviewers (from the ACC Electrophysiology Committee, Adult Congenital and Pediatric Cardiology Council, Association of International Governors, Heart Failure and Transplant Council, Imaging Council, Interventional Council, Surgeons Council, and the HRS 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 "2006 ACC/AHA/ESC Guideline for the Management of Patients With Atrial Fibrillation" and the 2 subsequent focused updates from 2011 (4-7). 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 (8).

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 is a list of these publications and statements deemed pertinent to this effort and is intended for use as a resource.

**Table 2. Associated Guidelines and Statements**

| Title | Organization | Publication Year/ Reference |
|---|---|---|
| **Guidelines** | | |
| Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) | NHLBI | 2003 (9) |
| Assessment of Cardiovascular Risk in Asymptomatic Adults | ACCF/AHA | 2010 (10) |
| Coronary Artery Bypass Graft Surgery | ACCF/AHA | 2011 (11) |
| Hypertrophic Cardiomyopathy | ACCF/AHA | 2011 (12) |
| Percutaneous Coronary Intervention | ACCF/AHA/SCAI | 2011 (13) |
| Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease | AHA/ACCF | 2011 (14) |
| Atrial Fibrillation* | CCS | 2011 (15) |
| Atrial Fibrillation | ESC | 2012 (16) |
| Device-Based Therapy | ACCF/AHA/HRS | 2012 (17) |
| Stable Ischemic Heart Disease | ACCF/AHA/ACP/ AATS/PCNA/SCAI/STS | 2012 (18) |
| Antithrombotic Therapy | ACCP | 2012 (19) |
| Heart Failure | ACCF/AHA | 2013 (20) |
| ST-Elevation Myocardial Infarction | ACCF/AHA | 2013 (21) |
| Non–ST-Elevation Acute Coronary Syndromes | ACC/AHA | 2014 In Press (22) |
| Valvular Heart Disease | AHA/ACC | 2014 (23) |
| Assessment of Cardiovascular Risk | ACC/AHA | 2013 (24) |

| | | |
|---|---|---|
| Lifestyle Management to Reduce Cardiovascular Risk | AHA/ACC | 2013 (25) |
| Management of Overweight and Obesity in Adults | AHA/ACC/TOS | 2013 (26) |
| Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults | ACC/AHA | 2013 (27) |
| **Statements** | | |
| Treatment of Atrial Fibrillation | AHRQ | 2012 (8) |
| Oral Antithrombotic Agents for the Prevention of Stroke in Nonvalvular Atrial Fibrillation: a Science Advisory for Healthcare Professionals | AHA/ASA | 2012 (28) |
| Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-Up, Definitions, Endpoints, and Research Trial Design | HRS/EHRA/ECAS | 2012 (29) |

*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; ACCF, American College of Cardiology Foundation; ACP, American College of Physicians; ACCP, American College of Chest Physicians; AHA, American Heart Association; AHRQ, Agency for Healthcare Research and Quality; ASA, American Stroke Association; AF, atrial fibrillation; 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 Cardiac Angiography and Interventions; STS, Society of Thoracic Surgeons, and TOS, The Obesity Society.

## 2. Background and Pathophysiology

AF is a common cardiac rhythm disturbance and increases in prevalence with advancing age. Approximately 1% of patients with AF are <60 years of age, whereas up to 12% of patients are 75 to 84 years of age (30). More than one third of patients with AF are ≥80 years of age (31, 32). 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 (33). For individuals of European descent, the lifetime risk of developing AF after 40 years of age is 26% for men and 23% for women (34). In African Americans, although risk factors for AF are more prevalent, the AF incidence appears to be lower (35). AF is often associated with structural heart disease and other co-occurring chronic conditions (Table 3; see also http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Chronic-Conditions/Downloads/2012Chartbook.pdf). The mechanisms causing and sustaining AF are multifactorial, and AF can be complex and difficult for clinicians to manage. AF symptoms range from non-existent to severe. Frequent hospitalizations, hemodynamic abnormalities, and thromboembolic events related to AF result in significant morbidity and mortality. AF is associated with a 5-fold increased risk of stroke (36) and stroke risk increases with age (37). AF-related stroke is likely to be more severe than non–AF-related stroke (38). AF is also associated with a 3-fold risk of HF (39-41), and 2-fold increased risk of both dementia (42) and mortality (36). Hospitalizations with AF as the primary diagnosis are

>467,000 annually in the United States, and AF is estimated to contribute to >99,000 deaths per year. Patients with AF are hospitalized twice as often as patients without AF; are 3 times more likely to have multiple admissions; and 2.1% of patients with AF died in the hospital compared to 0.1% without it (43, 44). AF is also expensive, adding approximately $8,700 per year (estimate from 2004 to 2006) for a patient with AF compared to a patient without AF. It is estimated that treating patients with AF adds $26 billion to the U.S. healthcare bill annually. AF affects between 2.7 million and 6.1 million American adults, and that number is expected to double over the next 25 years, adding further to the cost burden (43, 44).

AF web-based tools are available, including several risk calculators and clinical decision aids (http://www.cardiosource.org/Science-And-Quality/Clinical-Tools/Atrial-Fibrillation-Toolkit.aspx); however, these tools must be used with caution because validation across the broad range of AF patients encountered in clinical practice is incomplete.

**Table 3. 10 Most Common Comorbid Chronic Conditions Among Medicare Beneficiaries With AF**

| **Beneficiaries ≥65 y of age (N=2,426,865)** *(mean number of conditions=5.8; median=6)* | | | | **Beneficiaries <65 y of age (N=105,878)** *(mean number of conditions=5.8; median=6)* | | |
|---|---|---|---|---|---|---|
| | N | % | | | N | % |
| Hypertension | 2,015,235 | 83.0 | | Hypertension | 85,908 | 81.1 |
| Ischemic heart disease | 1,549,125 | 63.8 | | Ischemic heart disease | 68,289 | 64.5 |
| Hyperlipidemia | 1,507,395 | 62.1 | | Hyperlipidemia | 64,153 | 60.6 |
| HF | 1,247,748 | 51.4 | | HF | 62,764 | 59.3 |
| Anemia | 1,027,135 | 42.3 | | Diabetes mellitus | 56,246 | 53.1 |
| Arthritis | 965,472 | 39.8 | | Anemia | 48,252 | 45.6 |
| Diabetes mellitus | 885,443 | 36.5 | | CKD | 42,637 | 40.3 |
| CKD | 784,631 | 32.3 | | Arthritis | 34,949 | 33.0 |
| COPD | 561,826 | 23.2 | | Depression | 34,900 | 33.0 |
| Cataracts | 546,421 | 22.5 | | COPD | 33,218 | 31.4 |

AF indicates atrial fibrillation; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disorder; and HF, heart failure.
Reproduced with permission from the Centers for Medicare and Medicaid Services (45).

## 2.1. Definitions and Pathophysiology of AF

AF is a supraventricular tachyarrhythmia with uncoordinated atrial activation and consequently ineffective atrial contraction (4-7, 29, 31). Electrocardiogram (ECG) characteristics 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 (46-48). Consequences for individual patients vary, ranging from no symptoms to fatigue, palpitations, dyspnea, hypotension, syncope, or HF (49). 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 (50, 51). For example, initially asymptomatic patients may develop tachycardia-induced ventricular dysfunction and HF (tachycardia-induced cardiomyopathy) when the ventricular rate is not adequately controlled (52, 53). 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 (54-56). 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 (56). Sympathetic activation and vagal withdrawal such as 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, preventing successive impulses from propagating in the node—an effect called concealed conduction (56). 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 to AF (54).

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 (4-7, 51, 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 (59). Ventricular contractility is not constant during AF because of variable diastolic filling time and changes in the force-interval relationship (4-7, 60, 61). Overall, cardiac output may decrease and filling pressures may increase compared to 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 (61). Irregular R-R intervals also promote sympathetic activation (46, 47).



### 2.1.1. AF—Classification

AF may be described in terms of the duration of episodes and using a simplified scheme revised from the 2006 AF full-revision guideline, which is given in Table 4 (29, 31). Implanted loop recorders, pacemakers, and defibrillators offer the possibility of reporting frequency, rate, and duration of abnormal atrial rhythms, including AF (62, 63). Episodes often increase in frequency and duration over time.

**Table 4. AF Definitions: A Simplified Scheme**

| Term | Definition |
|---|---|
| **Paroxysmal AF** | • AF that terminates spontaneously or with intervention within 7 d of onset.<br>• Episodes may recur with variable frequency. |
| **Persistent AF** | • Continuous AF that is sustained >7 d. |

| | |
|---|---|
| **Longstanding persistent AF** | • Continuous AF of >12 mo duration. |
| **Permanent AF** | • Permanent AF is used when there has been a joint decision by the patient and clinician to cease further attempts to restore and/or maintain sinus rhythm.<br>• Acceptance of AF represents a therapeutic attitude on the part of the patient and clinician rather than an inherent pathophysiological attribute of the AF.<br>• Acceptance of AF may change as symptoms, the efficacy of therapeutic interventions, and patient and clinician preferences evolve. |
| **Nonvalvular AF** | • AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair. |

AF indicates atrial fibrillation.

The characterization of patients with AF by the 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 (29). 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 individuals without clinical or echocardiographic evidence of cardiopulmonary disease, hypertension, or diabetes mellitus (4-7). Because 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 tachycardias are characterized by an atrial rate of ≥100 bpm with discrete P waves and atrial activation sequences. Atrial activation is most commonly the same from beat to beat.



Focal atrial tachycardia is characterized by regular, organized atrial activity with discrete P waves, typically with an isoelectric segment between P waves (Figure 1) (64, 65). Electrophysiological mapping reveals a focal point of origin. The mechanism can be automaticity or a micro–re-entry circuit (66, 67). In multifocal atrial tachycardia, the atrial activation sequence and P-wave morphology vary (64).

### 2.1.1.2. Atrial Flutter and Macro–Re-Entrant Atrial Tachycardia

Early studies designated atrial flutter with a rate of 240 bpm to 340 bpm as "type I flutter," and this term has commonly been applied to typical atrial flutter (65, 68). An ECG appearance of atrial flutter with a rate faster than 340 bpm was designated as "type II flutter," the mechanism of which remains undefined (69). It is now recognized that tachycardias satisfying either of these descriptions can be due to re-entrant circuits or to rapid focal atrial tachycardia.

Typical atrial flutter is a macro–re-entrant 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" (64). This sequence of activation (also referred to as "counterclockwise atrial flutter") produces predominantly negative "saw tooth" 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 (65). 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, also referred to as “clockwise typical atrial flutter”) (65). Unusual 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 macro–re-entrant atrial tachycardia in these situations (70-72). 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 (69, 73). 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 (74).

AF may be misdiagnosed as atrial flutter when AF activity is prominent on ECG (75, 76). Atrial flutter may also arise during treatment with antiarrhythmic agents prescribed to prevent recurrent AF (77), 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 (78).

Atypical flutter, or “noncavotricuspid isthmus-dependent macro–re-entrant atrial tachycardia,” describes macro–re-entrant atrial tachycardias that are not one of the typical forms of atrial flutter that use the cavotricuspid isthmus (64). A variety of re-entrant circuits has been described, including “perimitral flutter” re-entry involving the roof of the left atrium (LA), and re-entry around scars in the left or right atrium, often from prior surgery or ablation (65, 67, 79). Complex re-entry circuits with >1 re-entry loop or circuit can occur and often coexist with common atrial flutter. These arrhythmias are not abolished by ablation of the cavotricuspid isthmus, but their recognition and distinction from common atrial flutter usually requires electrophysiologic study with atrial mapping (65). A variety of terms has been applied to these arrhythmias according to the re-entry circuit location, including “LA flutter” and “LA macro–re-entrant tachycardia” (65, 67, 79, 80).



**Figure 1.** Atrial Tachycardias

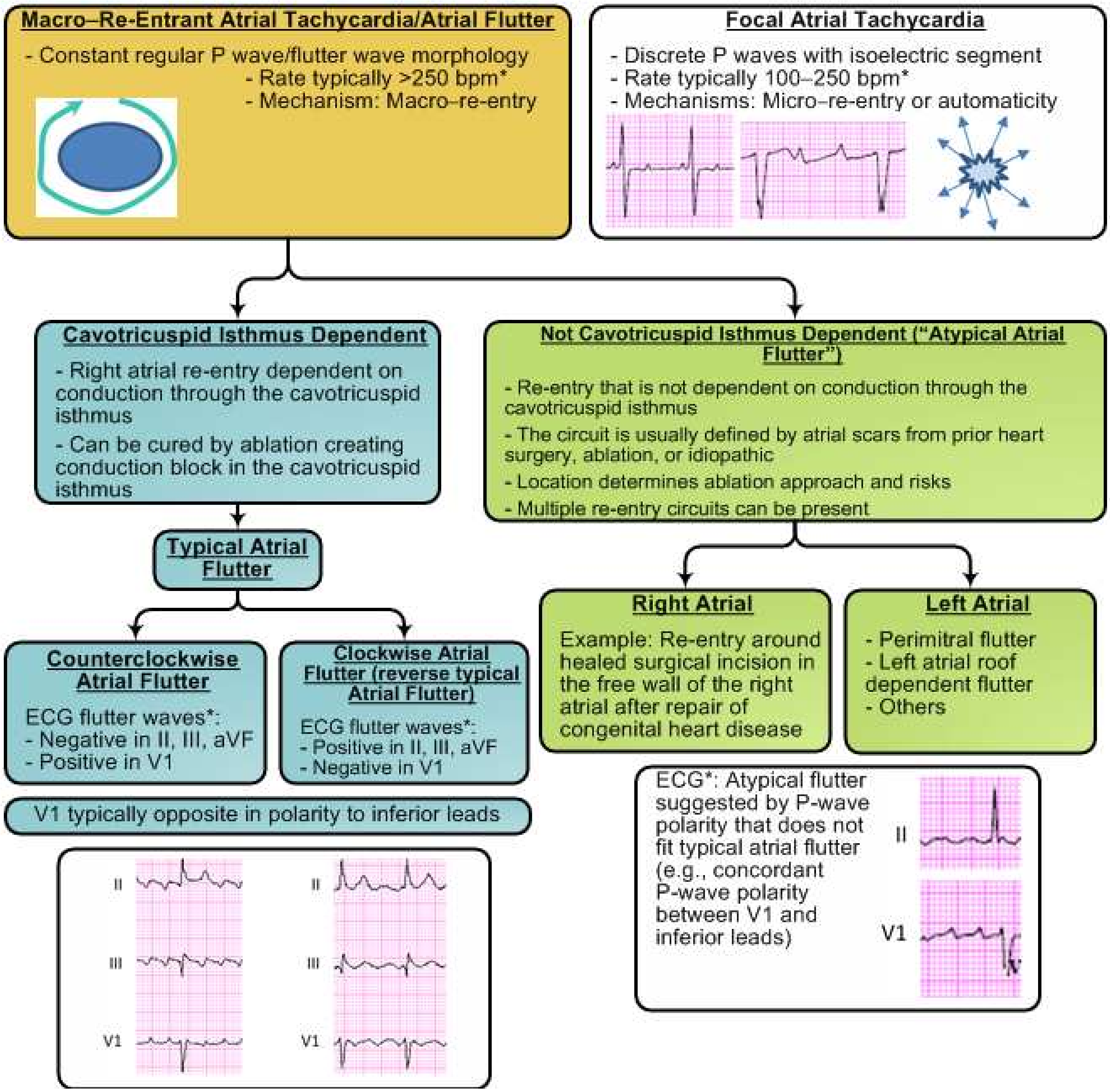


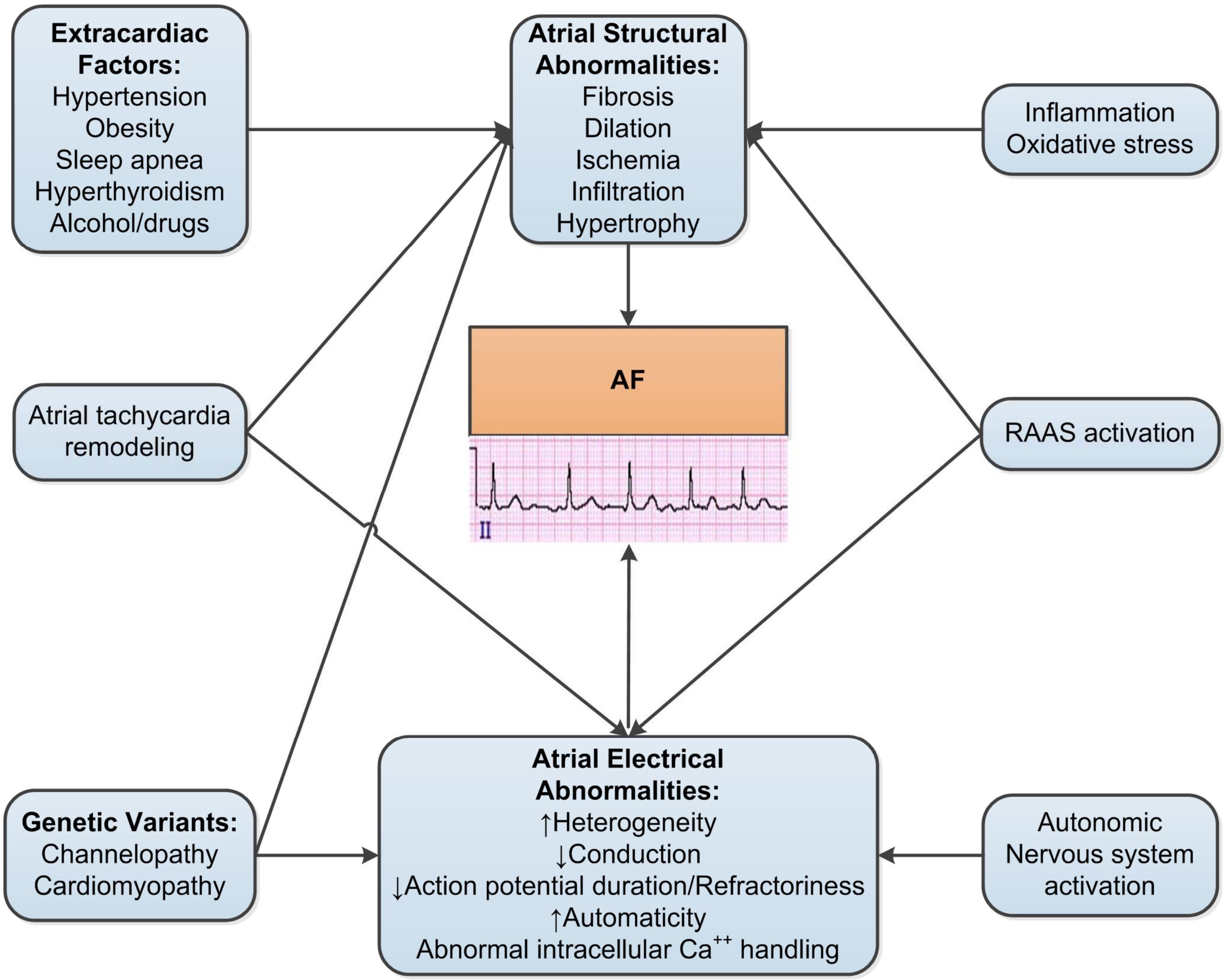

Diagram summarizing types of atrial tachycardias often encountered in patients with a history of AF, including those seen after catheter or surgical ablation procedures. P-wave morphologies are shown for common types of atrial flutter; however, the P-wave morphology is not always a reliable guide to the re-entry circuit location or to the distinction between common atrial flutter and other macro–re-entrant atrial tachycardias.
*Exceptions to P-wave morphology and rate are common in scarred atria.

AF indicates atrial fibrillation and ECG, electrocardiogram (72, 80).

## 2.2. Mechanisms of AF and Pathophysiology

AF occurs when structural and/or electrophysiologic abnormalities alter atrial tissue to promote abnormal impulse formation and/or propagation (Figure 2). These abnormalities are caused by diverse pathophysiologic mechanisms (4-7, 29, 81, 82), such that AF represents a final common phenotype for multiple disease pathways and mechanisms that are incompletely understood.

**Figure 2.** Mechanisms of AF




AF indicates atrial fibrillation; $Ca^{++}$ ionized calcium; and RAAS, renin-angiotensin-aldosterone system.

### 2.2.1. Atrial Structural Abnormalities

Any disturbance of atrial architecture potentially increases susceptibility to AF (4-7). Such changes (e.g., 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. Additional promoters include extracardiac factors such as hypertension, sleep apnea, obesity, alcohol/drugs, and hyperthyroidism, which have pathophysiologic 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 (83). 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 (4-7). These structural abnormalities can heterogeneously alter impulse conduction and/or refractoriness, generating an arrhythmogenic substrate.

A common feature of both experimental and human AF is myocardial fibrosis (84). 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 (85). 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 (86-91). Human studies show a strong correlation between regions of low voltage on electro-anatomic 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 (87) and decreased response to catheter ablation (86).

### 2.2.2. Electrophysiologic 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 electrophysiologic mechanisms that initiate and maintain AF (4-7, 29). 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 (92-94). 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 (29). Unique anatomic and electrophysiologic 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 re-entry 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. Re-entry is further favored by abbreviated action potentials and refractoriness in pulmonary vein myocytes (95). 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) (96) and melanocytes (97), 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, venae 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 after depolarizations (98-102).

#### 2.2.2.2. Maintenance of AF

Theories proposed to explain the perpetuation and maintenance of AF include 1) multiple independent re-entrant 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 re-entrant circuits (29, 82, 84, 103-109). 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 (29, 103, 106). Both rapid focal firing and re-entry 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 re-entry. Using a biatrial phase mapping approach, 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 (108). In most cases, these localized sources appeared to be re-entrant, while 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 (110).

Some investigators targeted regions in which electrogram recordings show rapid complex atrial fractionated electrograms, which are felt to be indicative of the substrate for AF or markers for ganglion plexi (see Section 2.2.2.3. for ablation of AF) (105). 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 (29, 94, 111). Activation of the parasympathetic and/or sympathetic limbs can provoke atrial arrhythmias (104, 112). Acetylcholine activates a specific potassium current, $I_{K,ACh}$, that heterogeneously shortens atrial action potential duration and refractoriness, increasing susceptibility to re-entry. Sympathetic stimulation increases intracellular calcium, which promotes automaticity and triggered activity. Increased parasympathetic and/or sympathetic activity prior to onset of AF has been observed in some animal models and humans (113, 114).

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 in proximity 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 (115-117).

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" (118). 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 (116). Adrenergic stimulation, as during exercise, can also provoke AF in some patients (119).

### 2.2.3. Pathophysiologic Mechanisms

#### 2.2.3.1. Atrial Tachycardia Remodeling

AF often progresses from paroxysmal to persistent over a variable period of time. Cardioversion of AF and subsequent maintenance of sinus rhythm are more likely to be successful when AF duration is <6 months (120). The progressive nature of AF is consistent with studies demonstrating that AF causes electrical and structural remodeling such that "AF begets AF" (4-7, 121, 122).



#### 2.2.3.2. Inflammation and Oxidative Stress

Inflammation (e.g., 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 (4-7, 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 tachypacing models, prednisone suppresses AF susceptibility and reduces plasma concentrations of C-reactive protein (123).



Aging, environmental stress, inflammation, and activation 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 (124). The antioxidant ascorbate attenuated electrical remodeling in the canine atrial tachypacing model and reduced postoperative AF in a small study in humans (125).

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

Stimulation of the renin-angiotensin-aldosterone system promotes structural and likely electrophysiologic effects in the atrium and ventricle that increase arrhythmia susceptibility (4-7, 81). 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, while selective cardiac overexpression of ACEs 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 (126).

### 2.2.3.4. Risk Factors and Associated Heart Disease

Multiple clinical risk factors, electrocardiographic and echocardiographic features, and biochemical makers are associated with an increased risk of AF (Table 5). One epidemiologic analysis found that 56% of the population-attributable risk of AF could be explained by ≥1 common risk factor (127). 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 noncardiac surgery, myocardial infarction (MI), pericarditis, myocarditis, hyperthyroidism, electrocution, pneumonia, and pulmonary embolism (11, 50, 128-130). AF that occurs in the setting of Wolff-Parkinson-White (WPW) syndrome, AV nodal re-entrant tachycardia, or atrial ectopic tachycardia may resolve after catheter ablation for these arrhythmias (69). It is important to recognize that there are few data to 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. Since long-term follow-up data are not available in these clinical scenarios and AF may recur, these patients should receive careful follow-up.

**Table 5. Selected Risk Factors and Biomarkers for AF**

| Clinical Risk Factors | References |
|---|---|
| Increasing age | (131) |
| Hypertension | (131) |
| Diabetes mellitus | (131) |
| MI | (131) |
| VHD | (131) |
| HF | (39, 131) |
| Obesity | (132-134) |
| Obstructive sleep apnea | (134) |
| Cardiothoracic surgery | (129) |
| Smoking | (135) |
| Exercise | (136-138) |
| Alcohol use | (139-141) |
| Hyperthyroidism | (142-144) |

| | |
|---|---|
| Increased pulse pressure | (145) |
| European ancestry | (146) |
| Family history | (147) |
| Genetic variants | (148-151) |
| **Electrocardiographic** | |
| LVH | (36) |
| **Echocardiographic** | |
| LA enlargement | (36, 152) |
| Decreased LV fractional shortening | (36) |
| Increased LV wall thickness | (36) |
| **Biomarkers** | |
| Increased CRP | (153, 154) |
| Increased BNP | (155, 156) |

AF indicates atrial fibrillation; BNP, B-type natriuretic peptide; CRP, C-reactive protein; HF, heart failure; LA, left atrial; LV, left ventricular; LVH, left ventricular hypertrophy; MI, myocardial infarction; and VHD, valvular heart disease.

*See Online Data Supplements 1 and 2 for additional data on electrophysiologic and pathophysiologic mechanisms (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000041/-/DC2).*



## 3. Clinical Evaluation: Recommendation

**Class I**

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



The diagnosis of AF in a patient is based on the patient's clinical history and physical examination and is confirmed by ECG, ambulatory rhythm monitoring (e.g., 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. Basic Evaluation of the Patient With AF

### 3.1.1. Clinical History and Physical Examination

The initial evaluation of a patient with suspected or proven AF involves characterizing the pattern of the arrhythmia (paroxysmal, persistent, longstanding persistent, or permanent), determining its cause, defining associated cardiac and extracardiac disease, and assessing thromboembolic risk. Symptoms, prior treatment, family history, and a review of associated conditions and potentially reversible risk factors as outlined in Table 5 should be recorded.

The physical examination suggests AF by the presence of an irregular pulse, irregular jugular venous pulsations, and variation in the intensity of the first heart sound or absence of a fourth sound previously heard during sinus rhythm. Physical examination may also disclose associated valvular heart disease or myocardial abnormalities. The pulse in atrial flutter is often regular and rapid, and venous oscillations may be visible in the jugular pulse.

### 3.1.2. Investigations

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; thyroid, renal, and hepatic function; and a blood count.

**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, a TEE before planned cardioversion revealed a LA or LAA thrombus (157, 158).

**Electrophysiological Study:** An electrophysiological study can be helpful when initiation of AF is due to a supraventricular tachycardia, such as AV node re-entrant tachycardia, AV re-entry 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.



**Additional Investigation of Selected Patients With AF:** 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 (159).

### 3.1.3. Rhythm Monitoring and Stress Testing

Prolonged or frequent monitoring may be necessary to reveal episodes of asymptomatic AF. ECG, ambulatory rhythm monitoring (e.g., telemetry, Holter monitor, and event recorders), and exercise testing can be useful to judge the adequacy of rate control. Patient-activated ECG 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 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 (160-163).** ***(Level of Evidence: B)***
3. **In patients with nonvalvular AF, the $CHA_2DS_2$-VASc score is recommended for assessment of stroke risk (164-166).** ***(Level of Evidence: B)***
4. **For patients with AF who have mechanical heart valves, warfarin is recommended and the target international normalized ratio (INR) intensity (2.0 to 3.0 or 2.5 to 3.5) should be based on the type and location of the prosthesis (167-169).** ***(Level of Evidence: B)***
5. **For patients with nonvalvular AF with prior stroke, transient ischemic attack (TIA), or a $CHA_2DS_2$-VASc score of 2 or greater, oral anticoagulants are recommended. Options include: warfarin (INR 2.0 to 3.0) (164-166)** ***(Level of Evidence: A)*****, dabigatran (170)** ***(Level of Evidence: B),*** **rivaroxaban (171)** ***(Level of Evidence: B),*** **or apixaban (172).** ***(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 (173-175).** ***(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. **Re-evaluation 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 regarding 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 newer 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 prior to initiation of direct thrombin or factor Xa inhibitors and should be re-evaluated when clinically indicated and at least annually (176-178).** ***(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 $CHA_2DS_2$-VASc score of 0, it is reasonable to omit antithrombotic therapy (176, 177).** ***(Level of Evidence: B)***
2. **For patients with nonvalvular AF with a $CHA_2DS_2$-VASc score of 2 or greater and who have end-stage 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 (178).** ***(Level of Evidence: B)***

**Class IIb**

1. **For patients with nonvalvular AF and a $CHA_2DS_2$-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 $CHA_2DS_2$-VASc scores of 2 or greater, treatment with reduced doses of direct thrombin or factor Xa inhibitors may be considered (e.g., 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 CHA$_2$DS$_2$-VASc score of 2 or greater, it may be reasonable to use clopidogrel (75 mg once daily) concurrently with oral anticoagulants but without aspirin (179). *(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 hemodialysis because of the lack of evidence from clinical trials regarding the balance of risks and benefits (170-172, 180-182). *(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 (183). *(Level of Evidence: B)***

*See the 2011 percutaneous coronary intervention guideline for type of stent and duration of dual antiplatelet therapy recommendations (13).

**Table 6. Summary of Recommendations for Prevention of Thromboembolism in Patients With AF**

| Recommendations | COR | LOE | References |
|---|---|---|---|
| Antithrombotic therapy based on shared decision-making, discussion of risks of stroke and bleeding, and patient's preferences | I | C | N/A |
| Antithrombotic therapy selection based on risk of thromboembolism | I | B | (160-163) |
| CHA$_2$DS$_2$-VASc score recommended to assess stroke risk | I | B | (164-166) |
| Warfarin recommended with mechanical heart valves**.** Target INR intensity should be based on the type and location of prosthesis | I | B | (167-169) |
| With prior stroke, TIA, or CHA$_2$DS$_2$-VASc score ≥2, oral anticoagulants recommended. Options include: | | | |
| • Warfarin | I | A | (164-166) |
| • Dabigatran, rivaroxaban, or apixaban | I | B | (170-172) |
| With warfarin, determine INR at least weekly during initiation and monthly when stable | I | A | (173-175) |
| Direct thrombin or factor Xa inhibitor recommended, if unable to maintain therapeutic INR | I | C | N/A |
| Re-evaluate the need for anticoagulation at periodic intervals | I | C | N/A |
| Bridging therapy with LMWH or UFH recommended with a mechanical heart valve if warfarin is interrupted. Bridging therapy should balance risks of stroke and bleeding | I | C | N/A |
| Without a mechanical heart valve, bridging therapy decisions should balance stroke and bleeding risks against the duration of time patient will not be anticoagulated | I | C | N/A |
| Evaluate renal function prior to initiation of direct thrombin or factor Xa inhibitors, and re-evaluate when clinically indicated and at least annually | I | B | (176-178) |
| For atrial flutter, antithrombotic therapy is recommended as for AF | I | C | N/A |
| With nonvalvular AF and CHA$_2$DS$_2$-VASc score of 0, it is reasonable to omit antithrombotic therapy | IIa | B | (176, 177) |

| | | | |
|---|---|---|---|
| With $CHA_2DS_2$-VASc score ≥2 and end-stage CKD (CrCl <15 mL/min) or on hemodialysis, it is reasonable to prescribe warfarin for oral anticoagulation | IIa | B | (178) |
| With nonvalvular AF and a $CHA_2DS_2$-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered | IIb | C | N/A |
| With moderate-to-severe CKD and $CHA_2DS_2$-VASc scores of ≥2, reduced doses of direct thrombin or factor Xa inhibitors may be considered | IIb | C | N/A |
| For PCI,* BMS may be considered to minimize duration of DAPT | IIb | C | N/A |
| Following coronary revascularization in patients with $CHA_2DS_2$-VASc score of ≥2, it may be reasonable to use clopidogrel concurrently with oral anticoagulants, but without aspirin | IIb | B | (179) |
| Direct thrombin, dabigatran, and factor Xa inhibitor, rivaroxaban, are not recommended 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 | III: No Benefit | C | (170-172, 180-182) |
| Direct thrombin inhibitor, dabigatran, should not be used with a mechanical heart valve | III: Harm | B | (183) |

*See the 2011 percutaneous coronary intervention guideline for type of stent and duration of dual antiplatelet therapy recommendations (13).
AF indicates atrial fibrillation; BMS, bare-metal stent; CKD, chronic kidney disease; COR, Class of Recommendation; CrCl, creatinine clearance; DAPT, dual antiplatelet therapy; INR, international normalized ratio; LOE, Level of Evidence; LMWH, low-molecular-weight heparin; N/A, not applicable; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; and UFH, unfractionated heparin.

### 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 (184-187). Nonvalvular AF increases the risk of stroke 5 times and AF in the setting of mitral stenosis increases the risk of stroke 20 times (188) over patients in sinus rhythm. Thromboembolism occurring with AF is associated with a greater risk of recurrent stroke, more severe disability, and mortality (189). Silent AF is also associated with ischemic stroke (184-187). The appropriate use of antithrombotic therapy, and the control of other risk factors including hypertension, and hypercholesterolemia, substantially reduces stroke risk.

Antithrombotic agents in routine use 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). While 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, 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 some studies (177, 182, 190-192). Careful consideration is required to balance the benefits and the risks of bleeding in each individual patient.

#### 4.1.1.1. Risk Stratification Schemes ($CHADS_2$, $CHA_2DS_2$-VASc, and HAS-BLED)

One meta-analysis has stratified ischemic stroke risk among patients with nonvalvular AF using the AF Investigators (193); the ($CHADS_2$) Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Prior Stroke or TIA or Thromboembolism (doubled) score (194); or the ($CHA_2DS_2$-VASc) Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, Prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65 to74 years, Sex category point score systems (Table 7) (16).

**Table 7. Comparison of the $CHADS_2$ and $CHA_2DS_2$-VASc Risk Stratification Scores for Subjects With Nonvalvular AF**

| Definition and Scores for $CHADS_2$ and $CHA_2DS_2$-VASc | |
|---|---|
| | **Score** |
| **$CHADS_2$ acronym** | |
| Congestive HF | 1 |
| Hypertension | 1 |
| Age ≥75 y | 1 |
| Diabetes mellitus | 1 |
| Stroke/TIA/TE | 2 |
| Maximum Score | 6 |
| **$CHA_2DS_2$-VASc acronym** | |
| Congestive HF | 1 |
| Hypertension | 1 |
| Age ≥75 y | 2 |
| Diabetes mellitus | 1 |
| Stroke/TIA/TE | 2 |
| Vascular disease (prior MI, PAD, or aortic plaque) | 1 |
| Age 65–74 y | 1 |
| Sex category (i.e., female sex) | 1 |
| Maximum Score | 9 |

| Stroke Risk Stratification With the $CHADS_2$ and $CHA_2DS_2$-VASc scores | |
|---|---|
| | **Adjusted stroke rate (% per y)** |
| **$CHADS_2$ acronym*** | |
| 0 | 1.9% |
| 1 | 2.8% |
| 2 | 4.0% |
| 3 | 5.9% |
| 4 | 8.5% |
| 5 | 12.5% |
| 6 | 18.2% |
| **$CHA_2DS_2$-VASc acronym†** | |
| 0 | 0% |
| 1 | 1.3% |
| 2 | 2.2% |
| 3 | 3.2% |
| 4 | 4.0% |
| 5 | 6.7% |
| 6 | 9.8% |
| 7 | 9.6% |
| 8 | 6.7% |
| 9 | 15.20% |

*These adjusted-stroke rates are based on data for hospitalized patients with AF and were published in 2001 (194). 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 (195). Actual rates of stroke in contemporary cohorts might vary from these estimates.

AF indicates atrial fibrillation; $CHADS_2$, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Prior Stroke or TIA or Thromboembolism (doubled); $CHA_2DS_2$-VASc, Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, Prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65–74 years, Sex category; HF, heart failure; LV, left ventricular; MI, myocardial infarction; PAD, peripheral artery disease; TE, thromboembolic; and TIA, transient ischemic attack (195, 196).

The $CHADS_2$ score has been validated in multiple nonvalvular AF cohorts, with findings indicating approximately a 2.0% increase in stroke rate for each 1-point increase in $CHADS_2$ score (from 1.9% with a score of 0 to 18.2% with a score of 6) (194, 197). A limitation of the $CHADS_2$ score is that a $CHADS_2$ 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 $CHADS_2$ score of 2 due to prior stroke may have a greater risk than a score of 2 would indicate.

Compared to the $CHADS_2$ score, the $CHA_2DS_2$-VASc score (16) 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) (195, 196). In this scheme, women cannot achieve a $CHA_2DS_2$-VASc score of 0. In a nationwide Danish registry from 1997 to 2008, the $CHA_2DS_2$-VASc index better discriminated stroke risk among subjects with a baseline $CHADS_2$ score of 0 to 1 with an improved predictive ability (165). In another study among patients with AF, the $CHA_2DS_2$-VASc score more clearly defined anticoagulation recommendations than did the $CHADS_2$ score (166). 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 (198). 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), 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 (Anticoagulation and Risk Factors in Atrial Fibrillation) (199-201). 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. HEMORR2HAGES includes the following variables: hepatic or renal disease, ethanol abuse, malignancy, older age, reduced platelet count or function, rebleeding, hypertension, anemia, genetic factors, excessive fall risk, and stroke. 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-BLED (15, 31) 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 (age >65 years), use of drugs that promote bleeding, or excess alcohol (202). A score of ≥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 better discriminates risk than the

HEMORR2HAGES or ATRIA scoring systems but all 3 scores had C-indexes <0.70 in their receiver operating curves, indicating only modest performance and poor predictive accuracy (203).

## 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 they can embolize through the systemic circulation to the brain or other sites. Stroke prevention trials (Figure 3) compared warfarin or aspirin with placebo, and 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 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 (177). 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% were women. Among 12 of the trials, there were nearly 3,003 subjects 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.

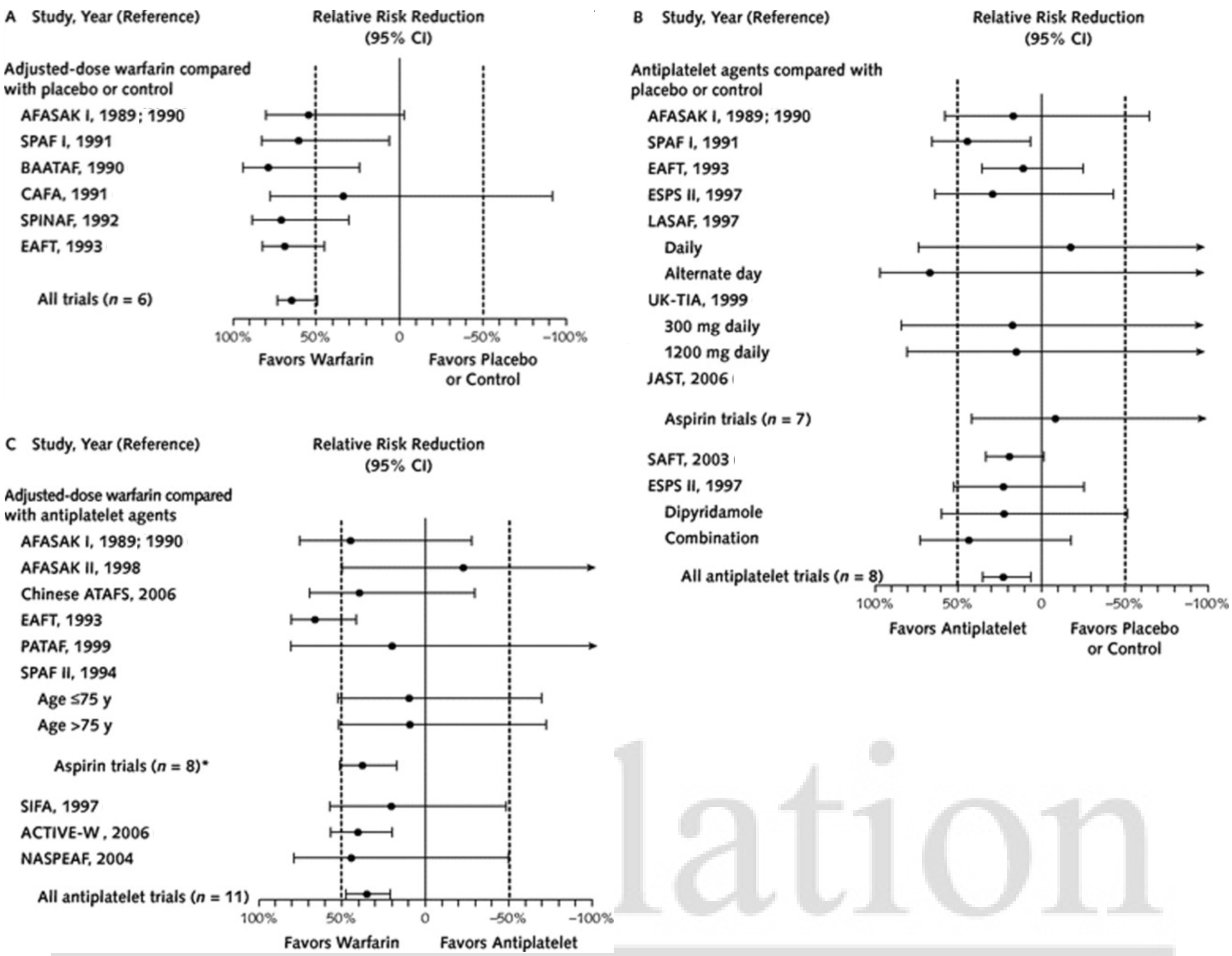


### 4.2.1. Antiplatelet Agents

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 (176, 177, 204). Antiplatelet therapy was compared to placebo or no treatment in 8 trials with a total of 4,876 subjects (177) (Figure 3). Seven of these 8 trials compared different doses of aspirin ranging from 25 mg twice a day to 1,300 mg once a day (177). 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 low-risk AF population.

Clopidogrel plus aspirin was evaluated for stroke prevention in the ACTIVE (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events)-W trial (191). 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. ACTIVE-W found a 40% RR reduction (95% CI: 18% to 56%; $p<0.001$) for stroke with warfarin compared with the dual antiplatelet regimen. ACTIVE-A compared clopidogrel combined with aspirin versus aspirin alone in patients with AF who were unsuitable for oral anticoagulation and who had ≥1 additional stroke risk factor (192). The combination of clopidogrel and aspirin resulted in a 28% RR reduction (95% CI: 17% to 38%; $p<0.0002$) in all strokes compared with aspirin alone. Major bleeding was significantly greater with the combination and was increased by 57% (95% CI: 29% to 92%; $p<0.001$). The absolute differences between the treatment arms were small, with major vascular events decreased by 0.8% per year and major hemorrhages increased by 0.7% per year. The results of ACTIVE-W and ACTIVE-A demonstrate that adjusted-dose warfarin for stroke prevention is significantly better than clopidogrel plus aspirin, and clopidogrel plus aspirin is superior to aspirin alone. The latter benefits are dampened by the significant increase in major bleeding events. No direct comparisons have been made between clopidogrel and aspirin and the new oral anticoagulants that have lower bleeding risks than warfarin. However, there is a direct comparison between aspirin and the factor Xa inhibitor apixaban in the AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Strokes) study, a double-blind study of 5,599 patients deemed unsuitable for warfarin therapy (182). Subjects were randomized to apixaban 5 mg twice daily (2.5 mg twice daily for those who had 2 of the following 3: age ≥80 years, weight ≤60 kg, serum creatinine ≥1.5 mg/dL) or to aspirin 81 mg or 325 mg once daily. The primary outcome of the study was the occurrence of any stroke or systemic embolism. After a mean follow-up of 1.1 years, the study was prematurely terminated owing to the superiority of apixaban over aspirin for preventing the primary outcome. Major bleeding risk between the 2 treatments was similar.

**Figure 3.** Antithrombotic Therapy to Prevent Stroke in Patients who Have Nonvalvular AF (Meta-Analysis)




ACTIVE-W indicates Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events-W; AF, Atrial Fibrillation; AFASAK, Atrial Fibrillation, Aspirin and Anticoagulant Therapy Study; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation; CI, confidence interval; EAFT, European Atrial Fibrillation Trial; ESPS, European Stroke Prevention Study; JAST, Japan AF Stroke Prevention Trial; LASAF, Low-Dose Aspirin, Stroke, Atrial Fibrillation; NASPEAF, National Study for Prevention of Embolism in Atrial Fibrillation; PATAF, Primary Prevention of Arterial Thromboembolism in Nonrheumatic Atrial Fibrillation; SAFT, Swedish Atrial Fibrillation Trial; SIFA, Studio Italiano Fibrillazione Atriale; SPAF I, Stroke Prevention in Atrial Fibrillation Study; SPINAF, Stroke Prevention in Atrial Fibrillation; and UK-TIA, United Kingdom-Transient Ischemic Attack.
Adapted with permission from Hart et al. (177).

### 4.2.2. Oral Anticoagulants

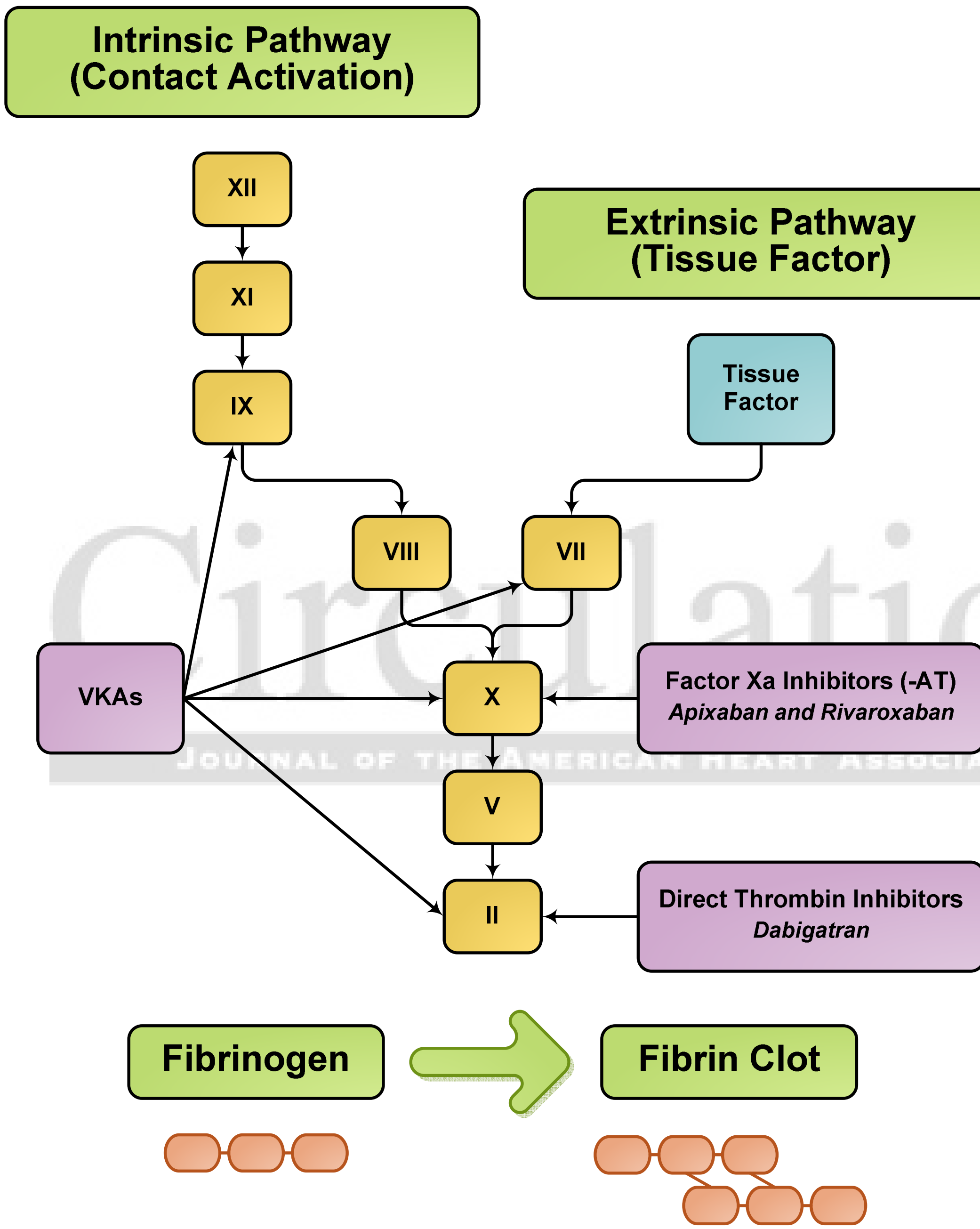
*See Online Data Supplement 3 for additional data and evidence tables on warfarin versus aspirin and the new oral anticoagulants (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000041/-/DC2).*

#### 4.2.2.1. Warfarin

Warfarin is a vitamin K antagonist in use since the 1950s as an oral anticoagulant for stroke prevention in patients with AF. Its multiple sites of action in the coagulation cascade are shown in Figure 4. Among 6 RCTs of 2,900 subjects in which adjusted-dose warfarin was compared with placebo or no treatment, the mean INR ranged from 2.0 to 2.9 (177, 205). Adjusted-dose warfarin resulted in a 64% RR reduction (95% CI: 49% to

74%) for ischemic and hemorrhagic stroke compared with the placebo. The absolute risk reduction was 2.7% per year which yielded a number needed to treat of 37 for 1 year to prevent 1 stroke and 12 for patients with prior stroke or TIA (177).

**Figure 4.** Coagulation Cascade




AT indicates antithrombin and VKAs, vitamin K antagonists.
Adapted with permission from Nutescu et al. (206).

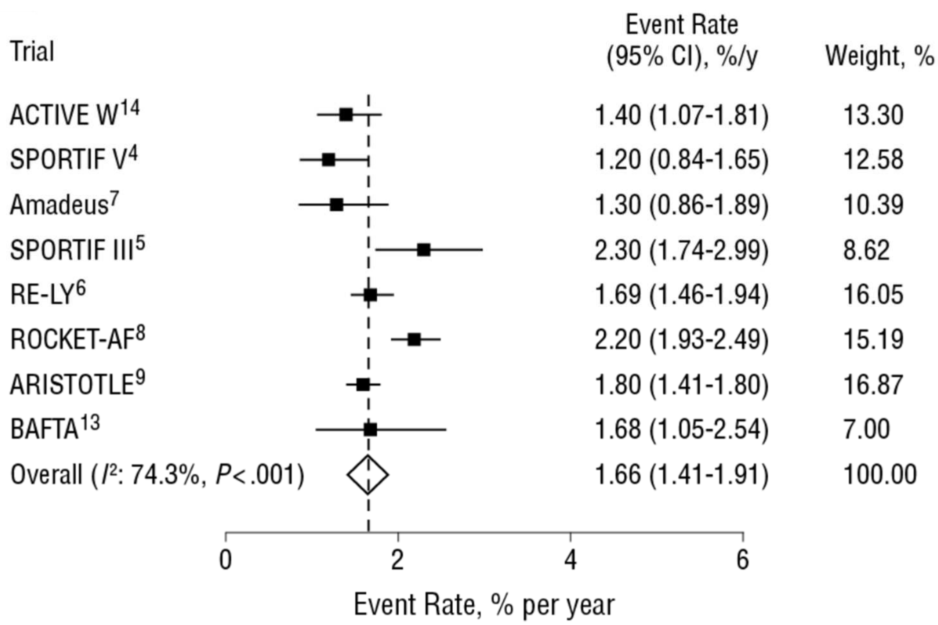
A Cochrane Collaboration review of warfarin versus placebo among subjects without prior cerebral events found that warfarin was associated with a significant risk reduction in all strokes, ischemic stroke, and the combined endpoint of stroke, MI, or vascular death (207). With an ischemic stroke rate of 4% per year in the control group, the absolute 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 1,000 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 reviews evaluated the efficacy and safety of oral anticoagulants compared to antiplatelet agents (208, 209). One review included those with no history of stroke or TIA and the other those with a history of stroke or TIA. Among 9,598 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 1,000 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) (208). 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 (190). 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 its underutilization (210-214). 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 were reported as 55% to 66% (170-172), whereas in some community settings, TTR has been reported as approximately 50% (215, 216). Despite underutilization of warfarin among eligible persons due to a variety of factors (210-214), 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 (217) (Figure 5).

**Figure 5.** Pooled Estimates of Stroke or Systemic Embolism in Patients With AF Treated With Warfarin




ACTIVE W indicates Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events-W; Amadeus, Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation; ARISTOTLE, Apixaban Versus Warfarin in Patients With AF; BAFTA, Birmingham Atrial Fibrillation Treatment of the Aged Study; CI, confidence interval; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF, Rivaroxaban Versus Warfarin in Nonvalvular Atrial Fibrillation; and SPORTIF, Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation.
Adapted with permission from Agarwal et al. (217).

*See Online Data Supplements 4 and 5 for additional data on warfarin and antiplatelet therapy (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000041/-/DC2).*

### 4.2.2.2. Newer Oral Anticoagulants

**Dabigatran** was the first new oral anticoagulant approved by the U.S. Food and Drug Administration (FDA) for prevention of stroke in patients with 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 (170). The mean $CHADS_2$ 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. 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 (218).

Dabigatran is renally excreted and patients with CrCl <30 mL/min were excluded from the RE-LY trial. CKD is associated with increased bleeding risk during both dabigatran therapy and warfarin therapy (219). 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% of subjects, 2 in 33%, and >2 in 32%). For the primary efficacy endpoint and intracranial bleeding, there was similar efficacy across the range of $CHADS_2$ scores (170). 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 to warfarin (220). Higher $CHADS_2$ scores were associated with increased risks for stroke or systemic embolism, bleeding, and death in patients with AF receiving oral anticoagulants (221). The benefits of dabigatran compared with warfarin in terms of efficacy and safety were similar in patient groups with paroxysmal, persistent, and permanent AF (162). A FDA postmarket analysis of gastrointestinal and intracranial bleeding of dabigatran versus warfarin indicates that bleeding rates do not appear to be higher for dabigatran (222).

A post hoc analysis of 1,989 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) (223). 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) (223).

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, or 110 mg twice daily and 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 RCT of dabigatran found a statistically significant increase in risk of MI and acute coronary syndromes (ACSs) in patients randomized to dabigatran (224). Interpretation of these results should be made with caution given the multiple limitations of this type of analysis, which includes the use of different controls and different patient populations.

**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. It is predominantly excreted by the kidneys. The evidence leading to approval was based on the ROCKET AF (Rivaroxaban Versus Warfarin in Nonvalvular Atrial Fibrillation) trial, which was an RCT comparing 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 (171). 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 $CHADS_2$ 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 (225). 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 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 $CHADS_2$ score of 2.1 (172). 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 newer 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 warfarin-treated patients, 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, apixaban's benefit was independent of type of AF, risk profile, $CHADS_2$ or $CHA_2DS_2$-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 (182) (Section 4.2). The mean $CHADS_2$ score was 2 and 36% of the subjects had a $CHADS_2$ score of 0 to 1. After a mean follow-up of 1.1 years, the study was prematurely terminated owing 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 (172, 182). Based on new pharmacokinetic profiles in a limited data set (226), apixaban prescribing recommendations were revised for use in patients with end-stage CKD 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 ≥80 years of age or body weight ≤60 kg. For patients with 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 (227) and betrixaban (228), are in 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 newer agents are currently considerably more expensive than warfarin. However, dietary limitations and the need for repeated INR testing are eliminated with the newer agents. If patients are stable, easily controlled, and satisfied with warfarin therapy, it is not necessary to change to 1 of the newer agents. However, it is important to discuss this option with patients who are candidates for the newer 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 such 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 regarding discontinuation of these newer agents that can increase the risk of thromboembolism, and coverage with another anticoagulant may be needed. In addition, reversal agents, while under development, are not presently 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 INR or activated partial thromboplastin time monitoring.

Importantly, patients with mechanical heart valves or hemodynamically significant mitral stenosis were excluded from all 3 major trials (RE-LY, ROCKET AF, and ARISTOTLE) (80, 85, 86); 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 Etexilate in Patients After Heart Valve Replacement) trial, a phase 2 dose-ranging study of the use of dabigatran compared with warfarin in patients with mechanical heart valves, was stopped because dabigatran users were more likely to experience strokes, MI, and thrombus forming on the mechanical heart valves than were warfarin users (183, 229, 230). There was also more bleeding after valve surgery in the dabigatran users than in the warfarin users, thus dabigatran is contraindicated for use in patients with mechanical heart valves. Similar drug safety and efficacy information is lacking for rivaroxaban and apixaban and mechanical heart valves. Bioprosthetic heart valves have not been studied with any of the newer anticoagulants. None of the 3 major trials included pregnant or lactating women, children, patients with reversible causes of AF, or patients with severe hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure >100 mm Hg). Patients with a recent stroke (within 7 to 14 days), patients with significant liver disease, and complex patients with multiple chronic conditions were excluded from all trials.

For patients with CKD, dose modifications of the new agents are available (Table 8); however, for those with severe or end-stage CKD, warfarin remains the anticoagulant of choice, as there are no or very limited data for these patients. Among patients on hemodialysis, warfarin has been used with acceptable risks of hemorrhage (178).

**Table 8. Dose Selection of Oral Anticoagulant Options for Patients with Nonvalvular AF and CKD** (Based on Prescribing Information for the United States)*

| **Renal Function** | **Warfarin** (231) | **Dabigatran†** (170) | **Rivaroxaban†** (171) | **Apixaban†** (172) |
|---|---|---|---|---|
| Normal/Mild Impairment | Dose adjusted for INR 2.0–3.0 | 150 mg BID (CrCl >30 mL/min) | 20 mg HS (CrCl >50 mL/min) | 5.0 or 2.5 mg BID‡ |
| Moderate Impairment | Dose adjusted for INR 2.0–3.0 | 150 mg BID or 75 mg BID§ (CrCl >30 mL/min) | 15 mg HS (CrCl 30–50 mL/min) | 5.0 or 2.5 mg BID‡ |
| Severe Impairment | Dose adjusted for INR 2.0–3.0‖ | 75 mg BID§ (CrCl 15–30 mL/min) | 15 mg HS (CrCl 15–30 mL/min) | No recommendation, See section 4.2.2.2.¶ |
| End-Stage CKD Not on Dialysis | Dose adjusted for INR 2.0–3.0‖ | Not recommended¶ (CrCl <15 mL/min) | Not recommended¶ (CrCl <15 mL/min) | No recommendation, See section 4.2.2.2.¶ |
| End-Stage CKD on Dialysis | Dose adjusted for INR 2.0–3.0‖ | Not recommended¶ (CrCl <15 mL/min) | Not recommended¶ (CrCl <15 mL/min) | No recommendation, See section 4.2.2.2.¶# |

*Renal function should be evaluated prior to initiation of direct thrombin or factor Xa inhibitors and should be re-evaluated when clinically indicated and at least annually. CrCl should be measured using the Crockoft-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 present: Cr ≥1.5 mg/dL, ≥80 years of age, body weight ≤60 kg (172). Apixaban is not recommended in patients with severe hepatic impairment.
§Modeling studies suggest that dabigatran 75 mg BID might be safe for patients with CrCl 15–30mL/min, but this has not been validated in a prospective cohort. Some countries outside the United States use 110 mg BID (170).
‖Dose-adjusted warfarin has been used, but observational data regarding 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 either ≥80 years of age or body weight ≤60 kg.

AF indicates atrial fibrillation; BID, twice daily; CKD, chronic kidney disease; Cr, creatinine; CrCl, creatinine clearance; HS, once daily in evening with food; and INR, international normalized ratio.

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 thrombin clotting time is a more accurate measure of anticoagulation levels, but the test is not approved in the United States nor is it widely available elsewhere (90). 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 both apixaban and rivaroxaban are not dialyzable and 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, dronedarone, 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; therefore, proton pump inhibitors may reduce absorption of dabigatran (232). Rivaroxaban and apixaban are contraindicated with drugs that inhibit cytochrome *P450 3A4* (*CYP3A4*), such as azole antimycotics, ritonavir, and clarithromycin.

Although the newer 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 (62, 184).

The ASSERT (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial) trial enrolled 2,580 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, atrial high-rate episodes >190 bpm for >6 minutes occurred in 10% of subjects (62). 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 to 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 (186). In a prospective study of 2,486 patients receiving arrhythmia management devices and 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 as compared to 1.1% per year for those with no or less atrial tachycardia/AF burden (187). In a study of 560 patients with HF, the recording of atrial high-rate events lasting >3.8 hours in 1 day was associated with a 9-fold increased thromboembolic event rate (233).

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 (185, 187).

### 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 the use of bridging of oral anticoagulants among patients with nonvalvular AF with adjusted-dose heparin or LMWH (234); however, additional studies (e.g., BRIDGE [Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery]) are on-going (235). The duration of interruption and timing of resumption of anticoagulation after the procedure is 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 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, $CHA_2DS_2$-VASc score ≥2), bridging with UFH or LMWH is a common practice, although data for LMWH are limited (23). 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 (234, 236-240). Radiofrequency catheter ablation of AF performed with a therapeutic INR does not increase bleeding risk and reduces the risk of emboli (236, 237). 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 (234, 238-243).

For oral factor Xa inhibitors and direct thrombin inhibitors, there is limited experience with drug withdrawal prior to surgical procedures (237). In the ROCKET AF trial, rivaroxaban was held for 2 days prior to elective surgery or invasive procedure and for 24 hours prior to semiurgent procedures (61). 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 pharmacologic 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) prior to the procedure is generally sufficient for patients with normal renal function (232). The need for complete hemostasis (e.g., for spinal puncture, spinal/epidural catheter, or major surgery) will demand a longer period of discontinuation of ≥48 hours for patients with normal renal function. 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 need to 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 reversing agents are not currently available but are under 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 (244-247). 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 (179). The use of clopidogrel without aspirin was associated with a reduction in bleeding and no increase in the rate of thrombotic events.

## 4.4. Nonpharmacologic Stroke Prevention

### 4.4.1. Percutaneous Approaches to Occlude the LAA

The LAA is the primary source for thromboembolism in AF (248). 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 approaches. The first strategy 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 and the Amplatzer Cardiac Plug. The WATCHMAN Device is deployed percutaneously via transeptal puncture and has a polyethylene membrane that covers a self-expanding nitinol cage with barbs to anchor the device in the LAA (249). The early WATCHMAN Device findings 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 1,588 patient years suggests noninferiority of this device to warfarin (249). A subsequent registry study demonstrated that the WATCHMAN Device achieved noninferiority to patients who could not receive warfarin (250). Lastly, data from subsequent experience with the WATCHMAN Device suggest that the earlier device-related complications were mitigated with increasing operator experience (251).

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 and a European-based trial found a 96% success rate for deployment/implantation but with a 7% incidence of serious complications (252). The second strategy is to tie off the LAA using an epicardial snare, referred to as the LARIAT device. 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 (4-7). 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 (253). The LARIAT device's long-term outcomes, 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 suitable 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 (254). 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 surgeon concern regarding 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 (255). One device, the Gillinov-

Cosgrove clip LAA excluder system, has FDA approval (256). Endocardial techniques include inversion of the appendage, amputation, and then oversewing the base from the endocardial aspect (255).

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, 2,546 patients undergoing TEE between 1993 and 2004 were retrospectively examined (257); 137 patients underwent a surgical attempt at LAA occlusion. Of these 137 patients, 52 underwent excision and 85 underwent exclusion (either suture or stapled). TEE-defined unsuccessful closures were defined 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, 50 of 137 closures were successful (40%). Success varied with the technique employed: excision (73% success rate), suture exclusion (23% success rate), and stapling (0% success rates). 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.

Success of LAA occlusion and efficacy with stroke prevention remains unclear regarding whether the appendage should be occluded at the time of concomitant heart surgery. 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 (258). During this trial, suture-based or stapler-based occlusion was permitted and 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 a lack of or an incomplete LAA occlusion were both strongly associated with the occurrence of a thromboembolic event (259).

In summary, the current data regarding LA occlusion at the time of concomitant cardiac surgery reveals 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 LAA occlusion may or may not have upon 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 (260-262).** ***(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 (263-266).** ***(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 (262, 267).** ***(Level of Evidence: B)***
2. **Intravenous amiodarone can be useful for rate control in critically ill patients without pre-excitation (268-270).** ***(Level of Evidence: B)***
3. **AV nodal ablation with permanent ventricular pacing is reasonable to control the heart rate when pharmacological therapy is inadequate and rhythm control is not achievable (271-273).** ***(Level of Evidence: B)***

**Class IIb**

1. **A lenient rate-control strategy (resting heart rate <110 bpm) may be reasonable as long as patients remain asymptomatic and LV systolic function is preserved (267).** ***(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 (274).** ***(Level of Evidence: B)***
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 (275, 276).** ***(Level of Evidence: B)***

**Table 9. Summary of Recommendations for Rate Control**

| Recommendations | COR | LOE | References |
|---|---|---|---|
| Control ventricular rate using a beta blocker or nondihydropyridine calcium channel antagonist for paroxysmal, persistent, or permanent AF | I | B | (260-262) |
| IV beta blockers or nondihydropyridine calcium channel blocker recommended to slow ventricular heart rate in the acute setting in patients without pre-excitation. In hemodynamically unstable patients, electrical cardioversion is indicated | I | B | (263-266) |
| For AF, assess heart rate control during exertion, adjusting pharmacological treatment as necessary | I | C | N/A |
| A heart rate control (resting heart rate <80 bpm) strategy is reasonable for symptomatic management of AF | IIa | B | (262, 267) |
| IV amiodarone can be useful for rate control in critically ill patients without pre-excitation | IIa | B | (268-270) |

| | | | |
|---|---|---|---|
| AV nodal ablation with permanent ventricular pacing is reasonable when pharmacological management is inadequate and rhythm control is not achievable | IIa | B | (271-273) |
| Lenient rate control strategy (resting heart rate <110 bpm) may be reasonable with asymptomatic patients and LV systolic function is preserved | IIb | B | (267) |
| Oral amiodarone may be useful for ventricular rate control when other measures are unsuccessful or contraindicated | IIb | C | N/A |
| AV nodal ablation should not be performed without prior attempts to achieve rate control with medications | III: Harm | C | N/A |
| Nondihydropyridine calcium channel antagonists should not be used in decompensated HF | III: Harm | C | N/A |
| With pre-excitation and AF, digoxin, nondihydropyridine calcium channel antagonists, or amiodarone, should not be administered | III: Harm | B | (274) |
| Dronedarone should not be used to control ventricular rate with permanent AF | III: Harm | B | (275, 276) |

AF indicates atrial fibrillation; AV, atrioventricular; COR, Class of Recommendation; HF, heart failure; IV, intravenous; LOE, Level of Evidence; LV, left ventricular; and N/A, not applicable.

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 and. 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 utilized for rate control, followed by nondihydropyridine calcium channel blockers, digoxin, and amiodarone. Patient comorbidities must be understood in order 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 inadequately anticoagulated or for whom AF is of uncertain duration. In hemodynamically stable patients with a rapid ventricular response, oral medications may be administered.

**Table 10. AF Rate Control Common Medication Dosage**

| | Intravenous Administration | Usual Oral Maintenance Dose |
|---|---|---|

| | | |
|---|---|---|
| **Beta blockers** | | |
| Metoprolol tartrate | 2.5–5.0 mg IV bolus over 2 min; up to 3 doses | 25–100 mg BID |
| Metoprolol XL (succinate) | N/A | 50–400 mg QD |
| Atenolol | N/A | 25–100 mg QD |
| Esmolol | 500 mcg/kg IV bolus over 1 min, then 50–300 mcg/kg/min IV | N/A |
| Propranolol | 1 mg IV over 1 min, up to 3 doses at 2 min intervals | 10–40 mg TID or QID |
| Nadolol | N/A | 10–240 mg QD |
| Carvedilol | N/A | 3.125–25 mg BID |
| Bisoprolol | N/A | 2.5–10 mg QD |
| **Nondihydropyridine calcium channel antagonists** | | |
| Verapamil | (0.075-0.15 mg/kg) IV bolus over 2 min, may give an additional 10.0 mg after 30 min if no response, then 0.005 mg/kg/min infusion | 180–480 mg QD (ER) |
| Diltiazem | 0.25 mg/kg IV bolus over 2 min, then 5-15 mg/h | 120–360 mg QD (ER) |
| **Digitalis glycosides** | | |
| Digoxin | 0.25 mg IV with repeat dosing to a maximum of 1.5 mg over 24 h | 0.125–0.25 mg QD |
| **Others** | | |
| Amiodarone | 300 mg IV over 1 h, then 10–50 mg/h over 24 h | 100–200 mg QD |

AF indicates atrial fibrillation; BID, twice daily; ER, extended release; IV, intravenous; N/A, not applicable; QD, once daily; QID, four times a day; and TID, three times a day.



## 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 (263, 266, 277). Orally administered beta blockers including atenolol, metoprolol, nadolol, propranolol, and sotalol have all been effectively utilized 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) (262). In patients with HF, carvedilol had efficacy for heart rate control and, in combination with digoxin, resulted in improved LV function (278). 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 (260).

*See Online Data Supplement 6 for additional data on beta blockers (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000041/-/DC2).*

### 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 (264). Intravenous verapamil is also effective in establishing acute ventricular rate control (266, 279, 280). 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 (281). These nondihydropyridine calcium channel blockers should not be used in patients with LV systolic dysfunction and decompensated HF owing to 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 (274, 282) (Section 7.8).

*See Online Data Supplement 7 for additional data on nondihydropyridine calcium channel blockers (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000041/-/DC2).*

### 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 (283). During chronic oral therapy, digoxin reduces the resting heart rate but it is ineffective at controlling the ventricular response during exercise (260). Digoxin may be combined with beta blockers or nondihydropyridine calcium channel blockers to improve ventricular rate control during exercise (260, 284, 285), 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 (286, 287). In the AFFIRM trial, digoxin was associated with an increase in mortality, which in post hoc analysis was irrespective of sex or HF (288). 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 (289). 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 (290). Because it can shorten cardiac action potential duration, digoxin should not be employed as sole therapy in patients with pre-excitation.

*See Online Data Supplement 8 for additional data on digoxin (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000041/-/DC2).*

### 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 (265, 291) and requires a longer time to achieve rate control (7 hours versus 3 hours for diltiazem). There are limited data on the efficacy of chronic oral therapy with amiodarone for rate control during persistent AF, but in 1 small trial it had similar efficacy to digoxin (292). 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 electrophysiologic effects as oral amiodarone (293), and intravenous amiodarone has the potential to accelerate the ventricular response and precipitate fatal arrhythmias in patients with AF and pre-excitation (294, 295). 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 the exercise heart rate control (296); 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 (275). Furthermore, dronedarone should not be used for ventricular rate control in patients with HF and LV systolic dysfunction as it increases the likelihood of the combined endpoint of stroke, MI, systemic embolism, or cardiovascular death (275, 276).



*See Online Data Supplement 9 for additional data on pharmacological agents for rate control (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000041/-/DC2).*

## 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 (273, 297-300). AV nodal ablation is usually reserved for elderly patients as 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 $CHA_2DS_2$-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 prior to the AV node ablation to ensure proper pacemaker function as malfunction due to lead dislodgement 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 (301). Postablation, the ventricular pacing rate is usually set between 90 bpm and 100 bpm and then gradually tapered over several months (302, 303, 303). 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 (17). 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 as compared with RV apical pacing (304). Upgrading to a biventricular pacing system should be considered for patients who have undergone AV nodal ablation coupled with a RV pacing system who develop moderate-to-severe LV systolic dysfunction (305).

*See Online Data Supplement 10 for additional data on AV junction ablation (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000041/-/DC2).*

## 5.3. Selecting and Applying a Rate Control Strategy

### 5.3.1. Broad Considerations in Rate Control

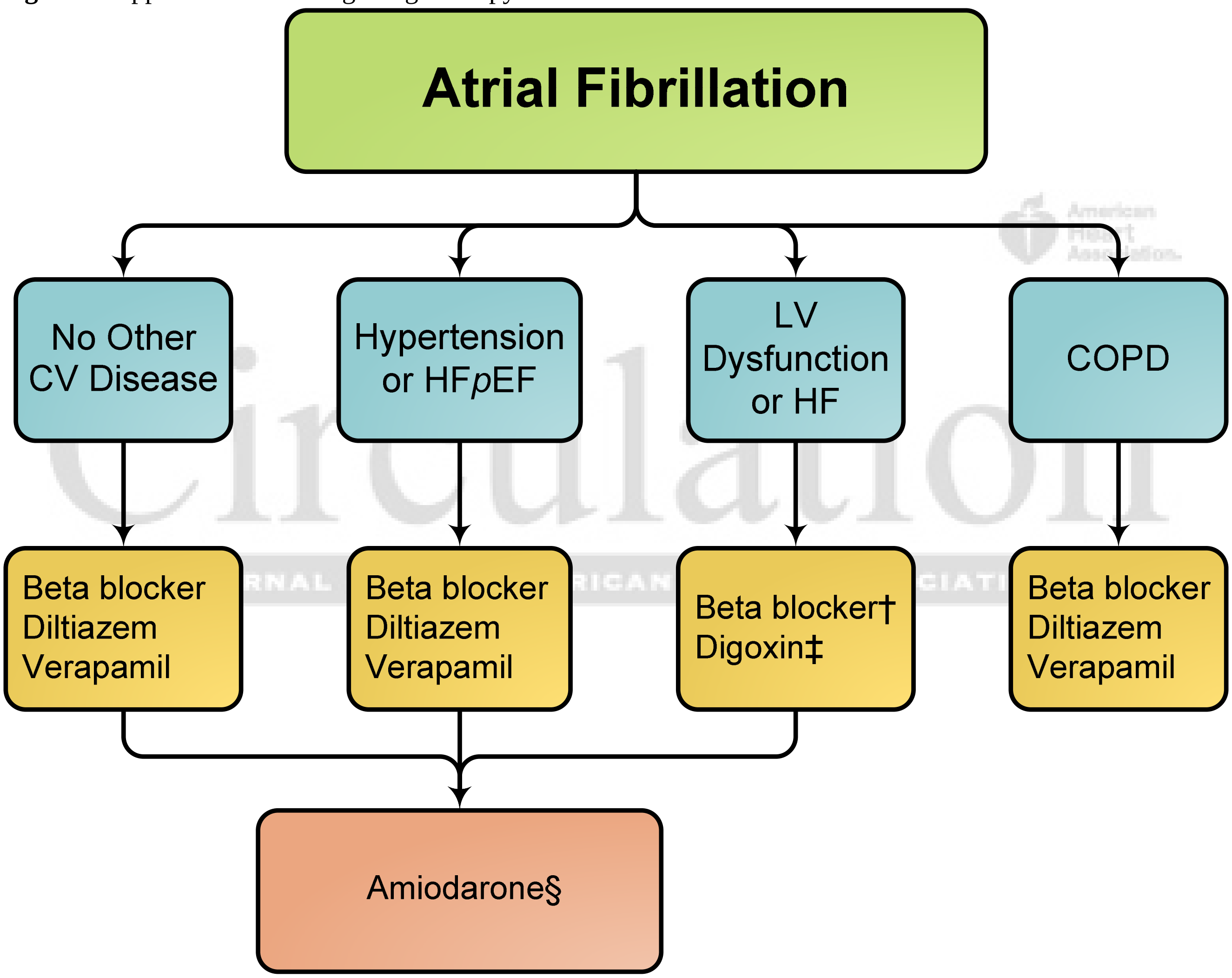
The optimal heart rate targets for rate control are controversial. The target used in the AFFIRM trial was a resting heart rate of either ≤80 bpm or averaging ≤100 bpm on ambulatory monitoring, without a rate >100% of the maximum age-adjusted predicted exercise heart rate. These conditions were achieved in 58% of patients during initial drug therapy (262). One RCT, the RACE (Rate Control Efficacy in Permanent Atrial Fibrillation)-II trial assessed lenient versus strict rate control (267). 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 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 (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000041/-/DC2).*

### 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.

**Figure 6.** Approach to Selecting Drug Therapy for Ventricular Rate Control*




*Drugs are listed alphabetically.
†Beta blockers should be instituted following stabilization of patients with decompensated HF. The choice of beta blocker (cardio-selective, etc.) depends on the patient's clinical condition.
‡Digoxin is not usually first-line therapy. It may be combined with a beta blocker and/or a nondihydropyridine calcium channel blocker when ventricular rate control is insufficient and may be useful in patients with HF.
§In part because of concern over its side-effect profile, use of amiodarone for chronic control of ventricular rate should be reserved for patients who do not respond to or are intolerant of beta blockers or nondihydropyridine calcium antagonists.

COPD indicates chronic obstructive pulmonary disorder; CV, cardiovascular; HF, heart failure; HF*p*EF, heart failure with preserved ejection fraction; and LV, left ventricular.

## 6. Rhythm Control

Long-term AF management may employ attempts to restore and maintain sinus rhythm, commonly referred to as “a rhythm-control strategy”; utilizing 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 for either strategy on mortality (262, 306). 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 (307, 308). 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 that is 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 (122, 309). For this reason, accepting AF as permanent in a patient may render future rhythm-control therapies less effective. This may be more relevant for a younger individual who wishes to remain a candidate for future developments in rhythm-control therapies. Early intervention with a rhythm-control strategy to prevent the progression of AF may be beneficial (310-312).



### 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. Thromboembolism Prevention: Recommendations

**Class I**

1. **For patients with AF or atrial flutter of 48-hour 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 prior to and 4 weeks after cardioversion, regardless of the $CHA_2DS_2$-VASc score and the method (electrical or pharmacological) used to restore sinus rhythm (313-316).** ***(Level of Evidence: B)***
2. **For patients with AF or atrial flutter of more than 48 hours 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-hour 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 regarding 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-hour duration or longer or of unknown duration who have not been anticoagulated for the preceding 3 weeks, it is reasonable to perform a TEE prior to 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 (157).** ***(Level of Evidence: B)***
2. **For patients with AF or atrial flutter of 48-hour duration or longer, or when the duration of AF is unknown, anticoagulation with dabigatran, rivaroxaban, or apixaban is reasonable for at least 3 weeks prior to and 4 weeks after cardioversion (223, 317, 318).** ***(Level of Evidence: C)***

**Class IIb**

1. **For patients with AF or atrial flutter of less than 48-hour 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 (319).** ***(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 direct-current cardioversion attempts may be made after adjusting the location of the electrodes or applying pressure over the electrodes, or following administration of an antiarrhythmic medication (320).** ***(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 period between cardioversion 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 intravenous ibutilide are useful for pharmacological cardioversion of AF or atrial flutter provided contraindications to the selected drug are absent (321-326).** ***(Level of Evidence: A)***

**Class IIa**

1. **Administration of oral amiodarone is a reasonable option for pharmacological cardioversion of AF (327, 328).** ***(Level of Evidence: A)***
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 (321).** ***(Level of Evidence: B)***

**Class III: Harm**

1. **Dofetilide therapy should not be initiated out of hospital owing to the risk of excessive QT prolongation that can cause torsades de pointes (325, 329).** ***(Level of Evidence: B)***

**Table 11. Summary of Recommendations for Electrical and Pharmacological Cardioversion of AF and Atrial Flutter**

| Recommendations | COR | LOE | References |
|---|---|---|---|
| **Thromboembolism prevention** | | | |
| With AF or atrial flutter for ≥48 h, or unknown duration, anticoagulate with warfarin for at least 3 wk prior to and 4 wk after cardioversion | I | B | (313-316) |
| With AF or atrial flutter for >48 h or unknown duration requiring immediate cardioversion, anticoagulate as soon as possible and continue for at least 4 wk | I | C | N/A |
| With AF or atrial flutter <48 h and high stroke risk, IV heparin or LMWH, or factor Xa or direct thrombin inhibitor, is recommended before or immediately after cardioversion, followed by long-term anticoagulation | I | C | N/A |
| Following cardioversion of AF, long-term anticoagulation should be based on thromboembolic risk | I | C | N/A |
| With AF or atrial flutter for ≥48 h or unknown duration and no anticoagulation for preceding 3 wk, it is reasonable to perform a TEE prior to cardioversion, and then cardiovert if no LA thrombus is identified, provided anticoagulation is achieved before TEE and maintained after cardioversion for at least 4 wk | IIa | B | (157) |
| With AF or atrial flutter ≥48 h, or unknown duration, anticoagulation with dabigatran, rivaroxaban, or apixaban is reasonable for ≥3 wk prior to and 4 wk after cardioversion | IIa | C | (223, 317, 318) |
| With AF or atrial flutter <48 h and low thromboembolic risk, IV heparin, LMWH, a new oral anticoagulant, or no antithrombotic may be considered for cardioversion | IIb | C | (319) |
| **Direct-current cardioversion** | | | |
| Cardioversion is recommended for AF or atrial flutter to restore sinus rhythm. If unsuccessful, repeat cardioversion attempts may be made | I | B | (320) |
| Cardioversion is recommended for AF or atrial flutter with RVR, that does not respond to pharmacological therapies | I | C | N/A |
| Cardioversion is recommended for AF or atrial flutter and pre-excitation with hemodynamic instability | I | C | N/A |
| It is reasonable to repeat cardioversions in persistent AF when sinus rhythm is maintained for a clinically meaningful time period between procedures | IIa | C | N/A |
| **Pharmacological cardioversion** | | | |
| Flecainide, dofetilide, propafenone, and IV ibutilide are useful for cardioversion of AF or atrial flutter provided contraindications to the selected drug are absent | I | A | (321-326) |
| Amiodarone is reasonable for pharmacological cardioversion of AF | IIa | A | (327, 328) |
| Propafenone or flecainide ("pill-in-the-pocket") to terminate AF out of hospital is reasonable once observed to be safe in a monitored setting | IIa | B | (321) |
| Dofetilide should not be initiated out of hospital | III: Harm | B | (325, 329) |

AF indicates atrial fibrillation; COR, Class of Recommendation; IV, intravenous; LA, left atrial; LOE, Level of Evidence; LMWH, low-molecular-weight heparin; N/A, not applicable; RVR, rapid ventricular response; and TEE, transesophageal echocardiogram.

Direct-current cardioversion involves the delivery of an electrical shock synchronized with the QRS complex to avoid inducing ventricular fibrillation as can occur by a shock applied 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 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 (320, 330).

A number of technical factors influence cardioversion efficacy, including energy, waveform, and electrode placement (8). A biphasic waveform is more effective than a monophasic waveform (331). Antero-posterior electrode placement is superior to anterolateral placement in some but not all studies (8, 332). 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 (333). The 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 a 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 (334, 335). 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. This guideline's Class I recommendation for anticoagulation with warfarin for ≥3 weeks prior to and continuing for ≥4 weeks after cardioversion is based on pathophysiological and observational data (315, 316). 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 (223, 317, 318).

TEE guidance is an alternative to 3 weeks of anticoagulation prior to cardioversion (157, 336). Therapeutic anticoagulation is achieved, followed by a TEE; if no thrombus is seen (including in the LAA), cardioversion is performed and anticoagulation is continued for a ≥4 weeks. The absence of left atrial 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 prior to cardioversion whereas outpatients were typically started on warfarin 5 days before cardioversion and anticoagulation status was verified at the time of cardioversion (157). Alternative strategies for achieving rapid anticoagulation include administration of LMWH (337) or a new oral anticoagulant. If thrombus is identified on TEE, the cardioversion should be postponed followed by ≥3 to 4 weeks of anticoagulation. A repeat TEE to ensure thrombus resolution is an option prior to another cardioversion attempt (315). If 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 can, however, be associated with thrombi and episodes of AF. Therefore, it is recommended that the anticoagulation 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 a cardioversion without TEE or antecedent anticoagulation (338). No RCTs comparing anticoagulation strategies in patients with AF duration <48 hours exist (335). If high-risk features are present, such as mitral stenosis or prior history of thromboembolism, long-term anticoagulation should be considered. Decisions regarding whether to initiate long-term systemic anticoagulation at the time of cardioversion in a patient with AF of <48 hours should be based on the patient's long-term risk of stroke using the $CHA_2DS_2$-VASc risk score discussed in Section 4.1.

For patients with AF requiring emergency cardioversion because of hemodynamic instability, the 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 newer anticoagulant and to continue this after the cardioversion unless contraindicated. For patients with AF or atrial flutter of ≥48 hours 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 risks 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 the 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 those patients with atrial flutter than in those with AF (339). Ibutilide pretreatment also improves the efficacy of transthoracic electrical cardioversion of AF (320). 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. ECG 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 (320). Some experts administer magnesium sulfate intravenously prior to administering ibutilide in an attempt to lower this risk (324). Intravenous amiodarone may facilitate slowing of the ventricular rate in AF, but the effect to restore sinus rhythm is often delayed. In 1 study, oral amiodarone loaded over the course of several weeks resulted in conversion of persistent AF to sinus rhythm in about 25% of patients (307). An oral dose of flecainide or propafenone can be used as a “pill-in-the-pocket” strategy to attempt to restore sinus rhythm shortly after the onset of symptomatic AF (321, 323). Because termination of AF may be associated with bradycardia owing to sinus node or AV node dysfunction or a proarrhythmic response, an initial conversion trial in a monitored setting is recommended before this approach is used in the unmonitored outpatient setting. A beta blocker or nondihydropyridine calcium channel antagonist should be administered ≥30 minutes before administering the Vaughan Williams Class IC agent to prevent a rapid ventricular response due to 1:1 AV conduction during atrial flutter (321).

**Table 12. Recommended Drug Doses for Pharmacological Cardioversion of AF**

| Drug | Route of Administration | Dosage | | Potential Adverse Effects | References |
|---|---|---|---|---|---|
| **Amiodarone** | Oral | 600–800 mg daily in divided doses to a total load of up to 10 g, then 200 mg QD as maintenance | | Phlebitis (IV), hypotension, bradycardia, QT prolongation, torsades de pointes (rare), GI upset, constipation, increased INR | (327, 328) |
| | 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 | | | |
| **Dofetilide** | Oral | CrCl (mL/min) | Dose (mcg BID) | QT prolongation, torsades de pointes; adjust dose for renal function, body size, and age | (325) |
| | | >60<br>40–60<br>20–40<br><20 | 500<br>250<br>125<br>Not recommended | | |
| **Flecainide** | Oral | 200–300 mg x 1* | | Hypotension, atrial flutter with 1:1 AV conduction, ventricular proarrhythmia; avoid in patients with CAD and significant structural heart disease | (321) |
| **Ibutilide** | IV | 1 mg over 10 min; may repeat 1 mg once if necessary (weight <60 kg use 0.01 mg/kg) | | QT prolongation, torsades de pointes, hypotension | (322, 326, 339) |
| **Propafenone** | Oral | 450–600 mg x 1* | | Hypotension, atrial flutter with 1:1 AV conduction, ventricular proarrhythmia; avoid in patients with CAD and significant structural heart disease | (321, 323) |

*Recommended given in conjunction with a beta blocker or nondihydropyridine calcium channel antagonist administered ≥30 minutes before administering the Vaughan Williams Class IC agent (321).

AF indicates atrial fibrillation; AV, atrioventricular; BID, twice a day; CAD, coronary artery disease; CrCl, creatinine clearance; GI, gastrointestinal; INR, international normalized ratio; IV, intravenous; and QD, once daily.
Adapted with permission from Fuster et al. (4-7).

## 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. **Amiodarone (307, 340-342)**
    b. **Dofetilide (325, 329)**
    c. **Dronedarone (343-345)**
    d. **Flecainide (340, 346)**
    e. **Propafenone (340, 347-350)**
    f. **Sotalol (340, 348, 351)**
3. **The risks of the antiarrhythmic drug, including proarrhythmia, should be considered before initiating therapy with each drug.** ***(Level of Evidence: C)***
4. **Owing to its potential toxicities, amiodarone should only be used after consideration of risks and when other agents have failed or are contraindicated. (307, 347, 352-355).** ***(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 (275).** ***(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 (276).** ***(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 AF recurrences. Decisions regarding anticoagulation should be based on the patient's individual 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 no or minimal 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 (e.g., 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 (e.g., after AF has been declared permanent), the antiarrhythmic drug should be discontinued.

Several systematic reviews have summarized the efficacy and safety of antiarrhythmic drugs for treating AF (340, 352, 356, 357). 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 owing to 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 (358). 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 $I_{Kr}$) 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 (359, 360). 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 prior MI, HF, and significant LV hypertrophy. Drugs that have prominent sodium channel-blocking effects (e.g., flecainide, Vaughan Williams Class IC drug) increase mortality in patients with MI from CAD (361). This consideration has been inferred for propafenone (Vaughan Williams Class IC agents), and these drugs should be avoided in patients with MI from CAD.

**Table 13. Dosage and Safety Considerations for Maintenance of Sinus Rhythm in AF**

| Drug | Usual Doses | Exclude/Use with Caution | Major Pharmacokinetic Drug Interactions |
|---|---|---|---|
| **Vaughan Williams Class IA** | | | |
| Disopyramide | • Immediate release: 100–200 mg once every 6 h<br>• Extended release: 200–400 mg once every 12 h | • HF<br>• Prolonged QT interval<br>• Prostatism, glaucoma<br>• Avoid other QT interval-prolonging drugs | • Metabolized by *CYP3A4*: caution with inhibitors (e.g., verapamil, diltiazem, ketoconazole, macrolide antibiotics, protease inhibitors, grapefruit juice) and inducers (e.g., rifampin, phenobarbital, phenytoin) |
| Quinidine | • 324–648 mg every 8 h | • Prolonged QT interval<br>• Diarrhea | • Inhibits *CYP2D6*: ↑concentrations of tricyclic antidepressants, metoprolol, antipsychotics; ↓efficacy of codeine<br>• Inhibits P-glycoprotein: ↑digoxin concentration |
| **Vaughan Williams Class IC** | | | |
| Flecainide | • 50–200 mg once every 12 h | • Sinus or AV node dysfunction<br>• HF<br>• CAD<br>• Atrial flutter<br>• Infranodal conduction disease<br>• Brugada syndrome<br>• Renal or liver disease | • Metabolized by *CYP2D6* (inhibitors include quinidine, fluoxetine, tricyclics; also genetically absent in 7%–10% of population) and renal excretion (dual impairment can ↑↑plasma concentration) |
| Propafenone | • Immediate release: 150–300 mg once every 8 h<br>• Extended release: 225–425 mg once every 12 h | • Sinus or AV node dysfunction<br>• HF<br>• CAD<br>• Atrial flutter<br>• Infranodal conduction disease<br>• Brugada syndrome<br>• Liver disease<br>• Asthma | • Metabolized by *CYP2D6* (inhibitors include quinidine, fluoxetine, tricyclics; also genetically absent in 7%–10% of population)—poor metabolizers have ↑beta blockade<br>• Inhibits P-glycoprotein: ↑digoxin concentration<br>• Inhibits *CYP2C9*: ↑warfarin concentration (↑INR 25%) |
| **Vaughan Williams Class III** | | | |
| Amiodarone | • Oral: 400–600 mg daily in divided doses for 2-4 wk; maintenance typically 100-200 mg QD | • Sinus or AV node dysfunction<br>• Infranodal conduction disease | • Inhibits most CYPs to cause drug interaction:↑concentrations of |

| | | | |
|---|---|---|---|
| | • 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 | • Lung disease<br>• Prolonged QT interval | warfarin (↑INR 0%–200%), statins, many other drugs<br>• Inhibits P-glycoprotein: ↑digoxin concentration |
| Dofetilide | • 125–500 mcg once every 12 h | • Prolonged QT interval<br>• Renal disease<br>• Hypokalemia<br>• Diuretic therapy<br>• Avoid other QT interval prolonging drugs | • Metabolized by *CYP3A*: verapamil, HCTZ, cimetidine, ketoconazole, trimethoprim, prochlorperazine, and megestrol are contraindicated; discontinue amiodarone at least 3 mo before initiation |
| Dronedarone | • 400 mg once every 12 h | • Bradycardia<br>• HF<br>• Long-standing persistent AF/flutter<br>• Liver disease<br>• Prolonged QT interval | • Metabolized by *CYP3A*: caution with inhibitors (e.g., verapamil, diltiazem, ketoconazole, macrolide antibiotics, protease inhibitors, grapefruit juice) and inducers (e.g., rifampin, phenobarbital, phenytoin)<br>• Inhibits *CYP3A*, *CYP2D6*, P-glycoprotein: ↑concentrations of some statins, sirolimus, tacrolimus, beta blockers, digoxin |
| Sotalol | • 40–160 mg once every 12 h | • Prolonged QT interval<br>• Renal disease<br>• Hypokalemia<br>• Diuretic therapy<br>• Avoid other QT interval prolonging drugs<br>• Sinus or AV nodal dysfunction<br>• HF<br>• Asthma | • None (renal excretion) |

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 from Brunton et al. (362).

### 6.2.1.1. Specific Drug Therapy

**Amiodarone** is an iodinated compound that, along with its metabolites, blocks multiple ion channels (e.g., $I_{Kr}$, $I_{Na}$, $I_{Kur}$, $I_{to}$, $I_{CaL}$, $I_{KAch}$, and $I_{Ks}$). It is a noncompetitive beta-adrenergic antagonist. It has a long half-life of weeks and large volume of distribution into adipose tissue. While 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 (≥600 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*, and 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 (307, 353, 355, 363). 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) (352). Trends for increased mortality (OR: 2.17; 95% CI: 0.63 to 7.51) were found, which 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) (364).

The major cardiovascular side effect of amiodarone is bradycardia. Marked QT prolongation can occur, but it is very rarely associated with torsades de pointes (359). Extracardiac toxicities, including thyroid, liver, pulmonary, and ocular and skin discoloration, are a major problem with amiodarone, so it 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 left ventricular 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 1C 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 (361)  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 the 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 (365). 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, tricyclic antidepressants, among others. Thus, drug interactions and genetic susceptibility can cause abnormally increased plasma concentrations of propafenone, resulting in significant beta blockade.

**Sotalol**, a $I_{Kr}$ inhibitor and beta blocker, is not effective for conversion of AF to sinus rhythm, but it 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 in the range of 30% to 50% (340). 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 11.59) were observed in a comparison study (352) 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 $I_{Kr}$ that may be considered for rhythm control in patients who are low risk for torsades de pointes induced by QT interval prolongation. Dofetilide has minimal noncardiac side effects. In the SAFIRE-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 (325). Torsades de pointes occurred with an incidence of 0.8%. Dofetilide was discontinued owing to 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 (329). In the United States, for initiation or dose escalation of therapy, inpatient ECG monitoring is mandatory, as was the case in clinical trials. Under these circumstances, dofetilide does not increase mortality in HF and post-MI populations (366). It is renally cleared, dosed according to CrCl, and adjusted or discontinued depending on 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 amiodarone's iodine moieties. It is associated with a lower incidence of adverse events than amiodarone but is also less efficacious (353). Its multiple electrophysiologic 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 (343).

Dronedarone increases mortality in patients with recently decompensated HF and depressed LV function (276) 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 (275). Therefore, dronedarone is contraindicated in patients who are not restored to sinus rhythm.

The major cardiac adverse effects of dronedarone are bradycardia and QT prolongation. Torsades de pointes is rare but has been reported. Like amiodarone, dronedarone inhibits 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* (e.g., 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 monitoring of hepatic serum enzymes, especially during the first 6 months of treatment, should be performed.



**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 AF recurrence after direct-current cardioversion (367). 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 (368). 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 (358). Quinidine has no negative inotropic effects and can be used when there is advanced renal dysfunction. Quinidine requires close ECG 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 (369). 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 (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000041/-/DC2).*

### 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 (370). Inpatient initiation or dose escalation of dofetilide in an electrocardiographically monitored environment is required because of the risk of untoward QT interval prolongation and arrhythmia provocation (325, 329). 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 the QT interval and serum potassium 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 (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 the length of hospitalization. The decision about whether to initiate other antiarrhythmic drugs in an inpatient or outpatient setting should be carefully individualized (371). 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 (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000041/-/DC2).*

### 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 with reduced LVEF (372-374).** ***(Level of Evidence: B)***

**Class IIb**

2. **Therapy with an ACE inhibitor or ARB may be considered for primary prevention of new-onset AF in the setting of hypertension (81, 375).** ***(Level of Evidence: B)***
3. **Statin therapy may be reasonable for primary prevention of new-onset AF after coronary artery surgery (128, 376).** ***(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 (81, 377).** ***(Level of Evidence: B)***

The goal of "upstream" therapy (i.e., 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 (81, 377-382). 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 AF recurrence 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 (81). Several systematic reviews of statin therapy to prevent AF have been performed (128, 378, 383, 384). The administration of statins may reduce postoperative AF in patients undergoing coronary artery bypass grafting (128, 376, 385).



*See Online Data Supplement 14 for additional data on upstream therapy (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000041/-/DC2).*

### 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 (356, 386-391).** ***(Level of Evidence: A)***
2. **Prior to 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 selected patients with symptomatic persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication (388, 392-394).** ***(Level of Evidence: A)***
2. **In patients with recurrent symptomatic paroxysmal AF, catheter ablation is a reasonable initial rhythm control strategy prior to therapeutic trials of antiarrhythmic drug therapy, after weighing risks and outcomes of drug and ablation therapy (395-397).** ***(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 (356, 398).** ***(Level of Evidence: B)***
2. **AF catheter ablation may be considered prior to 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 following 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)***

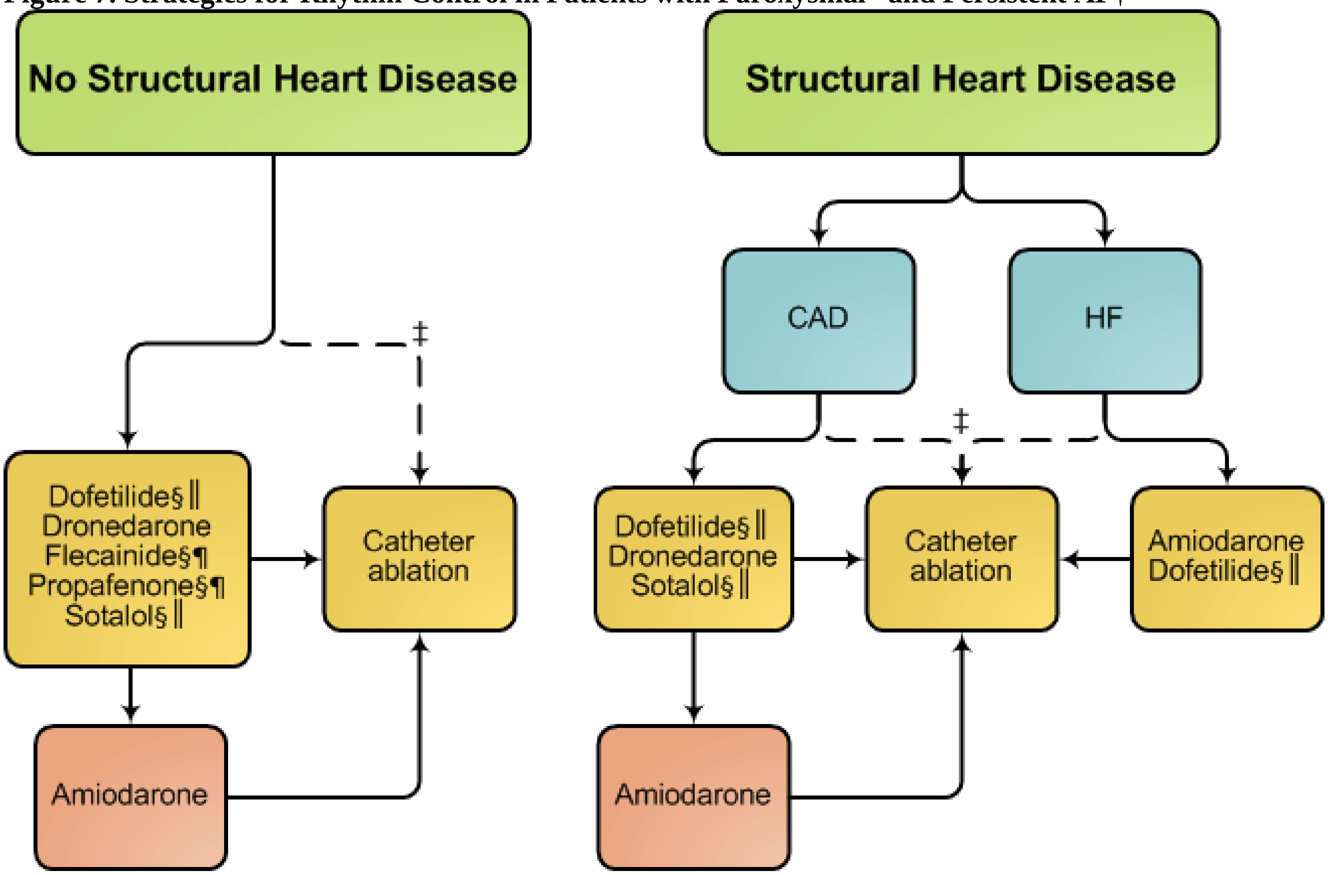
The role of catheter ablation in the management of AF continues to evolve rapidly, with improvements in the efficacy and safety of the procedure (29). The efficacy of radiofrequency catheter ablation for maintaining sinus rhythm is superior to current antiarrhythmic drug therapy for maintenance of sinus rhythm in selected patient populations. A number of systematic reviews of the efficacy of AF catheter ablation versus antiarrhythmic drug therapy have been performed (356, 386-389, 399, 400). Cryoballoon ablation is an alternative to point-by-point radiofrequency ablation to achieve pulmonary vein isolation (401). The evidence supporting the efficacy of catheter ablation is strongest for paroxysmal AF in younger patients with little to no structural heart disease (402) and in procedures performed in highly experienced centers. Studies have demonstrated a reduction of AF-related symptoms in these contexts (403). Evidence is insufficient to determine whether AF catheter ablation reduces all-cause mortality, stroke, and HF (8). 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 to 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 (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000041/-/DC2).*

### 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 verses longstanding 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 (29). It is important to recognize that most patients enrolled in trials of AF catheter ablation have generally been younger, healthy individuals with symptomatic paroxysmal AF refractory to ≥1 antiarrhythmic medication. The safety and efficacy of catheter ablation are less well established for other populations of patients, especially patients with longstanding persistent AF, very elderly patients, and patients with significant HF including tachycardia-induced cardiomyopathy (29) (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.

**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 IIa 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; CAD, coronary artery disease; HF, heart failure; and LVH, left ventricular hypertrophy.

Two RCTs compared radiofrequency catheter ablation with antiarrhythmic drug therapy as a first-line rhythm control treatment. The RAAFT (Radiofrequency Ablation Versus Antiarrhythmic Drug for Atrial Fibrillation Treatment) II 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% paroxysmal AF) with a higher 1-year freedom from AF (45% versus 28%; p=0.02) (396). 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 (404). 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 (397). 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 prior to 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 pharmacologic rhythm control approach rather than early repeat ablation should be considered (29). Patients who have had AF catheter ablation and 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 (405). A number of centers have reported late AF recurrences >1 year after catheter ablation (78, 406-409).

### 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 regarding the approach to anticoagulation prior to, during, and following catheter ablation (29). Both intraprocedural heparin and oral anticoagulation for ≥2 months postprocedure are recommended. AF catheter ablation should not be performed in patients who cannot be treated with anticoagulant therapy during and following 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 (236, 410-412). Several centers reported their experience with the use of direct thrombin and factor Xa inhibitors (mainly dabigatran) around the time of AF catheter ablation (237, 317, 413-416). Typically, dabigatran was held for 1 or 2 doses prior to 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 (237).

Continuation of anticoagulation >2 months following AF catheter ablation, if the procedure is perceived successful, should be based on consideration of the patient's thromboembolic risk profile (Section 4.1), bleeding risk, and patient choice. Recurrence of AF following ablation is 3- to 7-fold more likely to be asymptomatic compared with prior to ablation (417, 418), and late recurrences of AF can occur. Several large case series have reported a low risk of stroke after AF ablation (419-422). 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 (48, 300, 423). The degree to which LVEF improves varies according to patient characteristics (424). In cases where the 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 the 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 (425) 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 (426). 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 (427). A European observational multinational registry reported a complication rate of 7.7%, of which 1.7% were major complications (428). A report from a state-wide inpatient database described a complication rate of 5% with a 9% readmission rate (429). Much of the data regarding 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 (29). Factors associated with complication rates include older age, female sex, and a $CHADS_2$ score of ≥2 (429-431). 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 (29, 432, 433).

**Table 14. Complications of Radiofrequency Catheter Ablation for AF**

| Complication | Symptoms/Signs | Treatment |
|---|---|---|
| Air embolism | Acute ischemia, cardiac arrest, AV block, hypotension | Supplemental oxygen, fluids, CPR, or pacing if indicated |
| Atrial-esophageal fistula | Usually 1–4 wk after ablation, dysphagia, unexplained fever, chills, | CT or MRI of esophagus, avoiding endoscopy, immediate surgical correction |

| | | |
|---|---|---|
| | sepsis, neurological events (septic emboli) | |
| Cardiac tamponade/perforation | Abrupt or gradual fall in BP | Pericardiocentesis, emergent surgical drainage if pericardiocentesis fails |
| Phrenic nerve injury resulting in diaphragmatic paralysis | Shortness of breath, elevated hemidiaphragm | None, usually resolves spontaneously |
| Iatrogenic atrial flutter | Tachycardia | Cardioversion, antiarrhythmic drugs, or repeat ablation |
| Gastric motility disorder | Nausea, vomiting, bloating, abdominal pain | Depends on severity of symptoms |
| Mitral valve injury requiring surgery | Entrapment of catheter | Advance sheath with gentle catheter retraction, surgical removal |
| MI | Chest pain, ST changes, hypotension | Standard therapy |
| Pericarditis | Chest pain, typical quality | NSAIDs, colchicine, steroids |
| Pulmonary vein stenosis | Shortness of breath, cough, hemoptysis | PV dilation/stent or no therapy |
| Radiation injury | Pain and reddening at radiation site, can present late | Treat as burn injury |
| Stroke or TIA | Neurological deficit | Consider lysis therapy |
| Vascular access complication<br>• Femoral pseudo aneurysm | Pain or pulsatile mass at groin | Observation, compression, thrombin injection, possible surgery |
| • Arteriovenous fistula | Pain, bruit at groin site | Observation, compression, possible surgery |
| • Hematoma | Pain, swelling | Compression |
| Death | N/A | N/A |

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.

### 6.4. Pacemakers and Implantable Cardioverter-Defibrillators for the Prevention of AF

The primary role of pacemakers in the treatment of patients with AF is for 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 (17). Attempts to prevent AF episodes by proprietary overdrive atrial pacing algorithms that react to premature atrial complexes are inconsistent (17). 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. Surgery 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 (434).** ***(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 AF (435) but is not widely performed because of surgeons' reluctance to perform this complicated "cut and sew" atrial lines of ablation operation 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 (436).

Data regarding long-term outcomes in patients undergoing stand-alone AF surgery are limited. Of 282 patients prospectively studied from 2002 to 2009 undergoing the Cox maze IV procedure, 42% had paroxysmal AF and 58% had either persistent or longstanding persistent AF (436). 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 (436).

Nine RCTs comparing patients who undergo concomitant AF surgery with patients who undergo mitral valve surgery alone suggest greater freedom from AF in treated patients (437-445); 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 4,893 (5.3%) were stand-alone procedures (446). Propensity matching of 1,708 patients with and without cardiopulmonary bypass showed no difference in mortality risk between groups, but the "off bypass group" had fewer reoperations for bleeding, shorter hospital stay, 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 mini-thoracotomy surgical ablation of AF, 2 patients (1.8%) died within the perioperative period and the overall complication rate was 10% (447). At the 6-month follow-up (ECG, Holter monitor, event monitor, or pacemaker interrogation), 52 of 60 patients (87%) with paroxysmal AF were in sinus rhythm and 43 of 60 patients (72%) were off antiarrhythmic drugs. In patients with persistent or long-standing persistent AF, the success rates of freedom from AF were lower, at 18 of 32 patients (56%) and 11 of 22 patients (50%), respectively.

The FAST (Atrial Fibrillation Catheter Ablation Versus Surgical Ablation Treatment) trial compared the outcomes of catheter ablation and surgical ablation in a randomized study design (434). Patients either had left atrial dilation and hypertension (42 patients, 33%) or failed prior catheter ablation (82 patients, 67%). Freedom from atrial arrhythmias was greater after surgical ablation compared with catheter ablation, but the complication rate after surgical ablation was higher. Decisions regarding the choice of catheter-based or surgical ablation must be made on the basis of patient preference, and institutional experience and outcomes with each therapy (29).

## 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 (*http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000041/-/DC2*).

### 7.1. Athletes

Paroxysmal or persistent AF is common in athletes and may be autonomically mediated or triggered by other supraventricular tachycardias (448). 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 ECG 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 (449).

### 7.2. Elderly

The prevalence of AF increases with age and approximately 35% of patients with AF are ≥80 years of age (31, 32). 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. It is for this reason that the $CHA_2DS_2$-VASc 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 stroke risk factor (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 bradyarrhythmias, is often increased. Therefore a rate control strategy is often preferred (31), and direct-current cardioversion is less often warranted (450). Typically, rate control can be achieved with beta blockers or nondihydropyridine calcium channel antagonists. Care must be taken in these patients as they are often more susceptible to orthostatic hypotension or bradyarrhythmias 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 $CHA_2DS_2$-VASc score (51, 451).** ***(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 therapies.** ***(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 (452-455).** ***(Level of Evidence: B)***

**Class IIb**

1. **Sotalol, dofetilide, and dronedarone may be considered for a rhythm-control strategy in patients with HCM (12).** ***(Level of Evidence: C)***

Patients with HCM are considered separately because their unique pathology serves to distinguish 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 (456). AF is relatively common in HCM, increases with age, and is often poorly tolerated symptomatically (51). 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 (51). AF is associated with increased mortality in patients with HCM (3% in patients with AF versus 1% in sinus rhythm per year) (51, 457) 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 (51).

There is an important risk of stroke and systemic embolism in patients with HCM and AF (51, 458, 459). In a study of 480 patients with HCM, the OR for stroke in those with AF was 17.7 (51). 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 other $CHA_2DS_2$-VASc (or $CHADS_2$) score. 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 (4-7, 51, 170, 451).

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 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 are generally preferred (12, 460).

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 (12, 452, 454). The surgical maze procedure for AF shows some success (461); however, the role of a surgical maze procedure for patients undergoing other open chest surgical procedures (i.e., septal myectomy) is unresolved (12, 461).

## 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)***
3. **For patients with ACS and AF with $CHA_2DS_2$-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 (130, 462). In the Medicare population, AF is associated with increased in-hospital mortality (25.3% with AF versus 16.0% without AF), 30-day mortality (29.3% versus 19.1%), and 1-year mortality (48.3% versus 32.7%) (130). With multivariate adjustment, AF remains an independent predictor of mortality: in-hospital (OR: 1.21), 30-day (OR: 1.20), and 1-year (OR: 1.34) (130). Patients who develop AF during hospitalization have a worse prognosis than those with AF on admission (130). Stroke rates are increased in patients with MI and AF compared with rates in those without AF (3.1% for those with AF versus 1.3% for those in normal sinus rhythm) (462). Thus, AF is an independent predictor of poor long-term outcome in patients with ACS (463, 464). Specific recommendations for management of patients with AF in the setting of ACS are based primarily on consensus because no adequate trials have tested alternative strategies (21).

Patients treated for ACS normally require dual antiplatelet therapy with aspirin plus other platelet inhibitors, such as clopidogrel, and may require the addition of warfarin or a novel oral anticoagulant ("triple therapy") as treatment of AF (179) (Section 4.3). In patients with long-standing AF or a moderate-to-high $CHA_2DS_2$-VASc score, efforts should be directed to minimize duration of triple therapy and the decisions about stent insertion should consider the potential requirement for long-term anticoagulant therapy. For patients who develop transient AF as a complication of ACS and who do not have a prior history of AF, the need for anticoagulation and the duration of oral anticoagulation should be based on the patient's $CHA_2DS_2$-VASc score.

Use of dual antiplatelet therapy alone may be considered for patients with ACS who have AF and a low $CHA_2DS_2$-VASc score, with reconsideration of the indications for anticoagulation over time (192, 316). An option is to consider the use of oral anticoagulation plus clopidogrel with or without aspirin (179). The novel oral anticoagulants have not been evaluated in the context of AF and ACS and thus no recommendation for their use can be made.

Urgent direct-current cardioversion is appropriate in patients with ACS presenting with new-onset AF and intractable ischemia, hemodynamic instability, or inadequate rate control. Intravenous administration of a beta blocker is indicated for rate control in patients with ACS to reduce myocardial oxygen demands. Intravenous amiodarone is an appropriate alternative 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 (465, 466).

## 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 amongst those >60 years of age (144, 467, 468). Complications of AF in hyperthyroidism include HF and thromboembolism, although the correlation with thromboembolic disease is controversial (467-475). Treatment is directed primarily toward restoring an euthyroid state, which is usually associated with a spontaneous reversion of AF to sinus rhythm. Antiarrhythmic drugs and cardioversion often fail to achieve sustained sinus rhythm while thyrotoxicosis persists (476); 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 (477). 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 (478, 479). Anticoagulation for the patient with thyrotoxicosis and AF should be guided by $CHA_2DS_2$-VASc risk factors (Section 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 prior to initiation of therapy and patients should be monitored closely (480).

### 7.6. Acute Noncardiac Illness

A number of acute noncardiac conditions are associated with AF (e.g., 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 (481) and many of these patients will spontaneously convert 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 disorder (482-484). 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 (485). 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 (268). Digoxin can be used with calcium channel blockers, particularly in those with preserved LVEF (486). In patients refractory to drug therapy, AV nodal ablation and ventricular pacing may be necessary to control the ventricular rate. Anticoagulation, while 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, and rapid ventricular response who are hemodynamically compromised (64).** ***(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 (64).** ***(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 (64).** ***(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 as they accelerate the ventricular rate (487-489).** ***(Level of Evidence: B)***

AF is of specific concern in patients with WPW 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 is estimated at 15%, although the mechanism of increased AF risk is poorly understood (490, 491). Approximately 25% of patients with WPW syndrome have accessory pathways with short anterograde refractory periods (<250 ms), which are associated with a risk of rapid ventricular rates and ventricular fibrillation (492, 493). Patients with multiple accessory pathways are also at greater risk of ventricular fibrillation (492). The safety and efficacy of catheter ablation of accessory pathway is established (64); 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 (64). 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 (487, 489). Similarly, lidocaine use in pre-excited AF is considered potentially harmful (494). Oral amiodarone can slow or block accessory pathway conduction during chronic oral therapy. Although beta blockers theoretically pose a similar potential risk, there are few data regarding administration of these agents in rapid AF in patients with WPW; nevertheless, they should be used with caution (488, 495).

## 7.9. Heart Failure: Recommendations

**Class I**

1. **Control of resting heart rate using either a beta blocker or a nondihydropyridine calcium channel antagonist is recommended for patients with persistent or permanent AF and compensated HF with preserved EF (HF*p*EF) (262).** ***(Level of Evidence: B)***
2. **In the absence of pre-excitation, intravenous beta blocker administration (or a nondihydropyridine calcium channel antagonist in patients with HF*p*EF) 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 (496-499).** ***(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 (270, 497, 500, 501).** ***(Level of Evidence: B)***
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 HF*p*EF), is reasonable to control resting and exercise heart rate in patients with AF (260, 497).** ***(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 (262, 502, 503).** ***(Level of Evidence: B)***
3. **Intravenous amiodarone can be useful to control the 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 (52, 300, 504). (*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 HF*p*EF) 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 the 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 (505). AF is a strong independent risk factor for subsequent development of HF as well (39, 506). In addition to those with HF and depressed EFs, patients with HF due to diastolic dysfunction with HF*p*EF are also at greater risk for AF (507). 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.

Similar to other patient populations, the main goals of therapy for those with AF and HF are prevention of thromboembolism and symptom control. Most patients with AF and HF expect 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. It is important to recognize that AF with a rapid ventricular response is 1 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 to rate control the patient's AF and see if the HF and EF improve. The other strategy 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 (508). 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 (48, 300).

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 at 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 (509-514).



## 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. (147, 515-518). Premature AF, defined as a first-degree relative with an onset of AF prior to 66 years of age, is associated with a doubling in the risk of AF (147). Thus it is common, particularly among younger, healthier individuals with AF, to observe families with AF. In the last 10 years, many mutations have been identified in individuals and families with AF (519). 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 genome-wide association studies identified ≥9 distinct genetic loci for AF (148-151). Furthermore, combinations of AF-associated single nucleotide polymorphisms may identify individuals at high risk for arrhythmia (520, 521). However, the role of these common genetic variants in risk stratification (147, 522, 523), assessment of disease progression, and determination of clinical outcomes (149, 524, 525) is currently limited. Routine genetic testing related to AF is not indicated (526).

## 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 (527-530).** ***(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 (531).** ***(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 (532-534).** ***(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 (535).** ***(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 (531).** ***(Level of Evidence: B)***
4. **It is reasonable to administer antithrombotic medication in patients who develop postoperative AF, as advised for nonsurgical patients (536).** ***(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 following cardiac surgery (530, 537).** ***(Level of Evidence: B)***
2. **Administration of colchicine may be considered for patients postoperatively to reduce AF following cardiac surgery (538).** ***( 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 (539). 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 (540), increased cost (541), and mortality (542). 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 (4-7). Newer studies support this idea (385, 538).

In a meta-analysis of patients undergoing coronary revascularization, those who received preoperative statin therapy had less AF than those not treated with statins (385). 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 (538). 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 stay.

**Table 15. Summary of Recommendations for Specific Patient Groups and AF**

| Recommendations | COR | LOE | References |
|---|---|---|---|
| **Hypertrophic cardiomyopathy** | | | |
| Anticoagulation indicated in HCM with AF independent of the $CHA_2DS_2$-VASc score | I | B | (51, 451) |
| Antiarrhythmic drugs can be useful to prevent recurrent AF in HCM. Amiodarone, or disopyramide combined with beta blockers or nondihydropyridine calcium channel antagonist are reasonable | IIa | C | N/A |
| AF catheter ablation can be beneficial for HCM to facilitate a rhythm-control strategy when antiarrhythmics fail or are not tolerated | IIa | B | (452-455) |
| Sotalol, dofetilide, and dronedarone may be considered for a rhythm-control strategy in HCM | IIb | C | (12) |
| **AF complicating ACS** | | | |
| Urgent cardioversion of new onset AF in setting of ACS is recommended for patients with hemodynamic compromise, ongoing ischemia, or inadequate rate control | I | C | N/A |
| IV beta blockers are recommended to slow RVR with ACS and no HF, hemodynamic instability, or bronchospasm | I | C | N/A |
| With ACS and AF with $CHA_2DS_2$-VASc (score ≥2), anticoagulation with warfarin is recommended unless contraindicated | I | C | N/A |
| Amiodarone or digoxin may be considered to slow a RVR with ACS and AF, and severe LV dysfunction and HF or hemodynamic instability | IIb | C | N/A |
| Nondihydropyridine calcium antagonists might be considered to slow a RVR with ACS and AF only in the absence of significant HF or hemodynamic instability | IIb | C | N/A |
| **Hyperthyroidism** | | | |
| Beta blockers are recommended to control ventricular rate with AF complicating thyrotoxicosis, unless contraindicated | I | C | N/A |
| Nondihydropyridine calcium channel antagonist is recommended to control the ventricular rate with AF and thyrotoxicosis when beta blocker cannot be used | I | C | N/A |
| **Pulmonary diseases** | | | |
| Nondihydropyridine calcium channel antagonist is recommended to control the ventricular rate with COPD and AF | I | C | N/A |
| Cardioversion should be attempted with pulmonary disease patients who become hemodynamically unstable with new onset AF | I | C | N/A |
| **WPW and pre-excitation syndromes** | | | |
| Cardioversion recommended with AF, WPW, and RVR who are hemodynamically compromised | I | C | (64) |

| | | | |
|---|---|---|---|
| IV procainamide or ibutilide to restore sinus rhythm or slow ventricular rate recommended with pre-excited AF and RVR who are not hemodynamically compromised | I | C | (64) |
| Catheter ablation of accessory pathway is recommended in symptomatic patients with pre-excited AF, especially if the accessory pathway has a short refractory period | I | C | (64) |
| IV amiodarone, adenosine, digoxin, or nondihydropyridine calcium channel antagonists with WPW who have pre-excited AF is potentially harmful | III: Harm | B | (487-489) |
| **Heart failure** | | | |
| Beta blocker or nondihydropyridine calcium channel antagonist is recommended for persistent or permanent AF in patients with HF*p*EF | I | B | (262) |
| In the absence of pre-excitation, IV beta blocker (or a nondihydropyridine calcium channel antagonist with HF*p*EF) is recommended to slow ventricular response to AF in the acute setting, exercising caution in patients with overt congestion, hypotension or HF*r*EF | I | B | (496-499) |
| In the absence of pre-excitation, IV digoxin or amiodarone is recommended to acutely control heart rate | I | B | (270, 497, 500, 501) |
| Assess heart rate during exercise and adjust pharmacological treatment in symptomatic patients during activity | I | C | N/A |
| Digoxin is effective to control resting heart rate with HF*r*EF | I | C | N/A |
| Combination digoxin and beta blocker (or a nondihydropyridine calcium channel antagonist with HF*p*EF), is reasonable to control rest and exercise heart rate with AF | IIa | B | (260, 497) |
| Reasonable to perform AV node ablation with ventricular pacing to control heart rate when pharmacological therapy insufficient or not tolerated | IIa | B | (262, 502, 503) |
| IV amiodarone can be useful to control the heart rate with AF when other measures are unsuccessful or contraindicated | IIa | C | N/A |
| With AF and RVR, causing or suspected of causing tachycardia-induced cardiomyopathy, it is reasonable to achieve rate control by AV nodal blockade or rhythm control strategy | IIa | B | (52, 300, 504) |
| In chronic HF patients who remain symptomatic from AF despite a rate-control strategy, it is reasonable to use a rhythm-control strategy | IIa | C | N/A |
| Amiodarone may be considered when resting and exercise heart rate cannot be controlled with a beta blocker (or a nondihydropyridine calcium channel antagonist with HF*p*EF) or digoxin, alone or in combination | IIb | C | N/A |
| AV node ablation may be considered when rate cannot be controlled and tachycardia-mediated cardiomyopathy suspected | IIb | C | N/A |
| AV node ablation should not be performed without a pharmacological trial to control ventricular rate | III: Harm | C | N/A |
| For rate control, IV nondihydropyridine calcium channel antagonists, IV beta blockers and dronedarone should not be given with decompensated HF | III: Harm | C | N/A |
| **Familial (Genetic) AF** | | | |
| With AF and multigenerational AF family members, referral to a tertiary care center for genetic counseling and testing may be considered | IIb | C | N/A |
| **Postoperative cardiac and thoracic surgery** | | | |
| Beta blocker is recommended to treat postoperative AF unless contraindicated | I | A | (527-530) |
| A nondihydropyridine calcium channel blocker is recommended when a beta blocker is inadequate to achieve rate control with postoperative AF | I | B | (531) |

| | | | |
|---|---|---|---|
| Preoperative amiodarone reduces AF with cardiac surgery and is reasonable as prophylactic therapy for high risk of postoperative AF | IIa | A | (532-534) |
| It is reasonable to restore sinus rhythm pharmacologically with ibutilide or direct-current cardioversion with postoperative AF | IIa | B | (535) |
| It is reasonable to administer antiarrhythmic medications to maintain sinus rhythm with recurrent or refractory postoperative AF | IIa | B | (531) |
| It is reasonable to administer antithrombotic medications for postoperative AF | IIa | B | (536) |
| It is reasonable to manage new-onset postoperative AF with rate control and anticoagulation with cardioversion if AF does not revert spontaneously to sinus rhythm during follow-up | IIa | C | N/A |
| Prophylactic sotalol may be considered for patients with AF risk following cardiac surgery | IIb | B | (530, 537) |
| Colchicine may be considered postoperatively to reduce AF following cardiac surgery | IIb | B | (538) |

AF indicates atrial fibrillation; AV, atrioventricular; COPD, chronic obstructive pulmonary disease; COR, Class of Recommendation; HCM, hypertrophic cardiomyopathy; HF, heart failure; HF*p*EF, heart failure with preserved ejection fraction; HF*r*EF, heart failure with reduced ejection fraction; IV, intravenous; LOE, Level of Evidence; LV, left ventricular; N/A, not applicable; RVR, rapid ventricular response; and WPW, Wolff-Parkinson-White.

## 8. Evidence Gaps and Future Research Directions

The past decade has seen substantial progress in the understanding of AF mechanisms, clinical implementation of ablation for maintaining sinus rhythm, and new drugs for stroke prevention. Further studies are needed to better inform clinicians as to the risks and benefits of therapeutic options for an individual patient. Continued research is needed into the mechanisms that initiate and sustain AF. Better understanding of these tissue and cellular mechanisms will, hopefully, lead to more defined approaches to treating and abolishing AF. This includes new methodological approaches for AF ablation that would favorably impact survival, thromboembolism, and quality of life across different patient profiles. New pharmacologic 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 periprocedural period. Further investigations must be performed to better understand the links between the presence of AF, AF burden, and stroke risk, and also 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, epidemiologic, and clinical studies.

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**Key Words**: AHA Scientific Statements ■ atrial fibrillation ■ cardio-renal 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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†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.

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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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; 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

CAD = coronary artery disease

CKD = chronic kidney disease

CrCl = creatinine clearance

ECG = electrocardiogram

EF = ejection fraction

GDMT = guideline-directed medical therapy

HCM = hypertrophic cardiomyopathy

HF = heart failure

HF*p*EF = heart failure with preserved ejection fraction

INR = international normalized ratio

LA = left 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 = times in therapeutic range

UFH = unfractionated herparin

WPW = Wolff-Parkinson-White

## Appendix 4. Initial Clinical Evaluation in Patients With AF

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| **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 the 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 (e.g., 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 the 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 the ventricular rate is difficult to control |
| **Additional Testing (1 or several tests may be necessary)** | |
| 1. 6-min walk test | • If the adequacy of rate control is in question |
| 2. Exercise testing | • If the 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 the type of arrhythmia is in question |
| | • As a means of evaluating rate control |
| 4. TEE | • To identify LA thrombus (in the 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 |

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| 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.
Modified from Fuster, et al. (4-7).

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**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)**

| Committee Member | Employment | Consultant | Speaker's Bureau | Ownership/ Partnership/ Principal | Personal Research | Institutional, Organizational, or Other Financial Benefit | Expert Witness |
|---|---|---|---|---|---|---|---|
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| Joseph S. Alpert | University of Arizona Health Sciences Center—Professor of Medicine | • Bayer Pharmaceuticals (DSMB)†<br>• Boehringer Ingelheim<br>• Daiichi-Sankyo<br>• Duke Clinical Research Institute (DSMB)<br>• Janssen Pharmaceuticals (DSMB)<br>• Exeter CME<br>• Johnson & Johnson<br>• MedIQ<br>• NACCME—CME Co.<br>• Omnia Education<br>• Provera Education Co.<br>• Roche Diagnostics<br>• Sanofi-aventis<br>• Servier Pharmaceuticals | None | None | None | None | • Plaintiff, Accidental death-IHD, 2011 |
| Hugh Calkins | Johns Hopkins Hospital—Professor of Medicine, Director of Electrophysiology | • Atricure<br>• Biosense Webster<br>• Carecore<br>• Endosense<br>• iRhythm<br>• Medtronic*<br>• Sanofi-aventis | None | None | None | None | • Defendant, Syncope, 2011<br>• Defendant, SCD, 2012 |
| Joaquin E. Cigarroa | Oregon Health & Science University—Clinical Professor; Clinical Chief of Cardiology | • Edwards Lifesciences | None | None | None | • Bracco Diagnostics, IOP-118 (Co-PI)<br>• Oregon Health & Science University†<br>• GE Healthcare, GE- | • Defendant, Coronary artery disease review, 2011 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | 145-002 (Co-PI)<br>• GE Healthcare, VSCAN (Co-PI)<br>• Genentech, MLDL1278A (Co-PI)<br>• GlaxoSmithKline—SOLID-TIMI52 (Co-PI)<br>• Harvard Clinical Research Institute—DAPT (Co-PI)<br>• Hoffman LaRoche—ALECARDIO (Co-PI)<br>• Osiris Therapeutics—Prochymal (Co-PI) | |
| Joseph C. Cleveland | University of Colorado—Professor of Surgery; Denver Veteran's Administration Hospital—Chief, Cardiac Surgery | • Baxter Biosurgery<br>• Center for Personalized Education for Physicians<br>• Sorin | None | None | • Heartware Corp. | None | None |
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|---|---|---|---|---|---|---|---|
| | | • Pfizer*<br>• Portola*<br>• Pozen<br>• Sanofi-aventis* | | | | | |
| Michael E. Field | University of Wisconsin School of Medicine and Public Health—Assistant Professor of Medicine, Director of Cardiac Arrhythmia Service | None | None | None | None | None | None |
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| Ralph L. Sacco | University of Miami, Miller School of Medicine, Department of Neurology—Chairman | • Boehringer Ingelheim†‡ | None | None | • NIH<br>• DCRI (DSMB) | • AHA† | None |
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| Cynthia M. Tracy | George Washington University Medical Center—Associate Director and Professor of Medicine | None | None | None | • NIH | • Cheney Cardiovascular Institute—Board of Trustees† | None |
| Clyde W. Yancy | Northwestern University, Feinberg School of Medicine—Magerstadt Professor | None | None | None | None | • Patient Centered Outcomes Research Institute† | None |

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|---|---|---|---|---|---|---|---|
| | of Medicine; Division of Cardiology—Chief | | | | | | |

This table represents all relationships of committee members with industry and other entities that were reported by authors, including those not deemed to be relevant to this document, at the time this document was under development. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$10,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

*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.

# 2014 AHA/ACC/HRS Atrial Fibrillation Guideline Data Supplements

(Section numbers correspond to the full-text guideline.)

## Table of Contents

## Data Supplement 1. Electrophysiologic Mechanisms in the Initiation and Maintenance of AF (Section 2)

| Mechanism | References | |
|---|---|---|
| | Experimental | Human |
| **Multiple wavelet hypothesis** | (1-3) | (4-8) |
| • Heterogeneity in atrial electrophysiology | (3, 9) | (10-13) |
| **Focal firing** | (14-17) | (18-21) |
| • Pulmonary vein foci | | |
| ○ Electrophysiology | (16, 22-28) | (29, 30) |
| ○ Evidence for reentry | (24, 31-33) | (30, 34-36) |
| ○ Evidence for focal firing | (32) | (35) |
| • Nonpulmonary vein foci | (17) | (19, 21, 37-42) |
| **Rotor with fibrillatory conduction** | (9, 31-33, 43-46) | (34-36, 47-50) |
| • Dominant frequency gradients | (9, 32, 43, 46, 51) | (34, 49-52) |

AF indicates atrial fibrillation.

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

| Mechanism | References | |
|---|---|---|
| | Experimental | Human |
| **Atrial structural abnormalities** | (9, 53-55) | (56-62) |
| • Fibrosis | (63-70) | (55, 56, 62, 63, 71-73) |
| • Noninvasive imaging of fibrosis | (74, 75) | (76-79) |
| **Inflammation/oxidative stress** | (80-83) | (59, 80, 82-88) |
| • Steroids | (89-91) | N/A |
| • Statins | (92-94) | N/A |
| • Omega-3 polyunsaturated fatty acids | (95-100) | (96, 101-103) |
| **Renin-angiotensin-aldosterone system activation** | (104-114) | (72, 115, 116) |
| • Aldosterone | (117, 118) | (119-121) |
| • Transforming growth factor-$\beta_1$ | (68, 122, 123) | N/A |
| **Autonomic nervous system** | (3, 14-16, 27, 124-126) | (127-129) |
| **Genetic variants** | See Section 7.10 | |
| **Atrial tachycardia remodeling** | | |
| • Electrophysiologic | (9, 130-136) | (137, 138) |
| • Structural | (53, 132, 139-142) | N/A |
| • Intracellular calcium | (143-145) | (145-148) |
| **Extracardiac factors** | See Section 2.2 | |

AF indicates atrial fibrillation.

 

**Data Supplement 3. Oral Anticoagulants (Dabigatran, Rivaroxaban, Apixaban) vs. Warfarin (Section 4.2.2)**

| Study Name, Author, Year | Study Aim | Study Type/Size (N) | Intervention vs. Comparator (n) | Patient Population | | Study Intervention | Endpoints | | | P Values, OR: HR: RR: & 95% CI: | Adverse Events | Study Limitations |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *Inclusion Criteria* | *Exclusion Criteria* | | *Primary Endpoint & Results* | *Safety Endpoint & Results* | *Secondary Endpoint & Results* | | | |
| RE-LY Randomized Connolly SJ, et al., 2009 (149) 19717844 | To compare 2 fixed doses of dabigatran with open-label use of warfarin in pts with AF at increased risk of stroke | RCT, open-label, blinded doses of dabigatran (18,113) | Dabigatran 110 mg (6,015)<br><br>Dabigatran 150 mg (6,076)<br><br>Warfarin (6,021) | AF and ≥1 of the following: prior stroke or TIA; LVEF<40% , NYHA class II or higher HF Sx, age ≥75 y or an age of 65-74 y plus DM, HTN, or CAD<br><br>Mean CHADS2 of 2.1 | Severe heart-valve disorder, stroke within 14 d or severe stroke within 6 mo, condition that increased hemorrhage risk, CrCl <20 mL/min, active liver disease, pregnancy | Dabigatran in 2 fixed doses – oral prodrug, direct competitive inhibitor of thrombin<br><br>Warfarin INR 2-3, mean TTR 64% | Stroke or SE<br><br>Dabigatran1 10 mg 1.53%/y<br><br>Dabigatran 150 mg 1.11%/y<br><br>Warfarin 1.69%/y | Major Hemorrhage<br><br>Dabigatran 110 mg 2.71%/y<br><br>Dabigatran 150 mg 3.11%/y<br><br>Warfarin 3.36%/y<br><br>Intracranial Bleeding<br><br>Dabigatran 110 mg 0.23%/y<br><br>Dabigatran 150 mg 0.30%/y<br><br>Warfarin 0.74%/y<br>Major GI | Stroke<br><br>Dabigatran 110 mg 1.44%/y<br><br>Dabigatran 150 mg 1.01%/y<br><br>Warfarin 1.57%/y<br><br>Stroke, ST elevation, PE, MI, death, or major bleeding<br><br>Dabigatran 110 mg 7.09%/y<br><br>Dabigatran 150 mg 6.91%/y<br><br>Warfarin 7.64%/y | Dabigatran 110 mg RR: 0.91; 95% CI: 0.74-1.11; p<0.001 for noninferiority, p=0.34 for superiority<br><br>Dabigatran 150 mg RR: 0.66; 95% CI: 0.53-0.83; p<0.001 for noninferiority, p<0.001 for superiority | Dyspepsia | Open-label<br><br>Median duration of FU 2 y |

 

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| | | | | | | | | Dabigatran 110 mg 1.12%/y<br><br>Dabigatran 150 mg 1.51%/y<br><br>Warfarin 1.02%/y | | | | |
| ROCKET-AF Patel MR, et al., 2011 (150) 21830957 | 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)<br><br>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)<br><br>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<br><br>Warfarin INR 2-3, mean TTR 55% | Any stroke or SE<br><br>Per-protocol as treated Rivaroxaban 1.7%/y Warfarin 2.2%/y<br><br>Intention to Treat Rivaroxaban 2.1%/y Warfarin 2.4%/y | Major and non-major clinically relevant bleeding<br><br>Rivaroxaban 14.9/100 pt-years<br><br>Warfarin 14.5/100 pt-years<br><br>ICH Rivaroxaban 0.5/100 pt-years Warfarin 0.7/100 pt-years<br><br>Major GI Rivaroxaban 3.15% Warfarin 2.16% | Stroke, SE, or VD<br><br>Rivaroxaban 3.11/100 pt-years<br><br>Warfarin 3.64/100 pt-years<br><br>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<br><br>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<br><br>Lower TTR in warfarin group<br><br>1° analysis was prespecified as a per-protocol analysis<br><br>High-event rate after discontinuation of Tx |

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| ARISTOTLE Granger CB, et al., 2011 (151) 21870978 | To determine whether apixaban was noninferior to warfarin in reducing the rate of stroke (ischemic or hemorrhagic) or SE among pts with AF and ≥1 other risk factor for stroke | RCT, double-dummy, double-blinded (18,201) | Apixaban (9,120)<br><br>Warfarin (9,081) | AF and ≥1 stroke risk factor (age >75 y; previous stroke, TIA or SE; symptomatic HF within the prior 3 mo or LVEF≤40%; DM; or HTN)<br><br>Mean CHADS2 score of 2.1 | AF due to a reversible cause, moderate or severe mitral stenosis, conditions other than AF requiring OAC, stroke within the prior 7 d, a need for ASA>165 mg or for ASA and CP, or severe renal insufficiency (CrCl<25 mL/min) | 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)<br><br>Warfarin INR 2-3 Mean TTR 62.2% | Any stroke or SE<br><br>Apixaban 1.27%/y<br><br>Warfarin 1.6%/y | Major Bleeding<br><br>Apixaban 2.13%/y Warfarin 3.09%/y<br><br>ICH Apixaban 0.33%/y Warfarin 0.80%/y<br><br>Major GI Apixaban 0.76%/y Warfarin 0.86%/y | Stroke, SE, major bleeding, or death from any cause<br><br>Apixaban 6.13%/y Warfarin 7.20%/y | HR: 0.79; 95% CI: 0.66-0.95; p<0.001 for noninferiority, p=0.01 for superiority<br><br>HR: 0.85; 95% CI: 0.78-0.92; p<0.001 | No differences | Median duration of FU 1.8 y |
| AVERROES Connolly SJ, et al., 2011 (152) 21309657 | To determine the efficacy and safety of apixaban, at a dose of 5 mg BID, as compared with ASA, at a dose of 81-324 mg QD, for the Tx of pts with AF for whom VKA Tx was considered unsuitable | RCT double-blind, double-dummy (5,559) | Apixaban (2,808)<br><br>ASA (2,791) | ≥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 | Pts required long-term anticoagulation, VD requiring surgery, a serious bleeding event in the previous 6 mo or a high-risk bleeding, stroke | 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)<br><br>ASA | Any stroke or SE<br><br>Apixaban 1.6%/y<br><br>ASA 3.7%/y<br><br>p<0.001 | Major Bleeding<br><br>Apixaban 1.4% ASA 1.2%<br><br>Intracranial Bleeding Apixaban 0.4% ASA 0.4%<br><br>Major GI | Stroke, SE, MI, VD or major bleeding event<br><br>Apixaban 5.3%/y ASA 7.2%/y HR: 0.74; 95% CI: 0.60–0.90; p<0.003 | HR: 0.45; 95% CI: 0.32-0.62; p<0.001 | No differences | N/A |

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| | | | | because it had already been demonstrated to be unsuitable or because it was expected to be unsuitable.<br><br>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%<br>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; VD, valvular disease; and VKA, vitamin K antagonist.

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

| Study Name, Author, Year | Study Aim | Study Type/ Size (N) | Intervention vs. Comparator (n) | Patient Population | | Study Intervention | Endpoints | | | P Values, OR: HR: RR: & 95% CI: |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | ***Inclusion Criteria*** | ***Exclusion Criteria*** | | ***Primary Endpoint & Results*** | ***Safety Endpoint & Results*** | ***Secondary Endpoint & Results*** | |
| Aguilar MI, et al., 2005 (153) 16034869 | To characterize the efficacy and safety of oral anticoagulants for the 1° prevention of stroke in pts with chronic AF | Cochrane Collaboration Systematic Review (AFASAK I, BAATAF, CAFA, SPAF I, SPINAF) | 2,313 pts<br><br>Warfarin 1,154<br>PC 1,159 | AF (intermittent or sustained) | Prior stroke or TIA, mitral stenosis or prosthetic cardiac valves | Oral VKAs (warfarin) mean INR 2.0-2.6 | All Stroke (ischemic or ICH)<br><br>Warfarin 27<br>PC 71 | ICH, Major extracranial bleeds<br><br>ICH, Warfarin 5, PC 2<br><br>Extracranial bleeds, Warfarin | Stroke, MI or VD<br><br>Warfarin 69<br>PC 118 | All ischemic stroke or ICH<br>OR: 0.39; 95% CI: 0.26-0.59<br><br>Ischemic stroke<br>OR: 0.34; 95% CI: 0.23-0.52 |

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| | | | | | | | | 17, PC 16 | | Stroke, MI, VD<br>OR: 0.57; 95% CI: 0.42-0.77<br><br>All ICH<br>OR: 2.38; 95% CI: 0.54-10.50)<br><br>Major extracranial bleeds<br>OR: 1.07; 95% CI: 0.53-2.12 |

1° indicates primary; AF, atrial fibrillation; AFASAK, Atrial Fibrillation, Aspirin and Anticoagulant Therapy Study; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation ; ICH, intracranial hemorrhage; INR, international normalized ratio; MI, myocardial infarction; N/A, not applicable; OR, odds ratio; PC, placebo; Pts, patients; RR, relative risk; SPAF I, Stroke Prevention in Atrial Fibrillation Study; SPINAF, Stroke Prevention in Atrial Fibrillation; TIA, transient ischemic attack; VD, vascular death; and VKA, vitamin K antagonist.

## Data Supplement 5. Warfarin vs. Antiplatelet Therapy (Section 4.2)

| **Study Name, Author, Year** | **Study Aim** | **Study Type/ Size (N)** | **Intervention vs. Comparator (n)** | **Patient Population** | | **Study Intervention** | **Endpoints** | | | **P Values, OR: HR: RR: & 95% CI:** | **Study Limitations** |
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| | | | | ***Inclusion Criteria*** | ***Exclusion Criteria*** | | ***Primary Endpoint & Results*** | ***Safety Endpoint & Results*** | ***Secondary Endpoint & Results*** | | |
| Aguilar MI, et al., 2007 (154)<br>17636831 | 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 | Cochrane Collaboration Systematic Review (ACTIVE-W, AFASAK I, AFASAK II, ATHENS, NASPEAF, PATAF, SPAF IIa, SPAF IIb, | 9,598 pts<br><br>OAC<br>4,815<br><br>Antiplatelet<br>4,783 | AF (intermittent or sustained) | Prior stroke or TIA, mitral stenosis or prosthetic cardiac valves | Adjusted dose warfarin or other coumarins; antiplatelet therapies | All Stroke (ischemic or ICH)<br><br>OAC<br>132/4,815<br><br>Antiplatelet<br>190/4,783 | ICH, major extracranial bleeds | Stroke, MI, or VD | All Stroke<br>OR: 0.68; 95% CI: 0.54-0.85; p=0.00069<br><br>Ischemic stroke<br>OR: 0.53; 95% CI: 0.41-0.69<br><br>ICH<br>OR: 1.98; 95% CI: 1.20-3.28<br><br>Major Extracranial<br>OR: 0.97; 95% CI: 0.74-1.28 | N/A |

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| | | | | | | | | | | Major Extracranial (exclude ACTIVE W with CP+A)<br>OR: 1.90; 95% CI: 1.07-3.39<br><br>Stroke, MI, 485 VD<br>OR: 0.74; 95% CI: 0.61-0.90 | |
| Saxena R, et al., 2011 (155) 15494992 | To compare the value of anticoagulants and antiplatelet Tx for the long term prevention of recurrent vascular events in pts with non-rheumatic AF and previous TIA or minor ischemic stroke | Cochrane Collaboration Systematic Review (EAFT, SIFA) | 1,371 pts, warfarin 679, antiplatelet 692 | AF and prior minor stroke or TIA | Rheumatic VD | Oral VKAs (warfarin) mean INR>2.0; Antiplatelets 300 mg ASA; indobufen 200 mg BID | All major vascular events (VD, recurrent stroke, MI, or SE) | Any ICH; major extracranial bleed | All fatal or nonfatal recurrent strokes | All Major Vasc Events<br>OR: 0.67; 95% CI: 0.50-0.91<br><br>Recurrent Stroke<br>OR: 0.49; 95% CI: 0.33-0.72<br><br>Any ICH<br>OR: 1.99; 95% CI: 0.40-9.88<br><br>Major Extracranial bleed<br>OR: 5.16; 95% CI: 2.08-12.83 | N/A |
| Mant J, et al., 2007 BAFTA (156) 17693178 | To compare the efficacy of warfarin with that of ASA for the prevention of fatal and nonfatal stroke, ICH, and other clinically significant arterial embolism in a 1° care | RCT (973 pts) | 973 pts, ASA 485, warfarin 488 | Age ≥75 y, AF or flutter by EKG within 2 y from 1° care practices | Rheumatic heart disease, a major nontraumatic hemorrhage within 5 y, ICH, documented peptic ulcer disease within the previous year, esophageal varices, | ASA 75 mg QD;<br>Warfarin target INR 2.5, range 2-3 | Fatal or nonfatal disabling stroke (ischemic or hemorrhagic), other ICH, or clinically significant arterial embolism<br><br>Warfarin 24 (1.8%/y) | Hemorrhage Major extracranial Warfarin 18 (1.4%/y)<br>ASA 20 (1.6%/y)<br><br>All major hemorrhages Warfarin 25 (1.9%/y)<br>ASA 25 (2.0%/y) | Major vascular events (stroke, MI, PE, VD)<br>Warfarin 76 (5.9%/y)<br>ASA 100 (8.1%/y)<br><br>1° events plus major hemorrhage Warfarin 39 | RR: 0.48; 95% CI: 0.28-0.80; p=0.0027<br><br>Stroke<br>RR: 0.46; 95% CI: 0.26-0.79; p=0.003<br><br>All major hemorrhages<br>RR: 0.96; 95% CI: 0.53-1.75; p=0.90<br><br>Major vascular | Open-label with blind assessment s<br><br>67% of the warfarin group remained on Tx TTR was 67% |

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| | population of pts aged ≥75 y who had AF | | | | allergic hypersensitivity to study drugs, terminal illness, surgery within the last 3 mo, BP>180/110 | | ASA 48 (3.8%/y) | | (3.0%/y) ASA 64 (5.1%/y) | events (stroke, MI, PE, VD) RR: 0.73; 95% CI: 0.53-0.99; p=0.03<br><br>1° events plus major hemorrhage RR: 0.59; 95% CI: 0.38-0.89; p=0.008 | |

1° indicates primary; AF, atrial fibrillation; ACTIVE-W, Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events-W; AFASAK, Atrial Fibrillation, Aspirin and Anticoagulant Therapy Study; ATHENS, Primary Prevention of Arterial Thromboembolism in the Oldest Old with Atrial Fibrillation; BID, twice daily; BP, blood pressure; EAFT, European Atrial Fibrillation Trial; EKG, electrocardiogram; Hx, history; ICH, intracranial hemorrhage; MI, myocardial infarction; N/A, not applicable; NASPEAF, National Study for Prevention of Embolism in Atrial Fibrillation; PATAF, Primary Prevention of Arterial Thromboembolism in Nonrheumatic Atrial Fibrillation; PE, pulmonary embolism; pts, patients; QD, once daily; RR, relative risk; SE, systemic embolism; SIFA, Studio Italiano Fibrillazione Atriale; SPAF, Stroke Prevention in Atrial Fibrillation Study; TIA, transient ischemic attack; TTR, time in therapeutic range; Tx, therapy; and VD, vascular death.

## Data Supplement 6. Beta Blockers (Sections 5.1.1)

| Study Name, Author, Year | Study Aim | Study Type/ Size (N) | Intervention vs. Comparator (n) | Patient Population | | Study Intervention | Endpoints | | P Values, OR: HR: RR: & 95% CI: | Adverse Events | Study Limitations |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | ***Inclusion Criteria*** | ***Exclusion Criteria*** | | ***Primary Endpoint & Results*** | ***Secondary Endpoint & Results*** | | | |
| Abrams J, et al., 1985 (157) 3904379 | Evaluation of the efficacy and safety of esmolol in comparing to propranolol for the acute control of SVT | Randomized prospective, multicenter double-blind | IV esmolol vs. IV propranolol | Pts over age 18 y with ventricular rates >120 bpm 2° to AF, atrial flutter, SVT, atrial tachycardia, idiopathic sinus tachycardia and AV reentrant tachycardias | WPW syndrome, hypotension, sick sinus syndrome, AV conduction delay decompensated HF or noncardiac precipitated arrhythmias | Esmolol vs. propranolol | Composite endpoint of either ≥20% reduction from average baseline heart rate, reduction in heart rate to <100 bpm, or conversion to NSR esmolol 72% vs. propranolol 69% | N/A | No difference | Hypotension (esmolol 45% vs. propranolol 18%) | Small sample size<br><br>Only 66% of pts had AF |
| Farshi R, et al., 1999 (158) 9973007 | Comparison of the effects of 5 standard drug | Prospective, open-label crossover outpatient | N/A | Chronic AF pts who had a duration of ≥1 y | LVEF<0.35, WPW syndrome, sick sinus | Comparison of the effects of 5 standard drug | Comparison of 24 h mean ventricular rates | Peak ventricular response at 5 m of exercise: | p<0.01 for comparison of atenolol or atenolol and | N/A | N/A |

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| | regimens: digoxin, diltiazem, atenolol, digoxin plus diltiazem, and digoxin + atenolol on the mean 24-h heart rate | | | | syndrome, pacemaker or clinically significant renal, thyroid or hepatic disease | regimens: digoxin, diltiazem, atenolol, digoxin plus diltiazem, and digoxin + atenolol on the mean 24-h heart rate | Digoxin: 78.9±16.3<br>Diltiazem: 80.0±15<br>Atenolol: 75.9±11.7<br>Digoxin + Diltiazem: 67.3±14.1<br>Digoxin + atenolol: 65±9.4 | Digoxin: 175±36<br>Diltiazem: 151±27<br>Atenolol: 130±34<br>Digoxin + Diltiazem: 146±40<br>Digoxin + atenolol: 126±29 | digoxin compared to digoxin alone | | |

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)

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

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| Siu CW, 2009 et al., (161) 19487941 | To compare the clinical efficacy of IV diltiazem, digoxin, and amiodarone for acute VR in symptomatic AF | Randomized, prospective, open-label | IV diltiazem vs. IV amiodarone vs. IV digoxin | Hospitalized pts with symptomatic AF<48 h with ventricular response >120 bpm | Ventricular response >200 bpm, pre-excitation syndrome, hypotension, CHF, implanted pacemaker/defibrillator, recent MI, UA or stroke | IV diltiazem vs. IV amiodarone vs. IV digoxin | VR control (<90 bpm) within 24 h: ventricular response <90 bpm sustained for ≥4 h<br><br>Diltiazem 90% vs. amiodarone 74% vs. digoxin 74% | p<0.47 | N/A |

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)

| Study Name, Author, Year | Study Aim | Study Type/ Size (N) | Intervention vs. Comparator (n) | Patient Population | | Study Intervention | Endpoints | | P Values, OR: HR: RR: & 95% CI: | Study Limitations |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | ***Inclusion Criteria*** | ***Exclusion Criteria*** | | ***Primary Endpoint & Results*** | ***Secondary Endpoint & Results*** | | |
| IV Digoxin in Acute AF (162) 9129897 | To examine the effects of IV digoxin in acute AF | Randomized, prospective, multicenter, double-blind PC-controlled | IV digoxin vs. PC | Pts >18 y with AF≤7d | Ongoing Tx with digoxin or antiarrhythmics, sick sinus syndrome or $2^{nd}$ /$3^{rd}$ degree AV block without a pacemaker, WPW syndrome, heart rate <60 or >170 bpm, ongoing ischemia or recent MI | IV digoxin vs. PC | Conversion to sinus rhythm at 16 h<br><br>Digoxin 46% vs. PC 51% | Effect on heart rate:<br><br>91.2±20 vs. 116.2±25 | p=0.37<br><br>p<0.0001 | N/A |
| AFFIRM Olshansky B, et al., 2004 (163) 15063430 | To examine whether digoxin use was associated with adverse | Post hoc analysis | Nonrandomized comparison of digoxin vs. no digoxin | Pts with AF considered at high risk for stroke | N/A | Post hoc analysis including propensity analysis | Estimated HR of 1.41 for all-cause mortality for digoxin | Estimated HR of 1.61 for arrhythmic mortality<br><br>Estimated HR | p<0.001<br><br>p<0.009<br><br>p<0.016 | Post hoc analysis utilizing propensity scoring |

 

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| | mortality and morbidity | | | | | | | of 1.35 for CV mortality | | |

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)

| Study Name, Author, Year | Study Aim | Study Type/ Size (N) | Intervention vs. Comparator (n) | Patient Population | | Study Intervention | Endpoints | | | P Values, OR: HR: RR: & 95% CI: | Adverse Events |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | ***Inclusion Criteria*** | ***Exclusion Criteria*** | | ***Primary Endpoint & Results*** | ***Safety Endpoint & Results*** | ***Secondary Endpoint & Results*** | | |
| Delle Karth G, et al., 2001 (164) 11395591 | 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 | Randomized prospective, controlled | IV diltiazem bolus/infusion vs. IV amiodarone bolus vs. IV amiodarone bolus/infusion | Critically ill pts with recent-onset AF with ventricular rate >120 bpm | N/A | IV diltiazem bolus/ infusion vs. IV amiodarone bolus vs. IV amiodarone bolus/infusion | Sustained heart rate reduction ≥30% within 4 h<br><br>70% vs. 55% vs. 75% | Bradycardia or hypotension<br><br>35% vs. 0% vs. 5% | Uncontrolled tachycardia 0% vs. 45% vs. 5% | 1° endpoint: NS<br><br>2° endpoint p<0.00016<br><br>Safety endpoint p=0.01 | N/A |
| Connolly SJ, et al., 2011 (165) 22082198 | Assess impact of dronedarone on major vascular events in high-risk permanent AF | Randomized prospective, multicenter, double-blind, PC-controlled trial (3,236) | Dronedarone 400 mg po BID vs. PC | Permanent AF / flutter, age ≥65 y with ≥1 risk factor: CAD, CVA or TIA, CHF, LVEF≤0.40, PAD or age ≥75 y with HTN and DM | Paroxysmal or persistent AF, ICD, heart rate <50 bpm, QT interval corrected >500 ms | Dronedarone vs. PC | Composite of stroke, MI, SE, or CV death<br><br>Composite of unplanned hospitalization for CV event/ death | N/A | N/A | HR: 2.29; 95% CI: 1.34-3.94<br><br>HR: 1.95; 95% CI: 1.45-2.62 | Stroke HR: 2.32; 95% CI: 1.11-4.88<br><br>Unplanned hospitalization for CV event HR: 1.81; 95% CI: 1.44-2.70 |

1° indicates primary; 2°, 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.

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

| Study Name, Author, Year | Study Aim | Study Type/ Size (N) | Intervention vs. Comparator (n) | Patient Population | | Study Intervention | Endpoints *Primary Endpoint & Results* | P Values, OR: HR: RR: & 95% CI: | Study Limitations |
|---|---|---|---|---|---|---|---|---|---|
| | | | | *Inclusion Criteria* | *Exclusion Criteria* | | | | |
| Ozcan C, et al., 2001 (166) 11287974 | 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 | Observational single site | Comparison to 2 control populations<br><br>Age/sex matched from minnesota population<br><br>Consecutive pts with AF who received drug Tx | All pts who underwent AV nodal ablation and pacemaker implantation for medically refractory AF between 1990 and 1998 | N/A | AV nodal ablation pacemaker compared to 2 control groups | No difference in survival between ablation/pacemaker group and control group treated with drugs<br><br>Excess observed death in ablation/ pacemaker group relative to age/sex matched population | N/A | Observation, nonrandomized trial |

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)**

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

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)**

| Study Name, Author, Year | Study Aim | Study Type/ Size (N) | Intervention vs. Comparator (n) | Patient Population | Endpoints | | Adverse Events | Comments |
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| | | | | | ***Primary Endpoint & Results*** | ***Secondary Endpoint & Results*** | | |
| ADONIS, Singh BN, et al., 2007 (168) 17804843 | To assess the efficacy of dronedarone in maintenance of SR in pts with AF | RCT, double-blind (625) | Dronedarone 400 mg BID (417)<br><br>PC (208) | Age ≥21 y<br>≥1 episode AF in previous 3 mo | Time to the 1st recurrence of AF or atrial flutter<br><br>Dronedarone 158 d<br>PC 59 d<br>(p=0.002) | Ventricular rate after recurrence, dronedarone 104.6 bpm<br>PC 116.6 bpm<br>(p<0.001). | N/A | Dronedarone was more effective than PC in maintaining SR and in reducing ventricular rate during recurrent AF |
| AFFIRM Substudy, 2003 (169) 12849654 | To evaluate the efficacy of antiarrhythmic drugs for AF | RCT, open-label (410) | Amiodarone 200 mg/d vs. class I drug vs. sotalol | Substudy of pts randomized to rhythm control | 1° – proportion at 1 y alive, on Tx drug, and in SR<br><br>62% amiodarone vs. 23% class I drug (p<0.001)<br><br>60% amiodarone vs. 38% sotalol (p=0.002)<br><br>34% sotalol vs. 23% class I drug (p=0.488) | N/A | AEs leading to drug discontinuation<br>12.3% amiodarone<br>11.1% sotalol<br>28.1% class I agent<br><br>Amiodarone pulmonary toxicity 1.3% at 1 y and 2.0% at 2 y<br><br>1 case torsade de pointes - quinidine | Amiodarone more effective than sotalol or class I agent for SR without cardioversion<br><br>AEs were common |
| Aliot E, et al., 1996 (170) 8607394 | To assess the safety and efficacy of flecainide vs. propafenone in PAF or atrial flutter | RCT, open-label (97) | Flecainide 100-200 mg/d (48)<br><br>Propafenone 600 mg/d (49) | Inclusion: >18 y with symptomatic PAF or atrial flutter<br><br>Exclusion: AF last >72 h, Hx of MI or UA, Hx of VT, Hx of HF (NYHA class III or IV), LVEF<35%, PR>280 ms, QRS>150 ms, sick sinus syndrome or AV block in absence of pacemaker | Probability of SR at 1 y<br>0.619 flecainide<br>0.469 propafenone<br>(p=0.79) | N/A | 8.5% flecainide group had neurologic side effects<br><br>16.7% propafenone group GI side effects | Flecainide and propafenone similar efficacy (although small sample size and open-label design)<br><br>Nonsignificant trend toward higher side-effects with propafenone |

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| ANDROMEDA, Kober L, et al., 2008 (171) 18565860 | To evaluate the efficacy of dronedarone in HF pts | RCT, double-blind<br><br>(627) | Dronedarone (310)<br><br>PC (317) | Age >18 y, hospitalized for HF, LVEF<35%, NYHA class III or IV<br>(Did not require AF Dx, Hx of AF 37-40%) | Death from any cause or HF hospitalization<br>17.1% dronedarone<br>12.6% PC<br>HR: 1.38; 95% CI: 0.92-2.09; p=0.12 | N/A | Death<br>8.1% dronedarone<br>3.8% PC<br>HR: 2.13; 95% CI: 1.07-4.25; p=0.03 | Dronedarone is associated with increased mortality in pts with severe HF and reduced LVEF related to worsening of HF |
| ASAP, Page RL, et al., 2003 (172) 12615792 | To assess the frequency of asymptomatic AF in pts treated with azimilide | RCT, double-blind (1,380) | Azimilide 35-125 mg/d (891)<br><br>PC (489) | Inclusion: Symptomatic AF in SR at time of randomization<br><br>Exclusion: Rest angina or UA, class IV CHF, Hx of torsade de pointes, QTc >440 ms, resting SR<50 bpm | Time to 1st documented asymptomatic AF – no significant difference<br><br>40% reduction in asymptomatic AF episodes in the 100 mg or 125 mg azimilide group vs. PC (p=0.03) | N/A | N/A | N/A |
| ATHENA, Hohnloser SH, et al., 2009 (173) 19213680 | N/A | RCT, double-blind (4,628) | Dronedarone 400 mg BID (2,301)<br><br>PC (2,327) | Inclusion: AF (paroxysmal or persistent) and ≥1 of these: >70 y, HTN, DM, LVEF<40%, LAD>50 mm, Hx of TIA/stroke/embolism | 1° – 1st hospitalization due to CV event or death<br>31.9% dronedarone<br>39.4% PC<br>HR: 0.76; p<0.001 | Death due to any cause<br><br>CV death<br><br>CV hospitalization | N/A | N/A |
| Bellandi F, et al., 2001 (174) 11564387 | To evaluate the long-term efficacy and safety of propafenone and sotalol for maintaining SR | RCT, double-blind (194) | Propafenone HCL 900 mg/d (102)<br><br>Sotalol HCL 240 mg/d (106)<br><br>PC (92) | ≥18 y, recurrent AF (≥4 episodes previous 12 mo) and episode of AF at enrollment <48 h | Proportion of pts remaining in SR at 1 y FU<br><br>63% propafenone<br>73% sotalol<br>35% PC<br>(p=0.001) | N/A | 4% ventricular arrhythmia with sotalol<br><br>Drug discontinuation due to AEs – 9% propafenone, 10% sotalol, 3% PC | Sotalol and propafenone appear to have similar efficacy and are superior to PC at maintaining SR at 1 y |
| Benditt DG, et al., 1999 (175) 10496434 | To evaluate the efficacy of sotalol for maintaining of SR | RCT, double-blind (253) | Sotalol 80 mg BID (59)<br><br>Sotalol 120 mg BID (63)<br><br>Sotalol 160 mg | Inclusion: symptomatic AF or atrial flutter and SR at time of randomization<br><br>Dose reduction in presence of renal dysfunction | Time to first recurrent symptomatic AF or atrial flutter after steady state (intention to treat)<br><br>27 d PC | Proportion of pts free of AF 12 mo<br><br>28% PC<br>30% sotalol 80 mg<br>40% sotalol 120 | Bradycardia and fatigue most common AEs<br><br>No cases of torsade de pointes in this study | Outpatient initiation in 27% |

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| | | | BID (62)<br><br>PC (69) | Exclusion: QT>450 ms, sinus rate <50, other QT prolonging drugs, renal failure (CrCl<40 mL/min), Hx of HF, uncorrected hypokalemia, asymptomatic AF, sick sinus syndrome without pacer, MI<2 mo, syncope, TIA/stroke | 106 d sotalol 80 mg<br>229 d sotalol 120 mg<br>175 d sotalol 160 mg | mg<br>45% sotalol 160 mg | | |
| Byrne-Quinn E, et al., 1970 (176)<br>4911757 | To evaluate the efficacy of quinidine for maintenance of SR | RCT, double-blind<br>(65) | Quinidine 1.2 g/d (28)<br><br>PC (37) | Inclusion: Pts hospitalized for AF with plan for cardioversion<br><br>Exclusion: digoxin stopped 24 h prior | Percentage of pts at FU in SR<br><br>24.3% PC<br>57% quinidine | N/A | 1 death presumed related to quinidine | Small sample size, variable FU period (5-15 mo) |
| Carunchio A, et al., 1995 (177)<br>7642012 | To evaluate the efficacy and safety of flecainide and sotalol for maintenance of SR | RCT, open-label<br>(66) | Flecainide acetate 200 mg/d (20)<br><br>Sotalol HCL 240 mg/d (20)<br><br>PC (26) | N/A | Arrhythmia free survival at 12 mo<br><br>70% flecainide<br>60% sotalol<br>27% PC<br><br>p=0.002 AAD vs. PC<br>p=0.163 flecainide vs. sotalol | N/A | N/A | Flecainide and sotalol have similar efficacy in prevention of recurrence of AF<br><br>Side effects common but serious AE uncommon in this FU period |
| Channer KS, et al., 2004 (178)<br>14720531 | To evaluate the efficacy of amiodarone to prevent recurrent AF after cardioversion | RCT, double-blind<br>(161) | Amiodarone (short-term) 200 mg/d for 8 wk after DCCV (62)<br><br>Amiodarone (long-term) 200 mg/d for 52 wk after DCCV (61)<br><br>PC (38) | Inclusion: Age >18 y and sustained AF>72 h<br><br>Exclusion: LVEF<20%, significant valve disease, female <50 y, thyroid, lung or liver disease, contraindication to anticoagulation | Percentage in SR at 1 y<br><br>49% long-term amiodarone<br>33% short-term (8 wk after DCCV) amiodarone<br>5% PC | Spontaneous conversion to SR 21% amiodarone and 0% in PC<br><br>SR rhythm at 8 wk after DCCV – 16% PC, 47% short-term amiodarone, 56% long-term amiodarone | AEs leading to discontinuation<br><br>3% PC<br>8% short-term amiodarone<br>18% long-term amiodarone | Amiodarone pre-Tx allows chemical cardioversion in 1/5 of pts with persistent AF and is more effective at maintaining SR after DCCV<br><br>Given the long-term AEs with amiodarone, 8 wk of adjuvant Tx suggested as option by authors |

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| CTAF,<br>Roy D, et al., 2000 (179)<br>10738049 | Low dose amiodarone would be more efficacious in preventing recurrent AF than sotalol or propafenone | RCT<br>(403) | Amiodarone 200 mg/d (201)<br><br>Sotalol 160 mg BID (101)<br><br>Propafenone 150 QID (101) | Symptomatic AF within previous 6 mo but not persistent AF>6mo | Recurrence of AF during FU (mean 16 mo)<br>35% amiodarone<br>63% sotalol or propafenone<br>(p<0.001) | N/A | AEs requiring drug discontinuation 18% amiodarone vs. 11% sotalol or propafenone group (p=0.06) | Amiodarone is more effective than sotalol or propafenone in preventing recurrent AF (with a trend toward higher side-effects) |
| DAFNE,<br>Touboul P, et al., 2003 (180)<br>12919771 | To determine the most appropriate dose of dronedarone for prevention of AF after DCCV | RCT, double-blind<br>(199) | Dronedarone 800 mg/d (54)<br><br>Dronedarone 1,200 mg/d (54)<br><br>Dronedarone 1600 mg/d (43)<br><br>PC (48) | Inclusion: age 21-85 y, pts with persistent AF (>72 h and <12 mo) scheduled for DCCV<br><br>Exclusion: Hx of torsade de pointes, QT>500 ms, severe bradycardia, AV block, NYHA class III or IV HF, LVEF<35, ICD, WPW syndrome | Time to first documented AF recurrence at 6 mo<br><br>60 d for dronedarone 400 mg BID<br>5.3 d for PC<br>(p=0.001) | Spontaneous conversion of AF with dronedarone 5.8 to 14.8% pts | Premature discontinuation 22.6% 1600 mg, 3.9% 800 mg | Small sample size, dose-finding study |
| DIAMOND,<br>Pedersen OD, et al., 2001 (181)<br>11457747 | To evaluate the efficacy of dofetilide to maintain SR in pt with LV dysfunction | RCT, double-blind<br>(506) | Dofetilide 500 mcg/d (249)<br><br>PC (257) | Inclusion: Persistent AF associated with either HF or recent acute MI<br><br>Dose reduction for renal insufficiency<br><br>Exclusion: HR: <50 bpm, QTc>460 ms (500 ms with BBB), K<3.6 or >5.5, CrCl<20 mL/min | Probability of maintaining SR at 1 y<br><br>79% dofetilide<br>42% with PC<br>(p<0.001) | No effect on all-cause mortality<br><br>Dofetilide associated with reduced rate of rehospitalization | Torsade de pointes occurred in 4 dofetilide pts (1.6%) | N/A |
| DIONYSOS,<br>Le Heuzey JY, et al., 2010 (182)<br>20384650 | To evaluate the efficacy and safety of amiodarone and dronedarone in pts with persistent AF | RCT, double-blind<br>(504) | Amiodarone 600 mg QD for 28 d then 200 mg QD (255)<br><br>Dronedarone 400 mg BID (249) | Age ≥21 y with documented AF for >72 h for whom CV and AAD were indicated and oral anticoagulation | Recurrence of AF (including unsuccessful CV) or premature study discontinuation at 12 mo<br>75.1% dronedarone, 58.8% amiodarone, HR: 1.59; 95% CI: 1.28-1.98; p<0.0001 | N/A | 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; | Dronedarone was less effective than amiodarone in decreasing AF recurrence, but had a better safety profile |

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| | | | | | Mainly driven by AF recurrence with dronedarone compared with amiodarone (63.5 vs. 42.0%) | | 95% CI: 0.60 to 1.07; p=0.129), and mainly driven by fewer thyroid, neurologic, skin, and ocular events in the dronedarone group | |
| Dogan A, et al., 2004 (183) 15255456 | To evaluate the efficacy of propafenone for maintenance of SR after cardioversion | RCT, Single-blind (110) | Propafenone 450 mg/d (58)<br><br>PC (52) | Recent onset or persistent AF<br><br>Exclusion: MI, HF, CABG<6 mo, severe COPD, LA thrombus, thyroid disease, inability to consent to DCCV | Percentage of AF recurrences at 15 mo<br><br>39% propafenone<br>65% PC | Spontaneous conversion with drug predicted lower chance of recurrence | Discontinuation due to side effects: 4 pts on propafenone and 1 PC (p=0.36) | Propafenone is more effective than PC for prevention of recurrent AF |
| EURIDIS, Singh BN, et al., 2007 (168) 17804843 | To assess the efficacy of dronedarone in maintenance of SR in pts with AF | RCT, double-blind (612) | Dronedarone 400 mg BID (411)<br><br>PC (201) | ≥1 episode AF in previous 3 mo, Age ≥2y | Time to the 1st recurrence of AF or atrial flutter<br>96 d dronedarone<br>41 d in the PC (p=0.01) | After AF recurrence, mean rate=117.5 bpm, PC=102.3 bpm, dronedarone (p<0.001) | N/A | Dronedarone was more effective than PC in maintaining SR and in reducing ventricular rate during recurrent AF |
| FAPIS, Chimienti M, et al., 1996 (184) 8607393 | To compare the safety of flecainide to propafenone for Tx of PAF | RCT, open-label (200) | Flecainide acetate 200 mg/d (97)<br><br>Propafenone HCL 450-900 mg/d (103) | Paroxysmal AF without structural heart disease | Probability of remaining free of AEs at 12 mo<br><br>77% flecainide<br>75% propafenone<br><br>1 VT in propafenone group<br>2 accelerated ventricular response with flecainide | Drug discontinuation<br><br>4 flecainide<br>5 propafenone | N/A | AEs appear occur at similar rate with propafenone and flecainide in this population with AF and without evidence of structural disease |
| GEFACA, Galperin J, et al., 2001 (185) 11907636 | To evaluate the efficacy of amiodarone for restoration and maintenance of SR | RCT, double-blind (50) | Amiodarone 200 mg/d (47)<br><br>PC (48) | Persistent AF>2 mo duration<br><br>Exclusion: paroxysmal AF, age >75 y, HR<50 bpm, LA>60 mm | Recurrent AF in 37% amiodarone and 80% PC group<br><br>Spontaneous conversion 34% with amiodarone and 0% PC | N/A | AEs 15% of pts on amiodarone | Amiodarone restored SR in 1/3 pts, increased success of DCCV, reduced and delayed recurrence of AF |

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| 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<br><br>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<br>p=NS | N/A | 5 pts quinidine/verapamil discontinued Tx due to noncardiac AEs, 3 pts in sotalol discontinued due to bradycardia<br>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)<br><br>Sotalol HCL 320 mg/d (85)<br><br>PC (83) | Symptomatic AF, successful chemical or DCCV if persistent | Percentage recurrence AF during FU<br>69/85 sotalol<br>45/86 propafenone<br>73/83 PC<br>(p<0.001) | N/A | N/A | Long-term results show superiority of propafenone (question methods of comparison) |
| Kuhlkamp, 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)<br><br>PC (197) | Inclusion: Persistent AF with successful cardioversion (DC or chemical)<br><br>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)<br>48.7% metoprolol XL<br>59.9% PC<br>(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<br><br>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)<br><br>Quinidine sulfate 1000-1500 mg/d (117) | Symptomatic PAF | Percentage of pts with reported episodes of symptomatic AF<br><br>72% flecainide<br>74.3% quinidine<br>(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<br><br>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:<br>Mortality<br>Pro-arrhythmia<br>AEs<br>AF recurrence | N/A | N/A | N/A |

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| | | | PC | | | | | |
| PALLAS, Connolly SJ, et al., 2011 (165) 22082198 | To assess whether dronedarone would reduce major vascular events in high-risk permanent AF | RCT, double-blind (3236) | Dronedarone 400 mg BID<br><br>PC | Age >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<40%, PAD or age >75 y, HTN & DM | Coprimary outcomes: 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<br><br>Unplanned CV hospitalization or death,<br>127 pts receiving dronedarone and 67 pts receiving PC (HR: 1.95; 95% CI: 1.45-2.62; p<0.001) | Hospitalization for HF occurred in 43 pts in the dronedarone group and 24 in the PC group (HR: 1.81; 95% CI: 1.10- 2.99; p=0.02) | Most common AEs were diarrhea, asthenic condition, nausea and vomiting, dizziness, dyspnea, and bradycardia<br><br>ALT>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 p=0.02 | Dronedarone increased rates of HF, stroke, and death from CV causes in pts with permanent AF who were at risk for major vascular events. |
| Piccini JP, et al., 2009 (191) 19744618 | To evaluate randomized trials of amiodarone and dronedarone for safety and efficacy in AF | Meta-analysis | 4 trials of amiodarone vs. PC<br><br>4 trials of dronedarone vs. PC<br><br>1 comparison of amiodarone vs. dronedarone | Randomized PC-controlled trials of amiodarone and dronedarone for maintenance of SR in pts with AF | OR: 0.12 amiodarone vs. PC (95% CI: 0.08-0.19)<br><br>OR: 0.79 dronedarone vs. PC (95% CI: 0.33-1.87) | N/A | Amiodarone trend towards increased mortality<br><br>Amiodarone greater number AEs than dronedarone | Dronedarone is less effective than amiodarone but has fewer AEs |

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| Plewan A, et al., 2001 (192) 11482924 | N/A | RCT, open-label (128) | Sotalol 160 mg/d<br><br>Bisoprolol fumarate 5 mg/d | Persistent AF (mean duration: 9 mo). N=128<br>Male: 62%. Age (mean, SD): 59, ±10<br>Structural heart disease: 72%. LAD: 48 mm. LVEF: 41% | At 8 mo:<br>Mortality<br>Pro-arrhythmia<br>AEs<br>AF recurrence | N/A | N/A | N/A |
| PRODIS, Crijns HJ, et al., 1996 (193) 8842506 | N/A | RCT, double-blind (56) | Disopyramide phosphate 750 mg/d<br><br>Propafenone HCL 900 mg/d | Persistent AF (mean duration: 5 mo). N=56<br>Male: 68%. Age (mean, SD): 60, ±11<br>Structural heart disease: 65%. LAD: 46 mm. LVEF: NS | At 6 mo:<br>Mortality<br>Pro-arrhythmia<br>AEs<br>AF recurrence | N/A | N/A | N/A |
| RAFT, Pritchett EL, et al., 2003 (194) 14556870 | Assess the efficacy and safety of sustained-released propafenone for maintenance of SR | RCT, double-blind (523) | Propafenone hydrochloride 450-850 mg/d (397)<br><br>PC (126) | Inclusion: Symptomatic AF (type not specified)<br>SR at time of randomization<br><br>Exclusion: Permanent AF, NYHA class III or IV HF, cardiac surgery <6 mo, MI<12 mo, WPW syndrome, 2nd or 3rd degree AV block, QRS>160 ms, HR<50 bpm, Hx of VF, VT or ICD | At 9 mo:<br>Mortality<br>Pro-arrhythmia<br>AEs<br>AF recurrence | N/A | N/A | N/A |
| Reimold SC, et al., 1993 (195) 8438741 | To compare the efficacy of propafenone and sotalol for maintenance of SR | RCT, open-label (100) | Propafenone HCL 675 mg/d (50)<br><br>Sotalol HCL 320 mg/d (50) | Pts with AF with previous AAD failure | Percentage with SR at 3, 6, and 12 mo<br>46%, 41%, 30% propafenone<br>49%, 46% sotalol | N/A | N/A | Propafenone and sotalol similar efficacy |
| Richiardi E, et al., 1992 (196) 1600529 | To evaluate the efficacy and safety of oral propafenone vs. quinidine at preventing AF | RCT, open-label (200) | Propafenone 900 mg/d<br><br>Quinidine 1000 mg/d | ≥3 AF episodes in past 6 mo<br><br>Exclusion: LA size >55 mm, hepatic or renal insufficiency, MI<30 d, pregnant, decompensated HF, thyroid dysfunction | SR at 6 mo<br>60% propafenone<br>56% quinidine<br><br>SR at 1 y<br>48% propafenone<br>42% quinidine | p=NS | N/A | 10% side effects propafenone<br><br>24% side-effects quinidine<br><br>(p=0.02) |
| SAFE-T, Singh BN, et | To assess the efficacy of | RCT, double-blind | Amiodarone 300 mg/d | Inclusion: Persistent AF>72 h including at time of | Pharmacological Conversion to SR | Sustained SR improved QOL | NS difference in AEs among the 3 groups | N/A |

 

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| al., 2005 (197)<br>15872201 | amiodarone and sotalol in converting AF and maintenance of SR | (665) | Sotalol 320 mg/d<br><br>PC | randomization & on oral anticoagulation<br><br>Exclusion: Paroxysmal AF or atrial flutter, NYHA class III or IV HF, CrCl<60 mL/min, intolerance to beta blockers, Hx of long QT syndrome | 27.1% amiodarone<br>24.2% sotalol<br>0.8% PC<br><br>Median Time to Recurrence AF (intention to treat)<br>487 d amiodarone<br>74 d sotalol<br>6 d PC<br>p<0.001 | and exercise capacity | | |
| SAFIRE-D, Singh S, et al., 2000 (198)<br>11067793 | To determine the efficacy and safety of dofetilide in converting AF or atrial flutter to SR and maintaining SR for 1 y | RCT, double-blind<br>(250) | Dofetilide 250-1000 mcg/d<br><br>PC | Inclusion: Age 18-85 y with AF or atrial flutter 2-26 wk duration<br><br>Exclusion: Sinus node dysfunction, QRS>180 ms, QT interval>400 ms (QT>500 ms with BBB), sinus rate<50 bpm, Hx of renal or hepatic disease, use of verapamil, diltiazem, QT prolonging drugs | Pharmacological Conversion Rate<br><br>6.1% 125 mcg BID<br>9.8% 250 mcg BID<br>29.9% 500 mcg BID<br>1.2% PC<br><br>p=0.015 250 mcg and p<0.001 500 mcg (vs. PC)<br><br>Probability of SR at 1 y<br><br>0.40 125 mcg BID<br>0.37 250 mcg BID<br>0.58 500 mcg BID<br>0.25 PC | N/A | 2 cases of torsade de pointes during initiation phase (0.8%)<br><br>1 sudden death (proarrhythmic) on Day 8 (0.4%) | In-hospital initiation and dosage adjustment based on QTc and CrCl to minimize proarrhythmic risk |
| SOPAT, Patten M, et al., 2004 (199)<br>15321697 | To assess the effectiveness of 2 AAD on frequency of AF | RCT, double-blind<br>(1033) | High-dose Quinidine sulfate 480 mg/d and verapamil 240 mg/d (263)<br><br>Low-dose Quinidine sulfate 320 mg/d and | Age 18-80 y, symptomatic PAF<br><br>Exclusion: cardiogenic shock, LA thrombus, MI or cardiac surgery <3 mo, UA, valve disease requiring surgery, ICD or pacemaker, sick sinus syndrome, 2nd or 3rd degree AV block, QTc>440 ms, bradycardia, | Time to 1st recurrence of symptomatic PAF or premature discontinuation<br><br>105.7 d PC<br>150.4 d high-dose quinidine/verapamil<br>148.9 d low-dose quinidine/verapamil | AF burden (% says with symptomatic AF)<br><br>6.1% PC<br>3.4% high dose<br>4.5% low dose<br>2.9% sotalol<br>(p=0.026) | 1 death and 1 VT event related to high-dose quinidine/verapamil<br><br>2 syncopal events related to sotalol | Quinidine/verapamil fixed combination similar efficacy to sotalol but with risk of SAEs |

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| | | | verapamil 160 mg/d (255)<br><br>Sotalol HCL 320 mg/d (264)<br><br>PC (251) | renal or liver dysfunction, hypokalemia, bundle branch block<br><br>Mean time under Tx 233 d | 145.6 d sotalol (p<0.001) | | | |
| Stroobandt R, et al., 1997 (200) 9052343 | To assess the efficacy of propafenone at maintaining sinus rhythm | RCT, double-blind (102) | Propafenone HCL 150 mg TID (77)<br><br>PC (25) | Age >18 y with AF, enrolled in maintenance phase after attempt at pharmacological conversion with IV propafenone (and if unsuccessful DCCV) | Proportion of pts free from recurrent symptomatic AF at 6 mo<br>67% propafenone<br>35% PC<br>(p<0.001) | N/A | NS difference in AEs | Evidence for the efficacy of propafenone in maintaining sinus rhythm after cardioversion. Short duration of FU (6 mo) |
| SVA-3, Pritchett EL, et al., 2000 (201) 10987602 | To assess the effectiveness of azimilide in reducing symptomatic AF or atrial flutter | RCT, double-blind (384) | Azimilide 50 mg, 100 mg, or 125 mg<br><br>PC | Inclusion: Age ≥18 y, Symptomatic AF in SR at time of randomization<br><br>Exclusion: Rest angina or UA, class IV CHF, Hx of torsade de pointes, QTc>440 ms, resting SR<50 bpm | Time to 1st symptomatic AF recurrence<br><br>Azimilide 100 mg/125 mg QD vs. PC, HR: 1.58; p=0.005 | N/A | 2 sudden deaths in azimilide groups and 1 case of torsade de pointes | Initiated in outpatient setting |
| Villani R, et al., 1992 (202) 1559321 | To compare the efficacy of amiodarone to disopyramide | RCT, open-label (76) | Amiodarone 200 mg/d (41)<br><br>Disopyramide phosphate 500 mg/d (35) | | Recurrence of AF at end of FU<br>57% disopyramide (13 mo)<br>32% amidarone (14 mo) | N/A | Disopyramide discontinued due to AE 14% <1 wk and another 14% by end of trial<br><br>8.5% developed hyperthyroidism | Amiodarone is more effective than disopyramide for prevention of recurrent AF |

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)

| Study Name, Author, Year | Study Type | Intervention (n) | Rhythm at Time of Initiation | Place of Initiation | Patient Population | Adverse Events |
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| Benditt D, et al., 1999 (175) 10496434 | Prospective dose finding study | Sotalol 80 BID (59)<br>Sotalol 120 BID (63)<br>Sotalol 160 BID (62)<br>PC (69) | SR | 50 pts - outpatient<br>134 pts - inpatient | Structural heart disease 57%<br><br>Exclusion: Hx of torsade de pointes, CHF, QT>450 ms, hypokalemia hypomagnesemia, bradycardia | No cases of VT/VF/torsade<br><br>QT>520 ms in 7 pts (4 in 120 mg BID and 3 in 160 mg BID)<br><br>Premature discontinuation due to AEs 25% inpatients, but 6% of outpatients (bradycardia predominantly) |
| Chung MK, at al., 1998 (203) 9669266 | Retrospective | Sotalol | Not documented | Inpatient | 120 inpatients admitted for sotalol initiation<br><br>Structural heart disease (80%) | 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)<br><br>20 (16.7%) with significant bradycardia<br><br>8 (6.7%) excessive QT prolongation |
| SAFE-T, Singh BN, et al., 2005 (197) 15872201 | Prospective RCT | Total 665<br>Amiodarone 267<br>Sotalol 261<br>Placebo 137 | AF | Outpatient | Initiated sotalol or amiodarone in the outpatient setting during AF<br><br>Excluded CHF class III or IV, Hx of long QT, CrCl<60 | 1 case torsade in sotalol group (nonfatal, time of occurrence not specified)<br><br>13 deaths/267 (6 sudden) amiodarone group<br>15 deaths/261 (8 sudden) sotalol group<br>3 deaths/137 (2 sudden) PC group<br>(no significant difference) |
| Zimetbaum PJ, et al., 1999 (204) 10072241 | Prospective | 172<br>Amiodarone 66 (38%)<br>Flecainide 45 (26%)<br>Sotalol 20 (12%)<br>Disopyramide 16 (9%)<br>Propafenone 11 (6%)<br>Quinidine 8 (5%)<br>Procainamide 6 (4%) | SR | Outpatient | Pts with AF in sinus at time of initiation started on oral antiarrhythmic medication<br><br>Received 1 or 2 doses of AAD in hospital or clinic and monitored for ≤8 h and then 10 d continuous loop event recorder<br><br>Exlusion: QTc>550 ms, NYHA class III or IV CHF, or pacemaker | 6 symptomatic AEs (none before d 4)<br><br>Class Ic<br>3 atrial flutter with 1:1 d 6 or 7<br>1 symptomatic brady d 4<br><br>Sotalol<br>1 symptomatic bradycardia d 7<br>1 QT prolongation 370-520 ms d 4 |

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| Hauser TH, et al., 2003 (205) 12804730 | Prospective | 409<br>Amiodarone 212 (51.8%)<br>Class Ic 127 (31.1%)<br>Propafenone 64 (15.6%)<br>Flecainide 63 (15.4%)<br>Sotalol 37 (9.0%)<br>Class IA 33 (8.1%)<br>Quinidine 8 (2%)<br>Disopyramide 16 (3.9%)<br>Procainamide 9 (2.2%) | SR | Outpatient | Pts with AF in sinus at time of initiation started on oral AAD with daily 30 s recording or with Sx | Amiodarone<br>2 Death (sudden) d 7 and d 9<br>3 Bradycardia requiring pacemaker d 6, 7, and 8<br>9 Bradycardia requiring dose reduction<br><br>Class Ic<br>Bradycardia d 7 and d 9 dose reduction<br><br>Sotalol – none<br><br>Quinidine<br>Death (sudden) d 3 |
| CTAF, Roy D, et al., 2000 (179) 10738049 | Prospective open-label RCT | 403<br>Amiodarone 201<br>Sotalol 101<br>Propafenone 101 | Sinus≈60% | Outpatient | Exclusion: QTc>480, bradycardia <50 bpm | Arrhythmic deaths – 3 amiodarone group (2 had been off the drug >1 y) and 1 in sotalol/propafenone group<br><br>Cardiac arrest due to torsade – propafenone<br><br>Serious bradyarrhythmias –<br>6 amiodarone<br>7 in sotalol/propafenone group<br>Time to event after initiation not specified<br><br>All events occurred beyond 2 d of drug initiation mostly bradyarrhythmias |
| Kochiadakis GE, et al., 2004 (187) 15589019 | N/A | 254<br>Sotalol 85<br>Propafenone 86<br>PC 83 | Sinus | Inpatient | N/A | No torsades noted<br>Sotalol - 3 bradycardia during loading phase<br>Propafenone – 1 bradycardia, 1 QRS widening |

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. Upsteam Therapy (Section 6.2.2)**

| Study Name, Author, Year | Study Aim | Study Type/ Size (N) | Intervention vs. Comparator (n) | Patient Population | Endpoints | | Comments |
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| | | | | | ***Primary Endpoint & Results*** | ***Secondary Endpoint & Results*** | |

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| ANTIPAF, Goette A, et al., 2012 (206) 22157519 | Effect of olmesartan on AF burden in pts with paroxysmal AF and no structural heart disease | Prospective, PC-controlled RCT | Olmesartan 40 mg QD (214)<br><br>PC (211) | Pts with PAF and no other indication for ACE inhibitor or ARB Tx | No difference in the 1° endpoint of AF burden (p=0.770) | No difference in QOL, time to 1st AF recurrence, time to persistent AF and hospitalizations | In pts with AF (2° prevention) but without structural disease, 1 y of ARB does not appear to decrease AF burden |
| GISSI-AF, 2009 (207) 20435196 | N/A | Prospective, PC-controlled, RCT | Valsartan (722)<br><br>PC (720) | AF and underlying CV disease, diabetes, or left atrial enlargement | Co-primary endpoints:<br>Time to first recurrence of AF, 295 d valsartan, 271 d PC<br><br>Proportion of pts who had >1 recurrence of AF>12 mo, 26.9% valsartan, 27.9% PC OR: 0.95; p=0.66 | N/A | Tx with valsartan not associated with reduced AF |
| Healey JS, et al., 2005 (208) 15936615 | Systematic review of all RCT evaluating the benefit of trials of ACE inhibitor and ARBs in prevention of AF | Meta-analysis | N/A | 11 studies included with 56,308 pts | ACE inhibitor and ARB reduced incidence of AF (RR: 0.28; p=0.0002)<br><br>Reduction in AF greatest in pts with HF (RR: 0.44; p=0.007)<br><br>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) | 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 |
| J-RHYTHM II, Yamashita T, et al., 2011 (208, 209) 21148662 | N/A | Open label, RCT | Candesartan<br><br>Amlodipine | Pts with PAF (2° prevention) and HTN | N/A | N/A | Tx of HTN by candesartan was not superior to amlodipine for reduction in AF frequency |
| Schneider MP, et al., 2010 (210) 20488299 | N/A | Meta-analysis | N/A | 23 studies included with 87,048 pts | N/A | N/A | N/A |

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)**

| Study Name, Author, Year | Study Aim | Study Type/ Size (N) | Intervention vs. Comparator (n) | Type of AF | Ablation Technique | Endpoints | AF Free at 1 y | | | Crossover Rate to RFA | Adverse Events | Study Limitations |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | ***Primary Endpoint & Results*** | **Ablation** | **AAD** | **P value** | | | |
| Krittayaphong R, et al., 2003 (211) 12866763 | To compare the efficacy of amiodarone to RFA for maintenance of SR | RCT (30) | RFA<br><br>Amiodarone | Paroxysmal and persistent | Circumferential PVI with anatomic isolation | Freedom from AF at 12 mo | 79% | 40% | 0.018 | Not stated | 1 stroke in RFA arm<br><br>46.7% AE in amiodarone arm | Small sample size, single center |
| RAAFT, Wazni OM, et al., 2005 (212) 15928285 | To determine whether PVI is feasible as 1st line Tx for symptomatic AF | RCT (70) | RFA (33)<br><br>AAD (37) | Paroxysmal | Segmental PVI with electrical isolation | Freedom from AF at 12 mo (Any recurrence of symptomatic AF or asymptomatic AF>15 s)<br><br>87% RFA<br>37% AAD | 87% | 37% | p<0.001 | 49% | Pulmonary vein stenosis 2 (6%) in RFA group | N/A |
| CACAF, Stabile G, et al., 2005 (213) 16214831 | Compare RFA to AAD for prevention of AF in pts who failed AAD | RCT (137) | RFA (68)<br><br>AAD – primarily amiodarone (69) | Paroxysmal and persistent | Circumferential PVI with anatomic isolation | Freedom from AF at 12 mo<br><br>55.9% RFA<br>8.7% AAD<br>p<0.001 | 56% | 9% | p<0.001 | 57% | 4.4% major complications RFA | N/A |

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| Oral H, et al., 2006 (214)<br>16908760 | Persistent AF Compare RFA to AAD for prevention of AF | RCT (146) | RFA (77)<br><br>Cardioversion with short-term amiodarone (69) | Persistent | Circumferential PVI with anatomic isolation | Monthly freedom from AF off AAD<br><br>74% RFA<br>58% control<br>(intention to treat)<br>p=0.05<br><br>70% RFA<br>4% control<br>(on-Tx analysis)<br>p<0.001 | 70%<br><br>74% | 4%<br>(on-Tx analysis)<br><br>58%<br>(intention to treat analysis) | p<0.001<br><br>p=0.05 | 77% | N/A | 77% AAD crossed over to RFA |
| APAF<br>Pappone C, et al., 2006 (128)<br>14707026 | Paroxysmal AF | RCT (198) | RFA (99)<br><br>AAD (99) | Paroxysmal | Circumferential PVI with anatomic isolation | Freedom from AF at: 12 mo<br>86% RFA<br>22% AAD | 86% | 22% | p<0.001 | 42% | RFA: 1 TIA, 1 pericardial effusion not requiring drainage<br><br>AAD:<br>3 proarrhythmia flecainide,<br>7 thyroid disfunction amiodarone,<br>11 sexual dysfunction sotalol | Single center, high crossover rate (42 of 99, 42%) |
| A4<br>Jais P, et al., 2008 (215)<br>19029470 | Compare RFA to AAD in paroxysmal AF | RCT (112) | RFA (53)<br><br>AAD (59) | Paroxysmal | Circumferential PVI with electrical isolation | Freedom from AF at 12 mo | 89% | 23% | p<0.001 | 63% | RFA: (155 ablation procedures, 2 tamponade, 2 groin, hematoma)<br><br>AAD: 1 hyperthyroidism | N/A |
| Forleo GB, et al., 2009 (216)<br>19443515 | Compare RFA to AAD in pts with | RCT (70) | RFA (35)<br><br>AAD (35) | Paroxysmal and persistent | Circumferential PVI with electrical | N/A | 80% | 43% | p=0.001 | Not stated | N/A | N/A |

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| | diabetes | | | | isolation | | | | | | | |
| Thermocool<br>Wilber DJ, et al., 2010 (217)<br>20103757 | Compare RFA to AAD in paroxysmal AF | RCT (167) | RFA (106)<br><br>AAD (61) | Paroxysmal | Circumferential PVI with electrical isolation | Freedom from protocol-defined Tx failure (documented symptomatic AF, repeat ablation >80 d after initial, changes in drug regimen post blanking, absence of entrance block) | 66% | 16% | p<0.001 | 59% | 4.9% RFA<br><br>8.8% AAD | Catheter ablation is more effective than medical Tx alone in preventing recurrent Sx of paroxysmal AF in pts who have already failed Tx with 1 AAD |
| STOP-AF<br>Packer DL, et al., 2013 (218)<br>23500312 | Assess efficacy of cryoballoon catheter ablation to AAD Tx in PAF | RCT (245) | Cryoballoon ablation (163)<br><br>AAD (flecainide, propafenone, sotalol) (82) | Paroxysmal | Circumferential PVI with electrical isolation | Freedom from CTF (no detected AF, no AF interventions, no use of non-study drugs) 3-mo blanking period<br><br>69.9% cryoballoon (57.7% off drug) vs.<br>7.3% AAD (intention to treat)<br><br>60.1% single ablation (n=98) | 70% | 7.3% | p<0.001 | 79% | All events: cryoablation 12.3%, AAD 14.6%<br><br>Procedure event rate 6.3%<br><br>Phrenic nerve paralysis 11.2% (29) with 86.2% (25) resolved at 12 mo | N/A |
| RAAFT2<br>Morillo C, et al., 2014 (219) | Compare RFA to AAD as first-line therapy for pts with AF | RCT (127) | RFA (66)<br>AAD (61) | Paroxysmal (98%%) and Persistent | Circumferential PVI with electrical isolation | AF, atrial flutter, or atrial tachycardia >30 s at 24 months | 45% | 28% | p=0.02 | 47% | 9% RFA<br><br>5% AAD | >20% additional ablation |
| MANTRA-PAF | Compare | RCT (294) | RFA (146) | Symptomati | Circumferen | Cumulative | 13% | 19% | p=0.10 | 36% | RFA group – 1 | No difference |

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| Cosedis Nielsen J, et al., 2012 (220) 23094720 | RFA to AAD as 1st-line Tx for pts with AF | | AAD (class Ic or class III) (148) | c Paroxysmal AF prior to AAD Tx | tial PVI with voltage abatement | burden of AF<br><br>Per visit burden at 24 mo<br><br>Freedom from AF at 24 mo | 9% AF burden at 24 mo<br><br>85% | 18% AF burden at 24 mo71% | p=0.007<br><br>p=0.01 | | death due to procedural stroke and 3 tamponade | in cumulative burden of AF endpoint and no difference in burden at 3, 6, 12 or 18 mo |

A4 indicates Catheter Ablation Versus Antiarrhythmic Drugs for Atrial Fibrillation; AAD, antiarrhythmic drug; AE, adverse event; AF, atrial fibrillation; APAF, Ablate and Pace in Atrial Fibrillation; CACAF, Catheter Ablation for the Cure of Atrial Fibrillation; CTF, chronic treatment failure; N/A, not applicable; PAF, paroxysmal atrial fibrillation; Pt, patient; PVI, pulmonary vein isolation; RAAFT, Radiofrequency Ablation for Atrial Fibrillation Trial; RCT, randomized controlled trial; RFA, radiofrequency ablation; RR, relative risk; SR, sinus rhythm; STOP-AF, Sustained Treatment of Paroxysmal Atrial Fibrillation; Sx, symptom; TIA, transient ischemic attack; and Tx, therapy.

**Data Supplement 16. Meta-Analyses and Surveys of AF Catheter Ablation (Section 6.3)**

| Study Name, Author, Year | Study Aim | Study Size (N) | Patient Population | Study Intervention | Endpoints | Follow-Up | Adverse Events |
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| Bonnano C, et al., 2010 (221) 19834326 | Systematic review of RCT of RFA vs. AAD | 8 studies (844 pts) | N/A | N/A | 98 (23.2%) of 421 pts in the Tx group and 324 (76.6%) of 423 pts in the control group had atrial tachyarrhythmia recurrence | N/A | N/A |
| Calkins H, et al., 2009 (222) 19808490 | Systematic review of radiofrequency ablation for AF | 63 studies included (8789 pts) | Mean age 55.5 y | N/A | Single-procedure success rate of ablation off AAD Tx was 57% (95% CI: 50% to 64%)<br><br>Multiple procedure success rate of AAD was 71% (95% CI: 65% to 77%)<br><br>Multiple procedure success rate on AAD or with unknown AAD usage was 77% (95% CI: 73% to 81%) | Major complication rate 4.9%<br><br>Stroke/TIA 0.5%<br>Mortality 0.7%<br>Cardiac tamponade 0.8%<br>PV stenosis 1.6%<br>LA/esophageal fistula 0.0% | N/A |
| Parkash R, et al., 2011 (223) 21332861 | Systematic review of RCT to assess optimal technique for RFA of AF | N/A | N/A | N/A | Freedom from AF after a single procedure<br><br>RFA was found to be favorable in prevention of AF over AADs in either paroxysmal (5 studies, RR: 2.26; 95% CI: 1.74-2.94) or persistent AF (5 studies, RR: 3.20; 95% CI: 1.29-8.41) | 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) | N/A |
| Piccini JP, et al., 2009 (224) 20009077 | Meta-analysis of all RCTs comparing PVI and medical Tx for the | N/A | N/A | N/A | Freedom from recurrent AF at 12 mo<br><br>PVI was associated with markedly increased odds of freedom | N/A | Among those randomly assigned to PVI, 17% required a repeat PVI ablation before 12 mo. The |

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| | maintenance of sinus rhythm | | | | from AF at 12 mo of FU (n=266/344 [77%] vs. n=102/346 [29%]; OR: 9.74; 95% CI: 3.98-23.87) | | rate of major complications was 2.6% (n=9/344) in the catheter ablation group |

AAD indicates antiarrhythmic drug; AF, atrial fibrillation; ; FU, follow-up; LA, left atrial; N/A, not applicable; OR, odds ratio; pts, patients; PV, pulmonary vein; PVI, pulmonary vein isolation; RCT, randomized controlled trial; RFA, radiofrequency ablation; RR, relative risk; TIA, transient ischemic attack; and Tx, therapy.

**Data Supplement 17. Specific Patient Groups (Section 7)**

| Study | Aim of study | Study Size | Patient Population / Inclusion & Exclusion Criteria | Endpoint(s) | Statistical Analysis Reported | CI and/or P values | OR/HR/RR/ Other | Study Conclusion |
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| Roy D, et al., 2008 (225) 18565859 | 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 | 1,376 (682 in rhythm-control group and 694 in rate-control group) | 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<br><br>Exclusion criteria: Persistent AF for ≥12 mo, a reversible cause of AF or HF, decompensated HF within 48 h prior to intended randomization, use of AADs for other arrhythmias, 2nd degree or 3rd degree AVB (bradycardia of <50 bpm), Hx of the long-QT syndrome, previous ablation of an AV node, anticipated cardiac transplantation within 6 mo, renal failure requiring dialysis, lack of birth control in women of child-bearing potential, estimated life expectancy of <1 y, and an age <18 y | 1° outcome was time to death from CV causes | The 1° outcome, death from CV causes, occurred in 182 pts (27%) in the rhythm-control group and 175 pts (25%) in the rate-control group<br><br>Death from any cause (32% in the rhythm-control group and 33% in the rate-control group)<br><br>Ischemic or hemorrhagic stroke 3% and 4%, respectively<br><br>Worsening HF (defined as HF requiring hospitalization, administration of an IV diuretic, or change in Tx strategy)<br><br>Composite outcome of death from CV causes, stroke, or worsening HF | None of the 2° outcomes differed significantly between the Tx groups<br><br>95% CI: 0.86-1.30; p=0.53<br><br>95% CI: 0.80-1.17; p=0.73<br><br>95% CI: 0.40-1.35; p=0.32<br><br>95% CI: 0.72-1.06; p=0.17<br><br>95% CI: 0.77-1.06; p=0.20 | HR: 1.06<br><br>HR: 0.97<br><br>HR: 0.74<br><br>HR: 0.87<br><br>HR: 0.90 | The routine strategy of rhythm control does not reduce the rate of death from CV causes, as compared with a rate-control strategy in pts with AF and CHF |

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| AFFIRM, Olshansky B, et al., (163) 15063430 | To evaluate and compare several drug classes for long-term ventricular rate control | 2027 | Inclusion criteria: (All criteria must have been met). Episode of AF documented on EKG or rhythm strip within last 6 wk, ≥65 y or <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 <25% by echocardiogram (unless paced or LBBB present), or LVEF<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 <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<br><br>Exclusion criteria: Not presented. Based on the judgment that certain therapies are contraindicated or inclusion would confound the result. Criteria included cardiac, other medical, and nonmedical | Overall rate control with various drugs (average FU 3.5±1.3 y) | 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<br><br>Multivariate analysis revealed a significant association between 1st drug class and several clinical variables, including gender, Hx of CAD, pulmonary disease, CHF, HTN, qualifying episode being the 1st episode of AF, and baseline heart rate | N/A | N/A | 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 |

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| ANDROMEDA, Kober L, et al., 2008 (171) 18565860 | To evaluate the efficacy of dronedarone in reducing hospitalization due to CHF in pts with symptomatic HF | 627 | 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<br><br>Exclusion criteria: LV wall motion index of >1.2 (approximating an EF of >35%), acute MI within 7 d prior to screening, a heart rate <50 bpm, PR interval >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 >500 ms, a serum potassium level <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 | The 1° endpoint was the composite of death from any cause or hospitalization for HF | 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<br><br>After additional 6 mo, 42 pts in dronedarone group (13.5%) and 39 pts in PC group (12.3%) died<br><br>The 1° 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<br><br>p=0.60; 95% CI: 0.73-1.74<br><br>p=0.12; 95% CI: 0.92-2.09 | HR: 2.13<br><br>HR: 1.13<br><br>HR: 1.38 | 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 |

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| RACE II<br>Van Gelder IC, et al., 2010 (167)<br>20231232 | 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)<br><br>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<br><br>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)<br><br>Frequencies of Sx and AEs were similar in the 2 groups | Absolute risk difference, -2.0%<br><br>Absolute risk difference, CI: -7.6-3.5; p<0.001<br><br>90% CI: 0.58-1.21; p=0.001<br><br>p<0.001 | HR: 0.84 | Lenient rate control is as effective as strict rate control and easier to achieve in pts with permanent AF |
| Gaita F, et al., 2007 (226)<br>17531584 | 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<br><br>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<br><br>10 of these 16 success pts were off AAD Tx at final evaluation<br><br>77% success rate in PAF compared with 50% in the subgroup with permanent AF | NYHA FC in those achieving NSR 1.2±0.5 vs. 1.7±0.7 before the procedure, p=0.003 | N/A | RFCA proved a safe and effective therapeutic option for AF, improved functional status, and was able to reduce or postpone the need for long-term pharmacologic Tx |

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| 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<br>Mean age 55±10 y<br>Mean AF duration was 5.4±3.6 y<br>AF was paroxysmal in 14 (52%), persistent in 9 (33%), and permanent in 4 (15%)<br>Mean FU of 341±237 d | Maintenance of sinus rhythm after PV antrum isolation | 13 pts (48%) had AF recurrence<br><br>5 of the 13 with recurrence maintained sinus rhythm with AADs, 1 of 13 remained in persistent AF, 7 of 13 underwent a second PV antrum isolation. After 2nd ablation: 5 pts remained in SR<br><br>Final success rate=70% (19/27)<br><br>2 pts had recurrence after 2nd ablation; 1 maintained SR with AADs and 1 remained in persistent AF | 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<br><br>Paroxysmal AF=21 (64%) pts had paroxysmal AF<br><br>Persistent/permanent AF=12 (36%) had persistent/permanent AF<br><br>Duration AF=6.2±5.2 y<br>Average EF=0.63±0.12<br>Average left atrial volume index was 70±24 $mL/m^2$<br>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 periprocedureal 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 |

 

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| Di Donna P, et al., 2010 (229) 20173211 | Assess the outcome of a multicentre HCM cohort following RFCA for symptomatic AF refractory to medical Tx | 61 | Age 54±13 y;<br>Time from AF onset 5.7±5.5 y<br>Paroxysmal AF=35; (57%)<br>Recent persistent AF=15; (25%)<br>Long-standing persistent AF=11; (18%)<br>Ablation scheme: pulmonary vein isolation plus linear lesions<br>32 of 61 pts, 32 (52%) required redo procedures.<br>Antiarrhythmic Tx was maintained in 22 (54%)<br>FU: 29±16 mo<br>41 (67%) NSR at FU | N/A | In pts in NSR there was marked improvement in NYHA class (1.2±0.5 vs. 1.9±0.7 at baseline; p<0.001).<br>In pts (33%), with AF recurrence, there was less marked, but still significant, improvement following RFCA (NYHA class 1.8±0.7 vs. 2.3±0.7 at baseline; p=0.002) | Independent predictors of AF recurrence: increased left atrium volume HR per unit increase 1.009, 95% CI: 1.001-1.018; p=0.037, and NYHA class (HR: 2.24; 95% CI: 1.16 to 4.35; p=0.016) | N/A | RFCA was successful in restoring long-term sinus rhythm and improving symptomatic status in most HCM pts with refractory AF, including the subset with proven sarcomere gene mutations, although redo procedures were often necessary. Younger HCM pts with small atrial size and mild Sx proved to be the best RFCA candidates, likely due to lesser degrees of atrial remodelling |

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.

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