2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society

Developed in Collaboration With the Society of Thoracic Surgeons

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Preamble

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

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

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

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

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

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

Table 1. Applying Classification of Recommendations and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT: CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/Test: COR III: No benefit — Not Helpful; COR III: Harm — Excess Cost w/o Benefit or Harmful Treatment: No Proven Benefit; Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable 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 COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B 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.

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

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

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

The ACC/AHA practice guidelines are intended to assist clinicians in clinical decision making by describing a range of generally acceptable approaches to the diagnosis, management, and prevention of specific diseases or conditions. The guidelines attempt to define practices that meet the needs of most patients in

most circumstances. The ultimate judgment about care of a particular patient must be made by the clinician and patient in light of all the circumstances presented by that patient. As a result, situations may arise in which deviations from these guidelines may be appropriate. Clinical decision making should involve consideration of the quality and availability of expertise in the area where care is provided. When these guidelines are used as the basis for regulatory or payer decisions, the goal should be improvement in quality of 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. 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 this guideline 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 the 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. The reader is encouraged to consult the full-text guideline[4] for additional guidance and details about atrial fibrillation (AF), because the executive summary contains mainly the recommendations.

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

1. Introduction

1.1. Methodology and Evidence Review

The recommendations listed in this document are, whenever possible, evidence based. An extensive evidence review was conducted, focusing on 2006 through October 2012 and selected other references through March 2014. The relevant data are included in evidence tables in the Online Data Supplement. Searches were extended to studies, reviews, and other evidence conducted in human subjects, published in English, and accessible through PubMed, EMBASE, Cochrane, Agency for Healthcare Research and Quality Reports, and other selected databases relevant to this guideline. Key search words included but were not limited to the following: *age*, *antiarrhythmic, atrial fibrillation, atrial remodeling, atrioventricular conduction, 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 writing committee reviewed documents related to AF previously published by the ACC and AHA. References selected and published in this document are representative and not all-inclusive.

1.2. Organization of the Writing Committee

The 2014 AF writing committee was composed of clinicians with broad expertise related to AF and its treatment, including adult cardiology, electrophysiology, cardiothoracic surgery, and heart failure (HF). The writing committee was assisted by staff from the ACC and AHA. Under the guidance of the Task Force, the Heart Rhythm Society was invited to be a partner organization and provided representation. The writing

committee also included a representative from the Society of Thoracic Surgeons. The rigorous methodological policies and procedures noted in the Preamble differentiate ACC/AHA guidelines from other published guidelines and statements.

1.3. Document Review and Approval

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

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

1.4. Scope of the Guideline

The task of the 2014 writing committee was to establish revised guidelines for optimum management of AF. The new guideline incorporates new and existing knowledge derived from published clinical trials, basic science, and comprehensive

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 7)	NHLBI	2003[9]
Assessment of Cardiovascular Risk in Asymptomatic Adults	ACC/AHA	2010[10]
Coronary Artery Bypass Graft Surgery	ACC/AHA	2011[11]
Hypertrophic Cardiomyopathy	ACC/AHA	2011[12]
Percutaneous Coronary Intervention	ACC/AHA/SCAI	2011[13]
Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease	AHA/ACC	2011[14]
Atrial Fibrillation*	CCS	2012[15]
Atrial Fibrillation	ESC	2012[16]
Stable Ischemic Heart Disease	ACC/AHA/ACP/AATS/PCNA/SCAI/STS	2012[17]
Antithrombotic Therapy	ACCP	2012[18]
Device-Based Therapy	ACC/AHA/HRS	2012[19]
Heart Failure	ACC/AHA	2013[20]
ST-Elevation Myocardial Infarction	ACC/AHA	2013[21]
Unstable Angina/Non-ST-Elevation Myocardial Infarction	ACC/AHA	2014[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	2013[8a,8b]
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; ACCP, American College of Chest Physicians; ACP, American College of Physicians; AF, atrial fibrillation; AHA, American Heart Association; AHRQ, Agency for Healthcare Research and Quality; ASA, American Stroke Association; CCS, Canadian Cardiology Society; ECAS, European Cardiac Arrhythmia Society; EHRA, European Heart Rhythm Association; ESC, European Society of Cardiology; HRS, Heart Rhythm Society; JNC, Joint National Committee; NHLBI, National Heart, Lung, and Blood Institute; PCNA, Preventive Cardiovascular Nurses Association; SCAI, Society for Cardiovascular Angiography and Interventions; STS, Society of Thoracic Surgeons; and TOS, The Obesity Society.

Table 3. Definitions of AF: A Simplified Scheme

Term	Definition
Paroxysmal AF	• AF that terminates spontaneously or with intervention within 7 d of onset. • Episodes may recur with variable frequency.
Persistent AF	• Continuous AF that is sustained >7 d.
Long-standing persistent AF	• Continuous AF >12 mo in duration.
Permanent AF	• The term "permanent AF" is used when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm. • Acceptance of AF represents a therapeutic attitude on the part of the patient and clinician rather than an inherent pathophysiological attribute of AF. • Acceptance of AF may change as symptoms, 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.

review articles, along with evolving treatment strategies and new drugs. This guideline supersedes the "ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation"[5] and the 2 subsequent focused updates from 2011.[6,7] 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.[8a,8b]

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

2. Clinical Characteristics and Evaluation of AF

2.1. AF Classification

AF may be described in terms of the duration of episodes using a simplified scheme shown in Table 3.[5,29,30] Implanted loop recorders, pacemakers, and defibrillators offer the possibility of reporting frequency, rate, and duration of abnormal atrial rhythms, including AF.[31,32] Episodes often increase in frequency and duration over time.

2.2. Mechanisms of AF and Pathophysiology

AF occurs when structural and/or electrophysiological abnormalities alter atrial tissue to promote abnormal impulse formation and/or propagation (Figure 1). These abnormalities are caused by diverse pathophysiological mechanisms,[29,33,34] such that AF represents a final common phenotype for multiple disease pathways and mechanisms that are incompletely understood.

2.3. Risk Factors and Associated Heart Disease

Multiple clinical risk factors, electrocardiographic and echocardiographic features, and biochemical markers are associated with an increased risk of AF (Table 4).

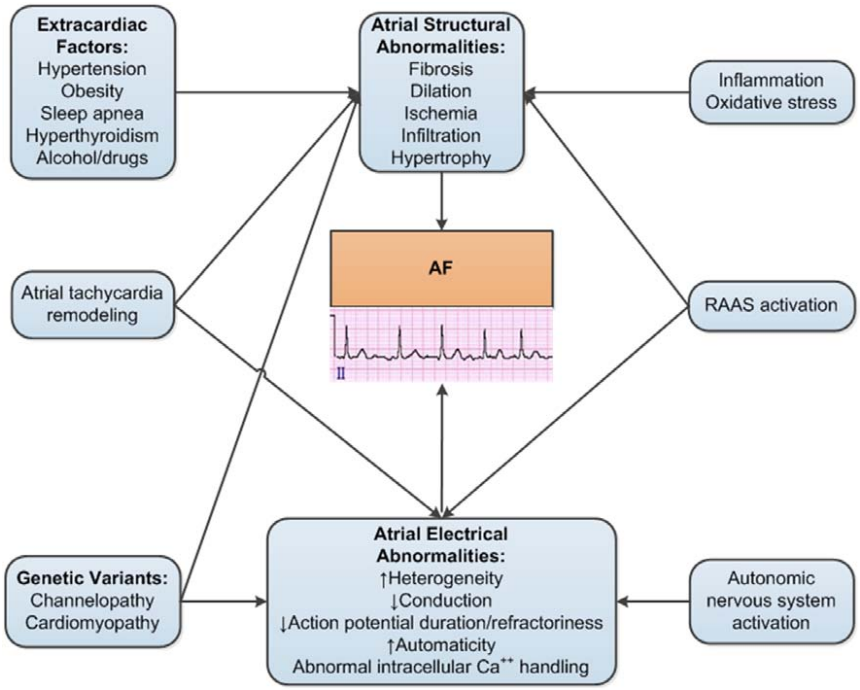

Figure 1. Mechanisms of AF. AF indicates atrial fibrillation; Ca^{++} ionized calcium; and RAAS, renin-angiotensin-aldosterone system.

Table 4. Selected Risk Factors and Biomarkers for AF

Clinical Risk Factors	References
Increasing age	35
Hypertension	35
Diabetes mellitus	35
MI	35
VHD	35
HF	35,36
Obesity	37–39
Obstructive sleep apnea	39
Cardiothoracic surgery	40
Smoking	41
Exercise	42–44
Alcohol use	45–47
Hyperthyroidism	48–50
Increased pulse pressure	51
European ancestry	52
Family history	53
Genetic variants	54–57
ECG	
LVH	58
Echocardiographic	
LA enlargement	58,59
Decreased LV fractional shortening	58
Increased LV wall thickness	58
Biomarkers	
Increased CRP	60,61
Increased BNP	62,63

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

2.4. Clinical Evaluation: Recommendation

See Appendix 3 for information on initial clinical evaluation in patients with AF.

Class I

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

3. Thromboembolic Risk and Treatment

3.1. Risk-Based Antithrombotic Therapy: Recommendations

See Table 5 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 relative risks 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.[64–67] (*Level of Evidence: B*)**
3. **In patients with nonvalvular AF, the CHA_2DS_2-VASc* score is recommended for assessment of stroke risk.[68–70] (*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.[71–73] (*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)[68–70] (*Level of Evidence: A*), dabigatran[74] (*Level of Evidence: B*), rivaroxaban[75] (*Level of Evidence: B*), or apixaban.[76] (*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.[77–79] (*Level of Evidence: A*)**
7. **For patients with nonvalvular AF unable to maintain a therapeutic INR level with warfarin, use of a direct thrombin or factor Xa inhibitor (dabigatran, rivaroxaban, or apixaban) is recommended. (*Level of Evidence: C*)**
8. **Reevaluation of the need for and choice of antithrombotic therapy at periodic intervals is recommended to reassess stroke and bleeding risks. (*Level of Evidence: C*)**
9. **Bridging therapy with unfractionated heparin or low-molecular-weight heparin (LMWH) is recommended for patients with AF and a mechanical heart valve undergoing procedures that require interruption of warfarin. Decisions on bridging therapy should balance the risks of stroke and bleeding. (*Level of Evidence: C*)**
10. **For patients with AF without mechanical heart valves who require interruption of warfarin or new anticoagulants for procedures, decisions about bridging therapy (LMWH or unfractionated heparin) should balance the risks of stroke and bleeding and the duration of time a patient will not be anticoagulated. (*Level of Evidence: C*)**
11. **Renal function should be evaluated before initiation of direct thrombin or factor Xa inhibitors and should be reevaluated when clinically indicated and at least annually.[80–82] (*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*)**

*CHA_2DS_2-VASc indicates Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65 to 74 years, Sex category.

Table 5. Summary of Recommendations for Risk-Based Antithrombotic Therapy

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
Selection of antithrombotic therapy based on risk of thromboembolism	I	B	64–67
CHA_2DS_2-VASc score recommended to assess stroke risk	I	B	68–70
Warfarin recommended for mechanical heart valves and target INR intensity based on type and location of prosthesis	I	B	71–73
With prior stroke, TIA, or CHA_2DS_2-VASc score ≥2, oral anticoagulants recommended. Options include:			
Warfarin	I	A	68–70
Dabigatran, rivaroxaban, or apixaban	I	B	74–76
With warfarin, determine INR at least weekly during initiation of therapy and monthly when stable	I	A	77–79
Direct thrombin or factor Xa inhibitor recommended if unable to maintain therapeutic INR	I	C	N/A
Reevaluate the need for anticoagulation at periodic intervals	I	C	N/A
Bridging therapy with UFH or LMWH recommended with a mechanical heart valve if warfarin is interrupted. Bridging therapy should balance risks of stroke and bleeding	I	C	N/A
For patients without mechanical heart valves, bridging therapy decisions should balance stroke and bleeding risks against duration of time patient will not be anticoagulated	I	C	N/A
Evaluate renal function before initiation of direct thrombin or factor Xa inhibitors, and reevaluate when clinically indicated and at least annually	I	B	80–82
For atrial flutter, antithrombotic therapy is recommended as for AF	I	C	N/A
With nonvalvular AF and CHA_2DS_2-VASc score of 0, it is reasonable to omit antithrombotic therapy	IIa	B	80,81
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	82
With nonvalvular AF and a CHA_2DS_2-VASc score of 1, no antithrombotic therapy or treatment with oral anticoagulant or aspirin may be considered	IIb	C	N/A
With moderate-to-severe CKD and CHA_2DS_2-VASc scores ≥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
After coronary revascularization in patients with CHA_2DS_2-VASc score ≥2, it may be reasonable to use clopidogrel concurrently with oral anticoagulants but without aspirin	IIb	B	83
Direct thrombin dabigatran and factor Xa inhibitor rivaroxaban are not recommended in patients with AF and end-stage CKD or on dialysis because of a lack of evidence from clinical trials regarding the balance of risks and benefits	III: No Benefit	C	74–76, 84–86
Direct thrombin inhibitor dabigatran should not be used with a mechanical heart valve	III: Harm	B	87

*See the 2011 PCI guideline for type of stent and duration of DAPT recommendations.[13]

AF indicates atrial fibrillation; BMS, bare-metal stent; 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 to 74 years, Sex category; CKD, chronic kidney disease; COR, Class of Recommendation; CrCl, creatinine clearance; DAPT, dual antiplatelet therapy; INR, international normalized ratio; LMWH, low-molecular-weight heparin; LOE, Level of Evidence; N/A, not applicable; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; and UFH, unfractionated heparin.

Class IIa

1. **For patients with nonvalvular AF and a CHA_2DS_2-VASc score of 0, it is reasonable to omit antithrombotic therapy.[80,81] (*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 chronic kidney disease (CKD) (creatinine clearance <15 mL/min) or are on hemodialysis, it is reasonable to prescribe warfarin (INR 2.0 to 3.0) for oral anticoagulation.[82] (*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 (eg, dabigatran, rivaroxaban, or apixaban), but safety and efficacy have not been established. (*Level of Evidence: C*)**
3. **In patients with AF undergoing percutaneous coronary intervention,† bare-metal stents may be considered to minimize the required duration of dual antiplatelet therapy. Anticoagulation may be interrupted at the time of the procedure to reduce the risk of bleeding at the site of peripheral arterial puncture. (*Level of Evidence: C*)**

†See the 2011 percutaneous coronary intervention guideline for type of stent and duration of dual antiplatelet therapy recommendations.[13]

4. **Following coronary revascularization (percutaneous or surgical) in patients with AF and a CHA_2DS_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.[83] (*Level of Evidence: B*)**

Class III: No Benefit

1. **The direct thrombin inhibitor dabigatran and the factor Xa inhibitor rivaroxaban are not recommended in patients with AF and end-stage CKD or on dialysis because of the lack of evidence from clinical trials regarding the balance of risks and benefits.[74–76,84–86] (*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.[87] (*Level of Evidence: B*)**

3.2. Risk Stratification Schemes ($CHADS_2$ and CHA_2DS_2-VASc)

One meta-analysis has stratified ischemic stroke risk among patients with nonvalvular AF using the following scoring systems: AF Investigators,[88] $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Prior Stroke or TIA or Thromboembolism [doubled]),[89] or 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 to 74 years, Sex category) (Table 6).

3.3. Considerations in Selecting Anticoagulants

For patients with CKD, dose modifications of the new agents are available (Table 7); 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.[82]

3.4. Cardiac Surgery—Left Atrial Appendage Occlusion/Excision: Recommendation

Class IIb

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

4. Rate Control: Recommendations

See Table 8 for a summary of recommendations for this section and Table 9 for common medication dosages for rate control of AF.

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.[93–95] (*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.[96–99] (*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*)**

Table 6. 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		Stroke Risk Stratification With the $CHADS_2$ and CHA_2DS_2-VASc Scores	
	Score		Adjusted Stroke Rate (% per y)
$CHADS_2$		$CHADS_2$*	
Congestive HF	1	0	1.9
Hypertension	1	1	2.8
Age ≥75 y	1	2	4.0
Diabetes mellitus	1	3	5.9
Stroke/TIA/TE	2	4	8.5
Maximum score	6	5	12.5
		6	18.2
CHA_2DS_2-VASc		CHA_2DS_2-VASc†	
Congestive HF	1	0	0
Hypertension	1	1	1.3
Age ≥75 y	2	2	2.2
Diabetes mellitus	1	3	3.2
Stroke/TIA/TE	2	4	4.0
Vascular disease (prior MI, PAD, or aortic plaque)	1	5	6.7
Age 65–74 y	1	6	9.8
Sex category (ie, female sex)	1	7	9.6
Maximum score	9	8	6.7
		9	15.20

*These adjusted stroke rates are based on data for hospitalized patients with AF and were published in 2001.[89] 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.[16,30,68,90,91] 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; MI, myocardial infarction; PAD, peripheral artery disease; TE, thromboembolism; and TIA, transient ischemic attack.[90,91]

Table 7. Dose Selection of Oral Anticoagulant Options for Patients With Nonvalvular AF and CKD (Based on Prescribing Information for the United States)*

Renal Function	Warfarin[92]	Dabigatran†[74]	Rivaroxaban†[75]	Apixaban†[76]
Normal/mild impairment	Dose adjusted for INR 2.0–3.0	150 mg BID (CrCl >30 mL/min)	20 mg QD with the evening meal (CrCl >50 mL/min)	5.0 or 2.5 mg BID‡
Moderate impairment	Dose adjusted for INR 2.0–3.0	150 mg BID (CrCl >30 mL/min)	15 mg QD with the evening meal (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 QD with the evening meal (CrCl 15–30 mL/min)	No recommendation. See Section 4.2.2.2 in the full-text guideline¶
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 in the full-text guideline¶
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 in the full-text guideline¶#

*Renal function should be evaluated before initiation of direct thrombin or factor Xa inhibitors and should be reevaluated when clinically indicated and at least annually. CrCl should be measured using the Cockcroft-Gault method.

†The concomitant use of P-glycoprotein inducers or inhibitors with dabigatran or the concomitant use of dual P-glycoprotein and strong CYP3A4 inducers or inhibitors with either rivaroxaban or apixaban, particularly in the setting of CKD, may require dosing adjustment or avoidance of concomitant drug use (see the FDA drug label at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202155s002lbl.pdf, Section 8.6 in the full-text guideline).

‡Use apixaban 2.5 mg BID if any 2 patient characteristics are present: Cr ≥1.5 mg/dL, ≥80 y of age, body weight ≤60 kg.[76] Apixaban is not recommended in patients with severe hepatic impairment.

§Dose-adjusted warfarin has been used, but observational data on safety and efficacy are conflicting.

‖Modeling studies suggest that dabigatran 75 mg BID might be safe for patients with CrCl 15–30 mL/min, but this has not been validated in a prospective cohort. Some countries outside the United States use 110 mg BID.[74]

¶No published studies support a dose for this level of renal function.

#In patients with end-stage CKD on stable hemodialysis, prescribing information indicates the use of apixaban 5 mg BID with dose reduction to 2.5 mg BID if the patient is ≥80 y of age or body weight is ≤60 kg.

AF indicates atrial fibrillation; BID, twice daily; CKD, chronic kidney disease; Cr, creatinine; CrCl, creatinine clearance; FDA, Food and Drug Administration; INR, international normalized ratio; and QD, once daily.

Class IIa

1. **A heart rate control (resting heart rate <80 beats per minute [bpm]) strategy is reasonable for symptomatic management of AF.[95,100] (*Level of Evidence: B*)**
2. **Intravenous amiodarone can be useful for rate control in critically ill patients without pre-excitation.[101–103] (*Level of Evidence: B*)**
3. **Atrioventricular (AV) nodal ablation with permanent ventricular pacing is reasonable to control heart rate when pharmacological therapy is inadequate and rhythm control is not achievable.[104–106] (*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 left ventricular systolic function is preserved.[100] (*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.[107] (*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, myocardial infarction, systemic embolism, or cardiovascular death.[108,109] (*Level of Evidence: B*)**

5. Rhythm Control: Recommendations

See Table 10 for a summary of recommendations for rhythm control.

5.1. Prevention of Thromboembolism

Class I

1. **For patients with AF or atrial flutter of 48 hours' duration or longer, or when the duration of AF is unknown, anticoagulation with warfarin (INR 2.0 to 3.0) is recommended for at least 3 weeks before and 4 weeks after cardioversion, regardless of the CHA_2DS_2-VASc score and the method (electrical or pharmacological) used to restore sinus rhythm.[110–113] (*Level of Evidence: B*)**
2. **For patients with AF or atrial flutter of more than 48 hours' duration or unknown duration that requires immediate cardioversion for hemodynamic instability,**

Table 8. 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	93–95
IV beta blocker or nondihydropyridine calcium channel blocker is recommended to slow ventricular heart rate in the acute setting in patients without pre-excitation. In hemodynamically unstable patients, electrical cardioversion is indicated	I	B	96–99
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	95,100
IV amiodarone can be useful for rate control in critically ill patients without pre-excitation	IIa	B	101–103
AV nodal ablation with permanent ventricular pacing is reasonable when pharmacological therapy is inadequate and rhythm control is not achievable	IIa	B	104–106
A lenient rate-control strategy (resting heart rate <110 bpm) may be reasonable when patients remain asymptomatic and LV systolic function is preserved	IIb	B	100
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	107
Dronedarone should not be used to control ventricular rate with permanent AF	III: Harm	B	108,109

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

anticoagulation should be initiated as soon as possible and continued for at least 4 weeks after cardioversion unless contraindicated. (*Level of Evidence: C*)

3. For patients with AF or atrial flutter of less than 48 hours' duration and with high risk of stroke, intravenous heparin or LMWH, or administration of a factor Xa or direct thrombin inhibitor, is recommended as soon as possible before or immediately after cardioversion, followed by long-term anticoagulation therapy. (*Level of Evidence: C*)
4. Following cardioversion for AF of any duration, the decision about long-term anticoagulation therapy should be based on the thromboembolic risk profile (Section 3). (*Level of Evidence: C*)

Class IIa

1. For patients with AF or atrial flutter of 48 hours' duration or longer or of unknown duration who have not been anticoagulated for the preceding 3 weeks, it is reasonable to perform transesophageal echocardiography before cardioversion and proceed with cardioversion if no left atrial thrombus is identified, including in the left atrial appendage, provided that anticoagulation is achieved before transesophageal echocardiography and maintained after cardioversion for at least 4 weeks.[114] (*Level of Evidence: B*)
2. For patients with AF or atrial flutter of 48 hours' duration or longer or when duration of AF is unknown, anticoagulation with dabigatran, rivaroxaban, or apixaban is reasonable for at least 3 weeks before and 4 weeks after cardioversion.[115–117] (*Level of Evidence: C*)

Class IIb

1. For patients with AF or atrial flutter of less than 48 hours' duration who are at low thromboembolic risk, anticoagulation (intravenous heparin, LMWH, or a new oral anticoagulant) or no antithrombotic therapy may be considered for cardioversion, without the need for postcardioversion oral anticoagulation.[118] (*Level of Evidence: C*)

5.2. Direct-Current Cardioversion

Class I

1. In pursuing a rhythm-control strategy, cardioversion is recommended for patients with AF or atrial flutter as a method to restore sinus rhythm. If cardioversion is unsuccessful, repeated attempts at direct-current cardioversion may be made after adjusting the location of the electrodes, applying pressure over the electrodes or following administration of an antiarrhythmic medication.[119] (*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*)

Table 9. Common Medication Dosage for Rate Control of AF

	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

*Multiple dosing schemes exist for the use of amiodarone.

AF indicates atrial fibrillation; BID, twice daily; ER, extended release; IV, intravenous; N/A, not applicable; QD, once daily; QID, 4 times a day; and TID, 3 times a day.

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*)**

5.3. Pharmacological Cardioversion

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.[120–125] (*Level of Evidence: A*)**

Class IIa

1. **Administration of oral amiodarone is a reasonable option for pharmacological cardioversion of AF.[126,127] (*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.[120] (*Level of Evidence: B*)**

Class III: Harm

1. **Dofetilide therapy should not be initiated out of hospital because of the risk of excessive QT prolongation that can cause torsades de pointes.[124,128] (*Level of Evidence: B*)**

5.4. Antiarrhythmic Drugs to Maintain Sinus Rhythm

Table 11 summarizes the range of antiarrhythmic drugs useful in the maintenance of sinus rhythm along with toxicity profiles.

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[129–132]**
   b. **Dofetilide[124,128]**
   c. **Dronedarone[133–135]**
   d. **Flecainide[130,136]**
   e. **Propafenone[130,137–140]**
   f. **Sotalol[130,138,141]**
3. **The risks of the antiarrhythmic drug, including proarrhythmia, should be considered before initiating therapy with each drug. (*Level of Evidence: C*)**
4. **Because of its potential toxicities, amiodarone should only be used after consideration of risks and when other agents have failed or are contraindicated.[129,137,142–145] (*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*)**

Table 10. Summary of Recommendations for Electrical and Pharmacological Cardioversion of AF and Atrial Flutter

Recommendations	COR	LOE	References
Prevention of thromboembolism			
With AF or atrial flutter for ≥48 h, or unknown duration, anticoagulate with warfarin for at least 3 wk before and 4 wk after cardioversion	I	B	110–113
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 TEE before 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	114
With AF or atrial flutter ≥48 h or unknown duration, anticoagulation with dabigatran, rivaroxaban, or apixaban is reasonable for ≥3 wk before and 4 wk after cardioversion	IIa	C	115–117
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	118
Direct-current cardioversion			
Cardioversion is recommended for AF or atrial flutter to restore sinus rhythm. If unsuccessful, cardioversion attempts may be repeated.	I	B	119
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 cardioversion in persistent AF when sinus rhythm can be 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	120–125
Amiodarone is reasonable for pharmacological cardioversion of AF	IIa	A	126,127
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	120
Dofetilide should not be initiated out of hospital	III: Harm	B	124,128

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

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.[108] (*Level of Evidence: B*)**
2. **Dronedarone should not be used for treatment of AF in patients with New York Heart Association class III and IV HF or patients who have had an episode of decompensated HF in the past 4 weeks.[109] (*Level of Evidence: B*)**

5.5. Upstream Therapy

Class IIa

1. **An angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) is reasonable for primary prevention of new-onset AF in patients with HF with reduced left ventricular ejection fraction.[147–149] (*Level of Evidence: B*)**

Class IIb

1. **Therapy with an ACE inhibitor or ARB may be considered for primary prevention of new-onset AF in the setting of hypertension.[150] (*Level of Evidence: B*)**
2. **Statin therapy may be reasonable for primary prevention of new-onset AF after coronary artery surgery.[151,152] (*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.[153] (*Level of Evidence: B*)**

Table 11. 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 • Extended release: 200–400 mg once every 12 h	• HF • Prolonged QT interval • Prostatism, glaucoma • Avoid other QT interval–prolonging drugs	• Metabolized by CYP3A4: caution with inhibitors (eg, verapamil, diltiazem, ketoconazole, macrolide antibiotics, protease inhibitors, grapefruit juice) and inducers (eg, rifampin, phenobarbital, phenytoin)
Quinidine	• 324–648 mg every 8 h	• Prolonged QT interval • Diarrhea	• Inhibits CYP2D6: ↑concentrations of tricyclic antidepressants, metoprolol, antipsychotics; ↓efficacy of codeine • Inhibits P-glycoprotein: ↑digoxin concentration
Vaughan Williams class IC			
Flecainide	• 50–200 mg once every 12 h	• Sinus or AV node dysfunction • HF • CAD • Atrial flutter • Infranodal conduction disease • Brugada syndrome • 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 • Extended release: 225–425 mg once every 12 h	• Sinus or AV node dysfunction • HF • CAD • Atrial flutter • Infranodal conduction disease • Brugada syndrome • Liver disease • Asthma	• Metabolized by CYP2D6 (inhibitors include quinidine, fluoxetine, tricyclics; also genetically absent in 7%–10% of population)—poor metabolizers have ↑beta blockade • Inhibits P-glycoprotein: ↑digoxin concentration • 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 • 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	• Sinus or AV node dysfunction • Infranodal conduction disease • Lung disease • Prolonged QT interval	• Inhibits most CYPs to cause drug interaction: ↑concentrations of warfarin (↑INR 0%–200%), statins, many other drugs • Inhibits P-glycoprotein: ↑digoxin concentration
Dofetilide	• 125–500 mcg once every 12 h	• Prolonged QT interval • Renal disease • Hypokalemia • Hypomagnesemia • Diuretic therapy • Avoid other QT interval–prolonging drugs	• Primary renal elimination involving glomerular filtration and active tubular secretion: 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 • HF • Long-standing persistent AF/flutter • Liver disease • Prolonged QT interval	• Metabolized by CYP3A: caution with inhibitors (eg, verapamil, diltiazem, ketoconazole, macrolide antibiotics, protease inhibitors, grapefruit juice) and inducers (eg, rifampin, phenobarbital, phenytoin) • 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 • Renal disease • Hypokalemia • Hypomagnesemia • Diuretic therapy • Avoid other QT interval–prolonging drugs • Sinus or AV nodal dysfunction • HF • 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 with permission from Roden et al.[146]

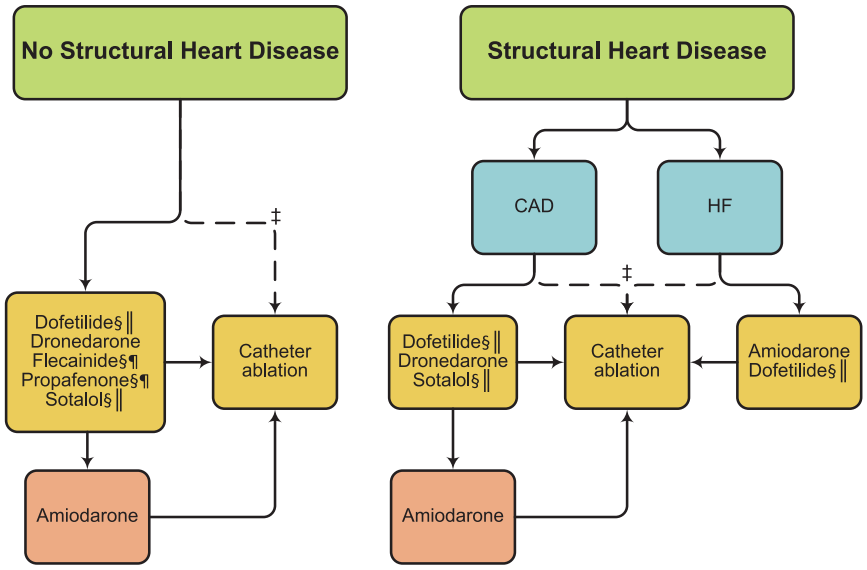

Figure 2. Strategies for rhythm control in patients with paroxysmal* and persistent AF.† *Catheter ablation is only recommended as first-line therapy for patients with paroxysmal AF (Class IIa recommendation). †Drugs are listed alphabetically. ‡Depending on patient preference when performed in experienced 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; AV, atrioventricular; CAD, coronary artery disease; HF, heart failure; and LVH, left ventricular hypertrophy.

5.6. AF Catheter Ablation to Maintain Sinus Rhythm

Figure 2 shows an approach to the integration of antiarrhythmic drugs and catheter ablation of AF in patients without and with structural heart disease.

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.[154–160] (*Level of Evidence: A*)**
2. **Before consideration of AF catheter ablation, assessment of the procedural risks and outcomes relevant to the individual patient is recommended. (*Level of Evidence: C*)**

Class IIa

1. **AF catheter ablation is reasonable for some patients with symptomatic persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication.[157,161–163] (*Level of Evidence: A*)**
2. **In patients with recurrent symptomatic paroxysmal AF, catheter ablation is a reasonable initial rhythm-control strategy before therapeutic trials of antiarrhythmic drug therapy, after weighing the risks and outcomes of drug and ablation therapy.[164–166] (*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.[154,167] (*Level of Evidence: B*)**
2. **AF catheter ablation may be considered before initiation of antiarrhythmic drug therapy with a class I or III antiarrhythmic medication for symptomatic persistent AF when a rhythm-control strategy is desired. (*Level of Evidence: C*)**

Class III: Harm

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

5.7. Surgical Maze Procedures

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.[168] (*Level of Evidence: B*)**

6. Specific Patient Groups and AF: Recommendations

See Table 12 for a summary of recommendations for this section.

6.1. Hypertrophic Cardiomyopathy

Class I

1. **Anticoagulation is indicated in patients with hypertrophic cardiomyopathy (HCM) with AF independent of the CHA_2DS_2-VASc score.[169,170] (*Level of Evidence: B*)**

Class IIa

1. **Antiarrhythmic medications can be useful to prevent recurrent AF in patients with HCM. Amiodarone or disopyramide combined with a beta blocker or nondihydropyridine calcium channel antagonists are reasonable for therapy. (*Level of Evidence: C*)**
2. **AF catheter ablation can be beneficial in patients with HCM in whom a rhythm-control strategy is desired when antiarrhythmic drugs fail or are not tolerated.[171–174] (*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*)**

6.2. AF Complicating Acute Coronary Syndromes

Class I

1. **Urgent direct-current cardioversion of new-onset AF in the setting of acute coronary syndromes (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 a 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 left ventricular 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*)**

6.3. Hyperthyroidism

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*)**

6.4. Pulmonary Disease

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*)**

6.5. Wolff-Parkinson-White and Pre-Excitation Syndromes

Class I

1. **Prompt direct-current cardioversion is recommended for patients with AF, Wolff-Parkinson-White syndrome, and rapid ventricular response who are hemodynamically compromised.[175] (*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.[175] (*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.[175] (*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 Wolff-Parkinson-White syndrome who have pre-excited AF is potentially harmful because these drugs accelerate the ventricular rate.[176–178] (*Level of Evidence: B*)**

Table 12. Summary of Recommendations for Specific Patient Groups and AF

Recommendations	COR	LOE	References
Hypertrophic cardiomyopathy			
Anticoagulation is indicated in HCM with AF independent of the CHA_2DS_2-VASc score	I	B	169,170
Antiarrhythmic drugs can be useful to prevent recurrent AF in HCM. Amiodarone or disopyramide combined with a beta blocker or nondihydropyridine calcium channel antagonist are reasonable	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	171–174
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 the 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 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 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
When beta blockers cannot be used, a nondihydropyridine calcium channel antagonist is recommended to control ventricular rate	I	C	N/A
Pulmonary diseases			
A nondihydropyridine calcium channel antagonist is recommended to control ventricular rate with AF and COPD	I	C	N/A
Cardioversion should be attempted for patients with pulmonary disease who become hemodynamically unstable with new-onset AF	I	C	N/A
WPW and pre-excitation syndromes			
Cardioversion is recommended for patients with AF, WPW syndrome, and RVR who are hemodynamically compromised	I	C	175
IV procainamide or ibutilide to restore sinus rhythm or slow ventricular rate is recommended for patients with pre-excited AF and RVR who are not hemodynamically compromised	I	C	175
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	I	C	175
IV amiodarone, adenosine, digoxin, or nondihydropyridine calcium channel antagonists in patients with WPW syndrome who have pre-excited AF is potentially harmful	III: Harm	B	176–178
Heart failure			
A beta blocker or nondihydropyridine calcium channel antagonist is recommended for persistent or permanent AF in patients with HF*p*EF	I	B	95
In the absence of preexcitation, an 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, with caution in patients with overt congestion, hypotension, or HF*r*EF	I	B	179–182
In the absence of pre-excitation, IV digoxin or amiodarone is recommended to control heart rate acutely	I	B	103,180,183,184
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
A combination of digoxin and beta blocker (or a nondihydropyridine calcium channel antagonist with HF*p*EF) is reasonable to control resting and exercise heart rate with AF	IIa	B	93,180
It is reasonable to perform AV node ablation with ventricular pacing to control heart rate when pharmacological therapy is insufficient or not tolerated	IIa	B	95,185,186
IV amiodarone can be useful to control heart rate with AF when other measures are unsuccessful or contraindicated	IIa	C	N/A

(*Continued*)

Table 12. Continued

Recommendations	COR	LOE	References
With AF and RVR causing or suspected of causing tachycardia-induced cardiomyopathy, it is reasonable to achieve rate control by AV nodal blockade or a rhythm-control strategy	IIa	B	187–189
In patients with chronic HF 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 is 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			
For patients with AF and multigenerational family members with AF, referral to a tertiary care center for genetic counseling and testing may be considered	IIb	C	N/A
Postoperative cardiac and thoracic surgery			
A beta blocker is recommended to treat postoperative AF unless contraindicated	I	A	190–193
A nondihydropyridine calcium channel blocker is recommended when a beta blocker is inadequate to achieve rate control with postoperative AF	I	B	194
Preoperative amiodarone reduces AF with cardiac surgery and is reasonable as prophylactic therapy for patients at high risk of postoperative AF	IIa	A	195–197
It is reasonable to restore sinus rhythm pharmacologically with ibutilide or direct-current cardioversion with postoperative AF	IIa	B	198
It is reasonable to administer antiarrhythmic medications to maintain sinus rhythm with recurrent or refractory postoperative AF	IIa	B	194
It is reasonable to administer antithrombotic medications for postoperative AF	IIa	B	199
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 after cardiac surgery	IIb	B	193,200
Colchicine may be considered postoperatively to reduce AF after cardiac surgery	IIb	B	201

ACS indicates acute coronary syndromes; AF, atrial fibrillation; AV, atrioventricular; 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 to 74 years, Sex category; 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.

6.6. Heart Failure

Class I

1. **Control of resting heart rate using either a beta blocker or nondihydropyridine calcium channel antagonist is recommended for patients with persistent or permanent AF and compensated HF with preserved ejection fraction (HF*p*EF).[95] (*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 left ventricular ejection fraction.[179–182] (*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.[103,180,183,184] (*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 ejection fraction. (*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.[93,180] (*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.[95,185,186] (*Level of Evidence: B*)**
3. **Intravenous amiodarone can be useful to control heart rate in patients with AF when other measures are unsuccessful or contraindicated. (*Level of Evidence: C*)**

4. **For patients with AF and rapid ventricular response causing or suspected of causing tachycardia-induced cardiomyopathy, it is reasonable to achieve rate control by either AV nodal blockade or a rhythm-control strategy.[187–189] (*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*)**

6.7. Familial (Genetic) AF

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*)**

6.8. Postoperative Cardiac and Thoracic Surgery

Class I

1. **Treating patients who develop AF after cardiac surgery with a beta blocker is recommended unless contraindicated.[190–193] (*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.[194] (*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.[195–197] (*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.[198] (*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.[194] (*Level of Evidence: B*)**
4. **It is reasonable to administer antithrombotic medication in patients who develop postoperative AF, as advised for nonsurgical patients.[199] (*Level of Evidence: B*)**
5. **It is reasonable to manage well-tolerated, new-onset postoperative AF with rate control and anticoagulation with cardioversion if AF does not revert spontaneously to sinus rhythm during follow-up. (*Level of Evidence: C*)**

Class IIb

1. **Prophylactic administration of sotalol may be considered for patients at risk of developing AF after cardiac surgery.[193,200] (*Level of Evidence: B*)**
2. **Administration of colchicine may be considered for patients postoperatively to reduce AF after cardiac surgery.[201] (*Level of Evidence: B*)**

7. Evidence Gaps and Future Research Directions

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

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KEY WORDS: AHA Scientific Statements ■ atrial fibrillation ■ cardiorenal 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

Committee Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
Craig T. January (Chair)	University of Wisconsin-Madison—Professor of Medicine, Cardiovascular Medicine Division	None	None	None	None	None	None	None
L. Samuel Wann (Vice Chair)	Columbia St. Mary's Cardiovascular Physicians—Clinical Cardiologist	• United Healthcare	None	None	None	None	None	4.1 5.0 6.3 7.3 7.10
Joseph S. Alpert	University of Arizona Health Sciences Center—Professor of Medicine	• Bayer Pharmaceuticals (DSMB)† • Boehringer Ingelheim • Daiichi-Sankyo • Johnson & Johnson • Roche Diagnostics • Sanofi-aventis • Servier Pharmaceuticals	None	None	None	None	None	4.1 5.0
Hugh Calkins	Johns Hopkins Hospital—Professor of Medicine, Director of Electrophysiology	• AtriCure • Biosense Webster • CareCore • iRhythm • Medtronic‡ • Sanofi-aventis	None	None	None	None	None	5.0 6.3 7.8
Joaquin E. Cigarroa	Oregon Health and Science University—Clinical Professor; Clinical Chief of Cardiology	None	None	None	None	None	None	None
Joseph C. Cleveland, Jr	University of Colorado—Professor of Surgery; Denver Veterans Affairs Hospital—Chief, Cardiac Surgery	None	None	None	None	None	None	None
Jamie B. Conti	University of Florida—Professor of Medicine; Division of Cardiovascular Medicine—Chief	None	None	None	• Boston Scientific‡ • Medtronic‡ • St. Jude Medical‡	• Boston Scientific‡ • Medtronic‡ • St. Jude Medical‡	None	5.0 6.3 7.8
Patrick T. Ellinor	Massachusetts General Hospital Heart Center, Cardiac Arrhythmia Service—Director	None	None	None	None	None	None	None
Michael D. Ezekowitz	Jefferson Medical College—Professor	• ARYx Therapeutics‡ • AstraZeneca • Boehringer Ingelheim‡ • Bristol-Myers Squibb‡ • Daiichi-Sankyo‡ • Eisai • Johnson & Johnson‡ • Medtronic‡ • Pfizer‡ • Portola‡ • Sanofi-aventis‡	None	None	• ARYx Therapeutics‡ • Boehringer Ingelheim‡ • Daiichi-Sankyo† • Portola†	None	None	4.1 5.0 6.3 7.8

(*Continued*)

Appendix 1. Continued

Committee Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
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	None
Katherine T. Murray	Vanderbilt University School of Medicine, Divisions of Clinical Pharmacology and Cardiology—Professor of Medicine	None	None	None	• GlaxoSmithKline†	None	None	None
Ralph L. Sacco	University of Miami, Miller School of Medicine, Department of Neurology—Chairman	• Boehringer Ingelheim†§	None	None	None	None	None	None
William G. Stevenson	Brigham and Women's Hospital, Cardiac Arrhythmia Program—Director; Harvard Medical School—Professor of Medicine	None	None	• Biosense Webster—Needle Ablation Patent†	• Biosense Webster‡	None	None	5.0 6.3 7.8
Patrick J. Tchou	Cleveland Clinic Foundation—Section of Cardiac Electrophysiology and Pacing, Department of Cardiovascular Medicine Heart and Vascular Institute	None	None	None	None	None	None	None
Cynthia M. Tracy	George Washington University Medical Center—Associate Director and Professor of Medicine	None	None	None	None	None	None	None
Clyde W. Yancy	Northwestern University, Feinberg School of Medicine—Magerstadt Professor of Medicine; Division of Cardiology—Chief	None	None	None	None	None	None	None

This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. 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.

According to the ACC/AHA, a person has a *relevant* relationship IF: a) the *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the *document*; or b) the *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the *document*, or makes a competing drug or device addressed in the *document*; or c) the *person, or a member of the person's household*, has a reasonable potential for financial, professional, or other personal gain or loss as a result of the issues/content addressed in the *document*.

*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply. Section numbers pertain to those in the full-text guideline.

†No financial benefit.

‡Indicates significant relationship.

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

ACC indicates American College of Cardiology; AHA, American Heart Association; DSMB, data safety monitoring board; and HRS, Heart Rhythm Society.

Appendix 2. Reviewer Relationships With Industry and Other Entities (Relevant)—2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

Reviewer	Representation	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
A. John Camm	Official Reviewer—HRS	St. George's, University of London—Professor of Clinical Cardiology	• Bayer • Biotronik • Boehringer Ingelheim • Boston Scientific • Bristol-Myers Squibb • ChanRx • Daiichi-Sankyo • Forest Laboratories • Johnson & Johnson • Medtronic • Novartis* • Sanofi-aventis • Servier • St. Jude Medical • Takeda • Xention	• Pfizer	None	• Biotronik† • Servier (DSMB) • St. Jude Medical (DSMB)	None	None
John Fisher	Official Reviewer—AHA	Albert Einstein College of Medicine—Professor of Medicine	• Medtronic*	None	None	None	• Biotronik* • Boston Scientific* • Medtronic* • St. Jude Medical*	None
Jonathan L. Halperin	Official Reviewer—ACC/AHA Task Force on Practice Guidelines	Mt. Sinai Medical Center—Professor of Medicine	• AstraZeneca • Bayer • Biotronik* • Boehringer Ingelheim* • Boston Scientific • Bristol-Myers Squibb • Daiichi-Sankyo • Janssen Pharmaceuticals • Johnson & Johnson • Medtronic • Pfizer • Sanofi-aventis	None	None	None	None	None
Jose Joglar	Official Reviewer—AHA	UT Southwestern Medical Center—Associate Professor of Internal Medicine	None	None	None	None	• Medtronic* • St. Jude Medical*	None

(*Continued*)

Appendix 2. Continued

Reviewer	Representation	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Peter Kowey	Official Reviewer—HRS	Lankenau Medical Office Building—Chief of Cardiology	• Astellas† • AstraZeneca* • Boehringer Ingelheim* • Bristol-Myers Squibb • Daiichi-Sankyo* • Forest Laboratories • GlaxoSmithKline* • Johnson & Johnson* • Medtronic • Merck* • Pfizer* • Portola • Sanofi-aventis*	None	• CardioNet*	None	None	None
John Strobel	Official Reviewer—ACC Board of Governors	Premier Healthcare, LLC—Clinical Cardiac EP; Indiana University—Assistant Clinical Professor of Medicine	None	• Boehringer Ingelheim • Bristol-Myers Squibb • Pfizer • Sanofi-aventis	None	None	None	• Plaintiff, ICD, 2012
Stuart Winston	Official Reviewer—ACC Board of Trustees	Michigan Heart, P. C. Michigan Heart and Vascular Institute—Cardiologist	None	None	None	None	• Biotronik† • Medtronic†	None
James R. Edgerton	Organizational Reviewer—STS	The Heart Hospital Baylor Plano—Cardiologist; University of Texas at Arlington—Adjunct Assistant Clinical Professor	None	• AtriCure*	None	None	None	None
Jeffrey L. Anderson	Content Reviewer—ACC/AHA Task Force on Practice Guidelines	Intermountain Medical Center—Associate Chief of Cardiology	• The Medicines Company • Sanofi-aventis	None	None	None	None	None
Nancy Berg	Content Reviewer—ACC EP Section Leadership Council	Park Nicollet Health Services—Registered Nurse	• Medtronic	None	None	• Mayo Clinic	• Medtronic†	None
Emmanouil Brilakis	Content Reviewer—ACC Interventional Section Leadership Council	UT Southwestern Medical School—Director, Cardiac Catheterization Laboratory, VA North Texas Healthcare System	• Boston Scientific* • Bridgepoint Medical* • Janssen Pharmaceuticals • Sanofi-aventis • St. Jude Medical	None	None	None	• Abbott Vascular† • AstraZeneca† • Cordis* • Daiichi-Sankyo* • Medtronic* • The Medicines Company*	None

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Appendix 2. Continued

Reviewer	Representation	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Yong-Mei Cha	Content Reviewer—AHA	Mayo Clinic, Division of Cardiovascular Diseases—Professor of Medicine	None	None	None	None	None	None
Jafna Cox	Content Reviewer—ACC Board of Governors	Queen Elizabeth II Health Sciences Center—Professor, Departments of Medicine, Community Health, and Epidemiology	• AstraZeneca • Bayer • Boehringer Ingelheim	None	None	• Bayer* • Pfizer*	None	None
Anne Curtis	Content Reviewer	University of Buffalo—Charles and Mary Bauer Professor of Medicine	• Biosense Webster • Bristol-Myers Squibb • Medtronic* • Pfizer • Sanofi-aventis • St. Jude Medical	None	None	None	None	None
Lesley H. Curtis	Content Reviewer—ACC/AHA Task Force on Practice Guidelines	Duke University School of Medicine—Associate Professor of Medicine	None	None	None	None	• Medtronic* • GE Healthcare* • GlaxoSmithKline* • Johnson & Johnson*	None
Kenneth Ellenbogen	Content Reviewer	VCU Medical Center—Director, Clinical EP Laboratory	• Biosense Webster • Biotronik* • Boston Scientific* • Cameron Health • Janssen Pharmaceuticals • Medtronic* • Sanofi-aventis • St. Jude Medical	None	None	• Biosense Webster* • Boston Scientific* • Medtronic* • Sanofi-aventis*	• Biosense Webster* • Boston Scientific* • CardioNet • Medtronic* • Sanofi-aventis* • St. Jude Medical*	• Represented hospital, ICD, 2012
N.A. Mark Estes III	Content Reviewer	Tufts University School of Medicine—Professor of Medicine	• Boston Scientific* • Medtronic	None	None	• Boston Scientific	• Boston Scientific* • Medtronic* • St. Jude Medical*	None
Gregg Fonarow	Content Reviewer	Ahmanson—UCLA Cardiomyopathy Center, Division of Cardiology	• Boston Scientific • Johnson & Johnson • The Medicines Company • Medtronic	None	None	• Novartis*	• Medtronic†	None

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Reviewer	Representation	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Valentin Fuster	Content Reviewer	Mount Sinai School of Medicine—Director, Zena and Michael A. Wiener Cardiovascular Institute	None	None	None	None	None	None
Richard Goodman	Content Reviewer—HHS	HHS Office of the Assistant Secretary for Health and National Center for Chronic Disease Prevention and Health Promotion Centers for Disease Control and Prevention—Senior Medical Advisor	None	None	None	None	None	None
Judith S. Hochman	Content Reviewer—ACC/AHA Task Force on Practice Guidelines	New York University School of Medicine—Clinical Chief of Cardiology	• GlaxoSmithKline • Janssen Pharmaceuticals	None	None	None	None	None
Warren Jackman	Content Reviewer	University of Oklahoma Health Sciences Center for Cardiac Arrhythmia Research Institute—Professor of Medicine	• Biosense Webster* • Endosense* • VytronUS*	• Biotronik* • Boston Scientific*	• Rhythmia Medical*	• Boston Scientific* • Rhythmia Medical*	None	None
Samuel Jones	Content Reviewer—ACC Board of Governors	USUHS—Associate Professor of Medicine	None	None	None	None	• Medtronic† • St. Jude Medical†	None
Paulus Kirchhof	Content Reviewer—HRS	University of Birmingham, School of Clinical and Experimental Medicine—Chair in Cardiovascular Medicine	None	None	None	• Sanofi-aventis (DSMB)	None	None
Bradley Knight	Content Reviewer	Northwestern Medical Center Division of Cardiology—Director of Clinical Cardiac EP	• Boston Scientific • Cameron Health†	• Biosense Webster • Biotronik • Boston Scientific • Medtronic	None	• Catheter Robotics	None	• Plaintiff, pacemaker surgery, 2012
Austin Kutscher	Content Reviewer	Hunterdon Cardiovascular Associates—Cardiologist	• Pfizer	• Bristol-Myers Squibb • Forest Laboratories	None	• Boehringer Ingelheim • Bristol-Myers Squibb	None	None

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Appendix 2. Continued

Reviewer	Representation	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Gregory Michaud	Content Reviewer	Harvard Medical School, Brigham and Women's Hospital—Assistant Professor	• Boston Scientific • Medtronic	None	None	• Boston Scientific* • St. Jude Medical*	None	None
William Miles	Content Reviewer	University of Florida, Department of Medicine—Cardiologist	None	None	None	• Medtronic—STOP-AF (PI) • Zoll Medical	None	None
Simone Musco	Content Reviewer—ACC Board of Governors	Saint Patrick Hospital—Cardiologist	None	• Bristol-Myers Squibb • Sanofi-aventis	None	None	None	None
Brian Olshansky	Content Reviewer—ACC EP Section Leadership Council	University of Iowa Hospital—Professor of Medicine	• Boehringer Ingelheim • Boston Scientific • Guidant • Medtronic* • Sanofi-aventis	None	None	• Boston Scientific (DSMB) • Sanofi-aventis (DSMB)	None	None
Huseyin Murat Ozdemir	Content Reviewer—AIG	Gazi University School of Medicine—Professor of Cardiology	• Bayer • Boehringer Ingelheim • Bristol-Myers Squibb • Novartis • Pfizer • Servier	None	None	None	None	None
Douglas Packer	Content Reviewer	Mayo Foundation St. Mary's Hospital Complex—Professor of Medicine	• Abiomed† • Biosense Webster† • Boston Scientific† • InfoBionic† • Johnson & Johnson† • Medtronic† • Janssen Pharmaceuticals† • Sanofi-aventis† • Siemens† • St. Jude Medical†	None	None	• Biosense Webster* • Boston Scientific* • CardioFocus • Endosense* • Hansen Medical • Medtronic* • Siemens • St. Jude Medical* • Thermedical*	• St. Jude Medical*	None
Richard Page	Content Reviewer	University of Wisconsin Hospital and Clinics—Chair, Department of Medicine	None	None	None	None	None	None
Robert Page	Content Reviewer—AHA PharmD	University of Colorado School of Pharmacy—Associate Professor	None	None	None	None	None	None

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Appendix 2. Continued

Reviewer	Representation	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Gurusher Panjrath	Content Reviewer—ACC HF and Transplant Section Leadership Council	George Washington University—Assistant Professor of Medicine	None	None	None	None	None	None
Eric Prystowsky	Content Reviewer—HRS	St. Vincent Hospital and Health Center—Director, Clinical EP Laboratory	• Bard* • Medtronic*	None	• CardioNet* • Topera* • Stereotaxis*	None	• CardioNet* • Stereotaxis*	None
Pasala Ravichandran	Content Reviewer—ACC Surgeons' Council	Oregon Health and Science University—Associate Professor	None	None	None	None	None	None
Anitra Romfh	Content Reviewer—ACC Adult Congenital and Pediatric Cardiology Section Leadership Council	Children's Hospital Boston—Cardiologist	None	None	None	None	None	None
Elizabeth Saarel	Content Reviewer—ACC Adult Congenital and Pediatric Cardiology Section Leadership Council	University of Utah School of Medicine and Primary Children's Medical Center—Associate Professor	None	None	None	None	None	None
Marcel Salive	Content Reviewer—HHS	National Institute on Aging, Division of Geriatrics and Clinical Gerontology	None	None	• Express Scripts*	None	None	None
John Sapp	Content Reviewer—HRS	Dalhousie University—Director of EP	• Biosense Webster	None	None	• Biosense Webster* • St. Jude Medical*	None	None
Frank W. Sellke	Content Reviewer—ACC/AHA Task Force on Practice Guidelines	Cardiovascular Institute, Rhode Island Hospital and Lifespan—Chief of Cardio-thoracic Surgery	None	None	None	None	• The Medicines Company	None
Win-Kuang Shen	Content Reviewer—ACC/AHA Task Force on Practice Guidelines	Mayo Clinic Arizona—Professor of Medicine, Consultant	None	None	None	None	None	None

(*Continued*)

Appendix 2. Continued

Reviewer	Representation	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
David J. Slotwiner	Content Reviewer	Long Island Jewish Medical Center—Associate Director, EP Laboratory	None	None	None	None	• Boston Scientific	None
Jonathan Steinberg	Content Reviewer	Valley Health System Arrhythmia Institute—Director; Columbia University College of Physicians and Surgeons—Professor of Medicine	• Ambucor • Biosense Webster • Boston Scientific • Medtronic	• Bristol-Myers Squibb* • Sanofi-aventis	None	• Biosense Webster* • Janssen Pharmaceuticals • Medtronic*	None	None
Vinod Thourani	Content Reviewer—ACC Surgeons' Council	Emory University School of Medicine—Associate Professor of Cardiothoracic Surgery	• Edwards Lifesciences • Sorin • St. Jude Medical	None	• Apica Cardiovascular†	• Maquet	None	None
Mellanie True Hills	Content Reviewer—Patient Advocate	StopAfib.org—Speaker and Chief Executive Officer	• AtriCure	None	None	None	• Bayer* • Boehringer Ingelheim* • Janssen Pharmaceuticals* • Johnson & Johnson* • Medtronic • Sanofi-aventis*	None
Albert Waldo	Content Reviewer—HRS	Case Western Reserve University—The Walter H. Pritchard Professor of Cardiology, Professor of Medicine, and Professor of Biomedical Engineering	• Abbott Vascular • AtriCure • Biosense Webster • Biotronik • Daiichi-Sankyo • Gilead • Janssen Pharmaceuticals* • Merck • Pfizer • Sanofi-aventis	• Janssen Pharmaceuticals* • Sanofi-aventis*	None	• Biotronik • Daiichi-Sankyo • Gilead* • St. Jude Medical*	None	None

This table represents the relationships of reviewers with industry and other entities that were disclosed at the time of peer review and determined to be relevant to this document. It 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. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Names are listed in alphabetical order within each category of review.

According to the ACC/AHA, a person has a *relevant* relationship IF: a) the *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the *document*; or b) the *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the *document*, or makes a competing drug or device addressed in the *document*; or c) the *person, or a member of the person's household*, has a reasonable potential for financial, professional, or other personal gain or loss as a result of the issues/content addressed in the *document.*

*Significant relationship.

†No financial benefit.

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; PI, principal investigator; STOP-AF, Sustained Treatment Of Paroxysmal Atrial Fibrillation; STS, Society of Thoracic Surgeons; UCLA, University of California, Los Angeles; USUHS, Uniformed Services University of the Health Sciences; UT, University of Texas; VA, Veterans Affairs; and VCU, Virginia Commonwealth University.

Appendix 3. Initial Clinical Evaluation in Patients With AF

Minimum Evaluation	
1. History and physical examination, to define	• Presence and nature of symptoms associated with AF • Clinical type of AF (paroxysmal, persistent, or permanent) • Onset of first symptomatic attack or date of discovery of AF • Frequency, duration, precipitating factors, and modes of initiation or termination of AF • Response to any pharmacological agents that have been administered • Presence of any underlying heart disease or reversible conditions (eg, hyperthyroidism or alcohol consumption)
2. ECG, to identify	• Rhythm (verify AF) • LVH • P-wave duration and morphology or fibrillatory waves • Pre-excitation • Bundle-branch block • Prior MI • Other atrial arrhythmias • To measure and follow R-R, QRS, and QT intervals in conjunction with antiarrhythmic drug therapy
3. TTE, to identify	• VHD • LA and RA size • LV and RV size and function • Peak RV pressure (pulmonary hypertension) • LV hypertrophy • LA thrombus (low sensitivity) • Pericardial disease
4. Blood tests of thyroid, renal, and hepatic function	• For a first episode of AF • When ventricular rate is difficult to control
Additional Testing (1 or several tests may be necessary)	
1. 6-min walk test	• If adequacy of rate control is in question
2. Exercise testing	• If adequacy of rate control is in question • To reproduce exercise-induced AF • To exclude ischemia before treatment of selected patients with a type IC* antiarrhythmic drug
3. Holter or event monitoring	• If diagnosis of type of arrhythmia is in question • As a means of evaluating rate control
4. TEE	• To identify LA thrombus (in LAA) • To guide cardioversion
5. Electrophysiological study	• To clarify the mechanism of wide-QRS-complex tachycardia • To identify a predisposing arrhythmia such as atrial flutter or paroxysmal supraventricular tachycardia • To seek sites for curative AF ablation or AV conduction block/modification
6. Chest radiograph, to evaluate	• Lung parenchyma, when clinical findings suggest an abnormality • Pulmonary vasculature, when clinical findings suggest an abnormality

*Type IC refers to the Vaughan Williams classification of antiarrhythmic drugs.

AF indicates atrial fibrillation; AV, atrioventricular; ECG, electrocardiogram; LA, left atrial; LAA, left atrial appendage; LV, left ventricular; LVH, left ventricular hypertrophy; MI, myocardial infarction; RA, right atrial; RV, right ventricular; TEE, transesophageal echocardiography; TTE, transthoracic echocardiogram; and VHD, valvular heart disease.

Adapted with permission from Fuster et al.[5]

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society

Craig T. January, L. Samuel Wann, Joseph S. Alpert, Hugh Calkins, Joaquin E. Cigarroa, Joseph C. Cleveland, Jr, Jamie B. Conti, Patrick T. Ellinor, Michael D. Ezekowitz, Michael E. Field, Katherine T. Murray, Ralph L. Sacco, William G. Stevenson, Patrick J. Tchou, Cynthia M. Tracy and Clyde W. Yancy

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Correction

In the article by January et al, "2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society," which published online March 28, 2014, and appeared in the December 2, 2014, issue of the journal (*Circulation*. 2014;130:2071–2104), several corrections were needed.

1. On page 2079, in the first column, the second paragraph, the Class III: No Benefit recommendation 1 read, "The direct thrombin inhibitor dabigatran and the factor Xa inhibitor rivaroxaban are not recommended in patients with AF and end-stage CKD or on hemodialysis because of the lack of evidence from clinical trials regarding the balance of risks and benefits." It has been changed to read, "The direct thrombin inhibitor dabigatran and the factor Xa inhibitor rivaroxaban are not recommended in patients with AF and end-stage CKD or on dialysis because of the lack of evidence from clinical trials regarding the balance of risks and benefits."
2. On page 2078, in Table 5, in the penultimate row, the Class III: No Benefit recommendation 1 read, "Direct thrombin dabigatran and factor Xa inhibitor rivaroxaban are not recommended in patients with AF and end-stage CKD or on hemodialysis because of a lack of evidence from clinical trials regarding the balance of risks and benefits." It has been changed to read, "Direct thrombin dabigatran and factor Xa inhibitor rivaroxaban are not recommended in patients with AF and end-stage CKD or on dialysis because of a lack of evidence from clinical trials regarding the balance of risks and benefits."
3. On page 2080, in Table 7, in row 1, the entry in the fourth column "Rivaroxaban" read, "20 mg HS." It has been changed to read, "20 mg QD with the evening meal."
4. On page 2080, in Table 7, in row 2, the entry in the third column "Dabigatran" read, "150 mg BID or 75 mg BID (CrCl >30 mL/min)." It has been changed to read, "150 mg BID (CrCl >30 mL/min)."
5. On page 2080, in Table 7, in row 2, the entry in the fourth column "Rivaroxaban" read, "15 mg HS." It has been changed to read, "15 mg QD with the evening meal."
6. On page 2080, in Table 7, in row 3, the entry in the fourth column "Rivaroxaban" read, "15 mg HS." It has been changed to read, "15 mg QD with the evening meal."
7. On page 2080, in Table 7, the footnote list read, "…§Modeling studies suggest that dabigatran 75 mg BID might be safe for patients with CrCl 15–30 mL/min, but this has not been validated in a prospective cohort. Some countries outside the United States use 110 mg BID. ‖Dose-adjusted warfarin has been used, but observational data on safety and efficacy are conflicting…" It has been changed to read, "§Dose-adjusted warfarin has been used, but observational data on safety and efficacy are conflicting. ‖Modeling studies suggest that dabigatran 75 mg BID might be safe for patients with CrCl 15–30 mL/min, but this has not been validated in a prospective cohort. Some countries outside the United States use 110 mg BID." Symbols in the table were adjusted accordingly.
8. On page 2080, in Table 7, the footnote abbreviation list read, "...CrCl, creatinine clearance; HS, once daily in evening with food; and INR, international normalized ratio." It has been changed to read, "...CrCl, creatinine clearance; FDA, Food and Drug Administration; INR, international normalized ratio; and QD, once daily."
9. On page 2082, in Table 9, in the first column, the last line, an asterisk (*) was inserted after "Amiodarone," and the following was added to the footnotes, "*Multiple dosing schemes exist for the use of amiodarone."
10. On page 2084, in Table 11, in the second row "Dofetilide" under the "Vaughan Williams class III" heading, in the "Exclude/Use With Caution" column, "Hypomagnesemia" was added to the bulleted list.
11. On page 2084, in Table 11, in the row "Dofetilide" row under the "Vaughan Williams class III" heading, in the "Major Pharmacokinetic Drug Interactions" column, the text read, "Metabolized by CYP3A: verapamil…". It has been changed to read, "Primary renal elimination involving glomerular filtration and active tubular secretion: verapamil…"

(*Circulation*. 2014;130:e270-e271.)

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12. On page 2075, in Table 2, page 2076 in the text, and page 2090 in the Reference Section, Reference 8 was removed and replaced with references 8a and 8b.

    Reference 8 read,

    8. Agency for Healthcare Research and Quality. Research protocol: treatment of atrial fibrillation. Available at: http://effectivehealthcare.ahrq.gov/ehc/products/358/946/AtrialFibrillationTreatment_AmendedProtocol_20120530.pdf. 2012. Accessed May 23, 2014.

    References 8a and 8b read,

    8a. Al-Khatib SM, Allen Lapointe N, Chatterjee R, et al. Treatment of Atrial Fibrillation. Comparative Effectiveness Review 119. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-2007-10066-I.) AHRQ Publication No.13-EHC095-EF. Rockville, MD: Agency for Healthcare Research and Quality; June 2013. Available at: http://www.effectivehealthcare.ahrq.gov/ehc/products/358/1559/atrial-fibrillation-report-130628.pdf. Accessed August 14, 2014.

    8b. Lopes RD, Crowley MJ, Shah BR, et al. Stroke Prevention in Atrial Fibrillation. Comparative Effectiveness Review No. 123. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-2007-10066-I.) AHRQ Publication No. 13-EHC113-EF. Rockville, MD: Agency for Healthcare Research and Quality; August 2013. Available at: http://www.effectivehealthcare.ahrq.gov/ehc/products/352/1668/stroke-atrial-fibrillation-report-130821.pdf. Accessed August 14, 2014.

These corrections have been made to the print version and to the current online version of the article, which is available at http://circ.ahajournals.org/content/130/23/2071.full.

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation—ONLINE AUTHOR LISTING OF COMPREHENSIVE RELATIONSHIPS WITH INDUSTRY AND OTHERS (April 2012)

Committee Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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						145-002 (Co-PI) • GE Healthcare, VSCAN (Co-PI) • Genentech, MLDL1278A (Co-PI) • GlaxoSmithKline—SOLID-TIMI52 (Co-PI) • Harvard Clinical Research Institute—DAPT (Co-PI) • Hoffman LaRoche—ALECARDIO (Co-PI) • Osiris Therapeutics—Prochymal (Co-PI)	
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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.)

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AF indicates atrial fibrillation.

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

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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) Dabigatran 150 mg (6,076) 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 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 Warfarin INR 2-3, mean TTR 64%	Stroke or SE Dabigatran110 mg 1.53%/y Dabigatran 150 mg 1.11%/y Warfarin 1.69%/y	Major Hemorrhage Dabigatran 110 mg 2.71%/y Dabigatran 150 mg 3.11%/y Warfarin 3.36%/y Intracranial Bleeding Dabigatran 110 mg 0.23%/y Dabigatran 150 mg 0.30%/y Warfarin 0.74%/y Major GI	Stroke Dabigatran 110 mg 1.44%/y Dabigatran 150 mg 1.01%/y Warfarin 1.57%/y Stroke, ST elevation, PE, MI, death, or major bleeding Dabigatran 110 mg 7.09%/y Dabigatran 150 mg 6.91%/y 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 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 Median duration of FU 2 y

								Dabigatran 110 mg 1.12%/y Dabigatran 150 mg 1.51%/y 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) Warfarin (7,133)	NVAF at moderate to high risk of stroke: Hx of stroke, TIA, or SE or ≥2 of the following (HF or LVEF<35% , HTN, age >75 y, DM (CHADS2 score of≥2) Mean CHADS2 score of 3.5	Severe valvular disease, transient AF caused by a reversible disorder, hemorrhage risk related criteria; severe, disabling stroke within 3 mo or any stroke within 14 d, TIA within 3 d; indication for anticoagulant Tx	Rivaroxaban Factor Xa inhibitor, 20 mg QD or 15 mg QD for those with CrCl of 39-40 mL/min Warfarin INR 2-3, mean TTR 55%	Any stroke or SE Per-protocol as treated Rivaroxaban 1.7%/y Warfarin 2.2%/y Intention to Treat Rivaroxaban 2.1%/y Warfarin 2.4%/y	Major and non-major clinically relevant bleeding Rivaroxaban 14.9/100 pt-years Warfarin 14.5/100 pt-years ICH Rivaroxaban 0.5/100 pt-years Warfarin 0.7/100 pt-years Major GI Rivaroxaban 3.15% Warfarin 2.16%	Stroke, SE, or VD Rivaroxaban 3.11/100 pt-years Warfarin 3.64/100 pt-years HR: 0.86; 95% CI: 0.74-0.99; p=0.034	Per-Protocol, as treated HR: 0.79; 95% CI: 0.66-0.96; p<0.001 for noninferiority Intention to treat HR: 0.88; 95% CI: 0.75-1.03; p<0.001 for noninferiority p=0.12 for superiority	N/A	Median duration of follow-up was 707 d Lower TTR in warfarin group 1° analysis was prespecified as a per-protocol analysis High-event rate after discontinuation of Tx

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) 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) 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) Warfarin INR 2-3 Mean TTR 62.2%	Any stroke or SE Apixaban 1.27%/y Warfarin 1.6%/y	Major Bleeding Apixaban 2.13%/y Warfarin 3.09%/y ICH Apixaban 0.33%/y Warfarin 0.80%/y Major GI Apixaban 0.76%/y Warfarin 0.86%/y	Stroke, SE, major bleeding, or death from any cause 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 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) 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) ASA	Any stroke or SE Apixaban 1.6%/y ASA 3.7%/y p<0.001	Major Bleeding Apixaban 1.4% ASA 1.2% Intracranial Bleeding Apixaban 0.4% ASA 0.4% Major GI	Stroke, SE, MI, VD or major bleeding event 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

				because it had already been demonstrated to be unsuitable or because it was expected to be unsuitable. Mean CHADS2 of 2.0	within the previous 10 d, severe renal insufficiency (a sCr>2.5 mg/dL) or a calculated CrCl<25 mL/min	81-325 mg/dL		Apixaban 0.4% ASA 0.4%				

1° indicates primary; AF, atrial fibrillation; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in AF; ASA, aspirin; AVERROES, Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; BID, twice daily; CAD, coronary artery disease; CHADS2, Congestive heart failure, Hypertension, Age 75 years, Diabetes mellitus, Stroke; ; CP, codeine phosphate; Cr, creatinine; CrCl, creatinine clearance; DM, diabetes mellitus; FU, follow-up; GI, gastrointestinal; HF, heart failure; HR, hazard ratio; HTN, hypertension; Hx, history; ICH, intracranial hemorrhage; INR, international normalized ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; N/A, not applicable; PAD, peripheral arterial disease; PE, pulmonary embolism; N/A, not applicable; NVAF, nonvalvular atrial fibrillation; NYHA, New York Heart Association; OAC, oral anticoagulation; pts, patient; QD, once daily; RCT, randomized controlled trial; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial; RR, relative risk; sCr, serum creatinine; SE, systemic embolism; Sx, symptom; TIA, transient ischemic attack; TTR, time in therapeutic range; Tx, therapy; 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 Warfarin 1,154 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) Warfarin 27 PC 71	ICH, Major extracranial bleeds ICH, Warfarin 5, PC 2 Extracranial bleeds, Warfarin	Stroke, MI or VD Warfarin 69 PC 118	All ischemic stroke or ICH OR: 0.39; 95% CI: 0.26-0.59 Ischemic stroke OR: 0.34; 95% CI: 0.23-0.52

								17, PC 16		Stroke, MI, VD OR: 0.57; 95% CI: 0.42-0.77 All ICH OR: 2.38; 95% CI: 0.54-10.50) Major extracranial bleeds 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
				Inclusion Criteria	*Exclusion Criteria*		*Primary Endpoint & Results*	*Safety Endpoint & Results*	*Secondary Endpoint & Results*		
Aguilar MI, et al., 2007 (154) 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 OAC 4,815 Antiplatelet 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) OAC 132/4,815 Antiplatelet 190/4,783	ICH, major extracranial bleeds	Stroke, MI, or VD	All Stroke OR: 0.68; 95% CI: 0.54-0.85; p=0.00069 Ischemic stroke OR: 0.53; 95% CI: 0.41-0.69 ICH OR: 1.98; 95% CI: 1.20-3.28 Major Extracranial OR: 0.97; 95% CI: 0.74-1.28	N/A

										Major Extracranial (exclude ACTIVE W with CP+A) OR: 1.90; 95% CI: 1.07-3.39 Stroke, MI, 485 VD 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 OR: 0.67; 95% CI: 0.50-0.91 Recurrent Stroke OR: 0.49; 95% CI: 0.33-0.72 Any ICH OR: 1.99; 95% CI: 0.40-9.88 Major Extracranial bleed 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; Warfarin target INR 2.5, range 2-3	Fatal or nonfatal disabling stroke (ischemic or hemorrhagic), other ICH, or clinically significant arterial embolism Warfarin 24 (1.8%/y)	Hemorrhage Major extracranial Warfarin 18 (1.4%/y) ASA 20 (1.6%/y) All major hemorrhages Warfarin 25 (1.9%/y) ASA 25 (2.0%/y)	Major vascular events (stroke, MI, PE, VD) Warfarin 76 (5.9%/y) ASA 100 (8.1%/y) 1° events plus major hemorrhage Warfarin 39	RR: 0.48; 95% CI: 0.28-0.80; p=0.0027 Stroke RR: 0.46; 95% CI: 0.26-0.79; p=0.003 All major hemorrhages RR: 0.96; 95% CI: 0.53-1.75; p=0.90 Major vascular	Open-label with blind assessments 67% of the warfarin group remained on Tx TTR was 67%

	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 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 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

	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 Diltiazem: 80.0±15 Atenolol: 75.9±11.7 Digoxin + Diltiazem: 67.3±14.1 Digoxin + atenolol: 65±9.4	Digoxin: 175±36 Diltiazem: 151±27 Atenolol: 130±34 Digoxin + Diltiazem: 146±40 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 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: Rest: 69±10 vs. 96±17 Exercise: 116±26 vs. 155±28+	p<0.001	Small sample size Most pts at entry were on digoxin and continued on digoxin

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 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 2nd /3rd 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 Digoxin 46% vs. PC 51%	Effect on heart rate: 91.2±20 vs. 116.2±25	p=0.37 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 Estimated HR	p<0.001 p<0.009 p<0.016	Post hoc analysis utilizing propensity scoring

	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 70% vs. 55% vs. 75%	Bradycardia or hypotension 35% vs. 0% vs. 5%	Uncontrolled tachycardia 0% vs. 45% vs. 5%	1° endpoint: NS 2° endpoint p<0.00016 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 Composite of unplanned hospitalization for CV event/ death	N/A	N/A	HR: 2.29; 95% CI: 1.34-3.94 HR: 1.95; 95% CI: 1.45-2.62	Stroke HR: 2.32; 95% CI: 1.11-4.88 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 Age/sex matched from minnesota population 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 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 anticoagulant or ASA Tx	N/A	N/A	Composite of CV death and morbidity at 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 Stroke 1.6% vs. 3.9%, HR: 0.35; 95% CI: 0.13-0.92 CV death 2.9% vs. 3.9%, HR: 0.79; 95% CI: 0.38-1.65

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
					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) PC (208)	Age ≥21 y ≥1 episode AF in previous 3 mo	Time to the 1st recurrence of AF or atrial flutter Dronedarone 158 d PC 59 d (p=0.002)	Ventricular rate after recurrence, dronedarone 104.6 bpm PC 116.6 bpm (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 62% amiodarone vs. 23% class I drug (p<0.001) 60% amiodarone vs. 38% sotalol (p=0.002) 34% sotalol vs. 23% class I drug (p=0.488)	N/A	AEs leading to drug discontinuation 12.3% amiodarone 11.1% sotalol 28.1% class I agent Amiodarone pulmonary toxicity 1.3% at 1 y and 2.0% at 2 y 1 case torsade de pointes - quinidine	Amiodarone more effective than sotalol or class I agent for SR without cardioversion 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) Propafenone 600 mg/d (49)	Inclusion: >18 y with symptomatic PAF or atrial flutter 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 0.619 flecainide 0.469 propafenone (p=0.79)	N/A	8.5% flecainide group had neurologic side effects 16.7% propafenone group GI side effects	Flecainide and propafenone similar efficacy (although small sample size and open-label design) Nonsignificant trend toward higher side-effects with propafenone

ANDROMEDA, Kober L, et al., 2008 (171) 18565860	To evaluate the efficacy of dronedarone in HF pts	RCT, double-blind (627)	Dronedarone (310) PC (317)	Age >18 y, hospitalized for HF, LVEF<35%, NYHA class III or IV (Did not require AF Dx, Hx of AF 37-40%)	Death from any cause or HF hospitalization 17.1% dronedarone 12.6% PC HR: 1.38; 95% CI: 0.92-2.09; p=0.12	N/A	Death 8.1% dronedarone 3.8% PC 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) PC (489)	Inclusion: Symptomatic AF in SR at time of randomization 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 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) 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 31.9% dronedarone 39.4% PC HR: 0.76; p<0.001	Death due to any cause CV death 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) Sotalol HCL 240 mg/d (106) 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 63% propafenone 73% sotalol 35% PC (p=0.001)	N/A	4% ventricular arrhythmia with sotalol 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) Sotalol 120 mg BID (63) Sotalol 160 mg	Inclusion: symptomatic AF or atrial flutter and SR at time of randomization Dose reduction in presence of renal dysfunction	Time to first recurrent symptomatic AF or atrial flutter after steady state (intention to treat) 27 d PC	Proportion of pts free of AF 12 mo 28% PC 30% sotalol 80 mg 40% sotalol 120	Bradycardia and fatigue most common AEs No cases of torsade de pointes in this study	Outpatient initiation in 27%

			BID (62) 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 229 d sotalol 120 mg 175 d sotalol 160 mg	mg 45% sotalol 160 mg		
Byrne-Quinn E, et al., 1970 (176) 4911757	To evaluate the efficacy of quinidine for maintenance of SR	RCT, double-blind (65)	Quinidine 1.2 g/d (28) PC (37)	Inclusion: Pts hospitalized for AF with plan for cardioversion Exclusion: digoxin stopped 24 h prior	Percentage of pts at FU in SR 24.3% PC 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) 7642012	To evaluate the efficacy and safety of flecainide and sotalol for maintenance of SR	RCT, open-label (66)	Flecainide acetate 200 mg/d (20) Sotalol HCL 240 mg/d (20) PC (26)	N/A	Arrhythmia free survival at 12 mo 70% flecainide 60% sotalol 27% PC p=0.002 AAD vs. PC p=0.163 flecainide vs. sotalol	N/A	N/A	Flecainide and sotalol have similar efficacy in prevention of recurrence of AF Side effects common but serious AE uncommon in this FU period
Channer KS, et al., 2004 (178) 14720531	To evaluate the efficacy of amiodarone to prevent recurrent AF after cardioversion	RCT, double-blind (161)	Amiodarone (short-term) 200 mg/d for 8 wk after DCCV (62) Amiodarone (long-term) 200 mg/d for 52 wk after DCCV (61) PC (38)	Inclusion: Age >18 y and sustained AF>72 h Exclusion: LVEF<20%, significant valve disease, female <50 y, thyroid, lung or liver disease, contraindication to anticoagulation	Percentage in SR at 1 y 49% long-term amiodarone 33% short-term (8 wk after DCCV) amiodarone 5% PC	Spontaneous conversion to SR 21% amiodarone and 0% in PC SR rhythm at 8 wk after DCCV – 16% PC, 47% short-term amiodarone, 56% long-term amiodarone	AEs leading to discontinuation 3% PC 8% short-term amiodarone 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 Given the long-term AEs with amiodarone, 8 wk of adjuvant Tx suggested as option by authors

CTAF, Roy D, et al., 2000 (179) 10738049	Low dose amiodarone would be more efficacious in preventing recurrent AF than sotalol or propafenone	RCT (403)	Amiodarone 200 mg/d (201) Sotalol 160 mg BID (101) Propafenone 150 QID (101)	Symptomatic AF within previous 6 mo but not persistent AF>6mo	Recurrence of AF during FU (mean 16 mo) 35% amiodarone 63% sotalol or propafenone (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, Touboul P, et al., 2003 (180) 12919771	To determine the most appropriate dose of dronedarone for prevention of AF after DCCV	RCT, double-blind (199)	Dronedarone 800 mg/d (54) Dronedarone 1,200 mg/d (54) Dronedarone 1600 mg/d (43) PC (48)	Inclusion: age 21-85 y, pts with persistent AF (>72 h and <12 mo) scheduled for DCCV 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 60 d for dronedarone 400 mg BID 5.3 d for PC (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, Pedersen OD, et al., 2001 (181) 11457747	To evaluate the efficacy of dofetilide to maintain SR in pt with LV dysfunction	RCT, double-blind (506)	Dofetilide 500 mcg/d (249) PC (257)	Inclusion: Persistent AF associated with either HF or recent acute MI Dose reduction for renal insufficiency 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 79% dofetilide 42% with PC (p<0.001)	No effect on all-cause mortality Dofetilide associated with reduced rate of rehospitalization	Torsade de pointes occurred in 4 dofetilide pts (1.6%)	N/A
DIONYSOS, Le Heuzey JY, et al., 2010 (182) 20384650	To evaluate the efficacy and safety of amiodarone and dronedarone in pts with persistent AF	RCT, double-blind (504)	Amiodarone 600 mg QD for 28 d then 200 mg QD (255) 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 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

					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) PC (52)	Recent onset or persistent AF Exclusion: MI, HF, CABG<6 mo, severe COPD, LA thrombus, thyroid disease, inability to consent to DCCV	Percentage of AF recurrences at 15 mo 39% propafenone 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) PC (201)	≥1 episode AF in previous 3 mo, Age ≥2y	Time to the 1st recurrence of AF or atrial flutter 96 d dronedarone 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) Propafenone HCL 450-900 mg/d (103)	Paroxysmal AF without structural heart disease	Probability of remaining free of AEs at 12 mo 77% flecainide 75% propafenone 1 VT in propafenone group 2 accelerated ventricular response with flecainide	Drug discontinuation 4 flecainide 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) PC (48)	Persistent AF>2 mo duration Exclusion: paroxysmal AF, age >75 y, HR<50 bpm, LA>60 mm	Recurrent AF in 37% amiodarone and 80% PC group 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

Kalusche D, et al., 1994 (186) 7846939	To compare the efficacy of sotalol to a fixed combination of quinidine and verapamil	RCT, open-label (82)	Quinidine sulfate 1000 mg/d Sotalol HCL 240-400 mg/d	N/A	SR at 6 and 12 mo 75.7% and 67.3% quinidine/verapamil 63.4 and 49.9% sotalol p=NS	N/A	5 pts quinidine/verapamil discontinued Tx due to noncardiac AEs, 3 pts in sotalol discontinued due to bradycardia No proarrhythmia noted	N/A
Kochiadakis GE, et al., 2004 (187) 15589019	Compare the efficacy and safety of sotalol and propafenone for prevention of recurrent AF	RCT, single-blind (254)	Propafenone HCL 240 mg/d (86) Sotalol HCL 320 mg/d (85) PC (83)	Symptomatic AF, successful chemical or DCCV if persistent	Percentage recurrence AF during FU 69/85 sotalol 45/86 propafenone 73/83 PC (p<0.001)	N/A	N/A	Long-term results show superiority of propafenone (question methods of comparison)
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) PC (197)	Inclusion: Persistent AF with successful cardioversion (DC or chemical) Exclusion: Concomitant Tx with any class I or class 3 AAD, beta blocker or CCB	Percentage of pts with recurrent AF during FU (up to 6 mo) 48.7% metoprolol XL 59.9% PC (p=0.005)	Mean HR was lower with recurrent AF in pts on metoprolol (107 vs. 98; p=0.015)	SAEs similar with metoprolol or PC	Metoprolol XL prevents recurrent AF after cardioversion Short duration of FU
Naccarelli GV, et al., 1996 (189) 8607392	To compare the efficacy of flecainide to quinidine for PAF	RCT, open-label (239)	Flecainide acetate 200-300 mg/d (122) Quinidine sulfate 1000-1500 mg/d (117)	Symptomatic PAF	Percentage of pts with reported episodes of symptomatic AF 72% flecainide 74.3% quinidine (p=0.54)	Combined endpoint efficacy and tolerability at 1 y 70% flecainide vs. 55.4% quinidine (p<0.007)	N/A	Flecainide and quinidine have similar efficacy but flecainide is better tolerated
PAFAC, Fetsch T, et al., 2004 (190) 15302102	To compare the efficacy of quinidine and sotalol to PC for maintenance of SR in pt with persistent AF	RCT, double-blind (848)	Quinidine sulfate 480 mg/d Sotalol HCL 320 mg/d	Persistent AF lasting >7 d (mean duration: 15 mo), N=848, male: 66%, age (mean, SD): 63, ±9, structural heart disease: NS, left anterior descending: 45 mm, LVEF: 60%	At 12 mo: Mortality Pro-arrhythmia AEs AF recurrence	N/A	N/A	N/A

			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 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 Unplanned CV hospitalization or death, 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 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 4 trials of dronedarone vs. PC 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) OR: 0.79 dronedarone vs. PC (95% CI: 0.33-1.87)	N/A	Amiodarone trend towards increased mortality Amiodarone greater number AEs than dronedarone	Dronedarone is less effective than amiodarone but has fewer AEs

Plewan A, et al., 2001 (192) 11482924	N/A	RCT, open-label (128)	Sotalol 160 mg/d Bisoprolol fumarate 5 mg/d	Persistent AF (mean duration: 9 mo). N=128 Male: 62%. Age (mean, SD): 59, ±10 Structural heart disease: 72%. LAD: 48 mm. LVEF: 41%	At 8 mo: Mortality Pro-arrhythmia AEs 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 Propafenone HCL 900 mg/d	Persistent AF (mean duration: 5 mo). N=56 Male: 68%. Age (mean, SD): 60, ±11 Structural heart disease: 65%. LAD: 46 mm. LVEF: NS	At 6 mo: Mortality Pro-arrhythmia AEs 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) PC (126)	Inclusion: Symptomatic AF (type not specified) SR at time of randomization 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: Mortality Pro-arrhythmia AEs 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) Sotalol HCL 320 mg/d (50)	Pts with AF with previous AAD failure	Percentage with SR at 3, 6, and 12 mo 46%, 41%, 30% propafenone 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 Quinidine 1000 mg/d	≥3 AF episodes in past 6 mo Exclusion: LA size >55 mm, hepatic or renal insufficiency, MI<30 d, pregnant, decompensated HF, thyroid dysfunction	SR at 6 mo 60% propafenone 56% quinidine SR at 1 y 48% propafenone 42% quinidine	p=NS	N/A	10% side effects propafenone 24% side-effects quinidine (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

al., 2005 (197) 15872201	amiodarone and sotalol in converting AF and maintenance of SR	(665)	Sotalol 320 mg/d PC	randomization & on oral anticoagulation 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 24.2% sotalol 0.8% PC Median Time to Recurrence AF (intention to treat) 487 d amiodarone 74 d sotalol 6 d PC p<0.001	and exercise capacity		
SAFIRE-D, Singh S, et al., 2000 (198) 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 (250)	Dofetilide 250-1000 mcg/d PC	Inclusion: Age 18-85 y with AF or atrial flutter 2-26 wk duration 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 6.1% 125 mcg BID 9.8% 250 mcg BID 29.9% 500 mcg BID 1.2% PC p=0.015 250 mcg and p<0.001 500 mcg (vs. PC) Probability of SR at 1 y 0.40 125 mcg BID 0.37 250 mcg BID 0.58 500 mcg BID 0.25 PC	N/A	2 cases of torsade de pointes during initiation phase (0.8%) 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) 15321697	To assess the effectiveness of 2 AAD on frequency of AF	RCT, double-blind (1033)	High-dose Quinidine sulfate 480 mg/d and verapamil 240 mg/d (263) Low-dose Quinidine sulfate 320 mg/d and	Age 18-80 y, symptomatic PAF 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 105.7 d PC 150.4 d high-dose quinidine/verapamil 148.9 d low-dose quinidine/verapamil	AF burden (% says with symptomatic AF) 6.1% PC 3.4% high dose 4.5% low dose 2.9% sotalol (p=0.026)	1 death and 1 VT event related to high-dose quinidine/verapamil 2 syncopal events related to sotalol	Quinidine/verapamil fixed combination similar efficacy to sotalol but with risk of SAEs

			verapamil 160 mg/d (255) Sotalol HCL 320 mg/d (264) PC (251)	renal or liver dysfunction, hypokalemia, bundle branch block 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) 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 67% propafenone 35% PC (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 PC	Inclusion: Age ≥18 y, Symptomatic AF in SR at time of randomization 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 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) Disopyramide phosphate 500 mg/d (35)		Recurrence of AF at end of FU 57% disopyramide (13 mo) 32% amidarone (14 mo)	N/A	Disopyramide discontinued due to AE 14% <1 wk and another 14% by end of trial 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
Benditt D, et al., 1999 (175) 10496434	Prospective dose finding study	Sotalol 80 BID (59) Sotalol 120 BID (63) Sotalol 160 BID (62) PC (69)	SR	50 pts - outpatient 134 pts - inpatient	Structural heart disease 57% Exclusion: Hx of torsade de pointes, CHF, QT>450 ms, hypokalemia hypomagnesemia, bradycardia	No cases of VT/VF/torsade QT>520 ms in 7 pts (4 in 120 mg BID and 3 in 160 mg BID) Premature discontinuation due to AEs 25% inpatients, but 6% of outpatients (bradycardia predominantly)
Chung MK, at al., 1998 (203) 9669266	Retrospective	Sotalol	Not documented	Inpatient	120 inpatients admitted for sotalol initiation 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) 20 (16.7%) with significant bradycardia 8 (6.7%) excessive QT prolongation
SAFE-T, Singh BN, et al., 2005 (197) 15872201	Prospective RCT	Total 665 Amiodarone 267 Sotalol 261 Placebo 137	AF	Outpatient	Initiated sotalol or amiodarone in the outpatient setting during AF Excluded CHF class III or IV, Hx of long QT, CrCl<60	1 case torsade in sotalol group (nonfatal, time of occurrence not specified) 13 deaths/267 (6 sudden) amiodarone group 15 deaths/261 (8 sudden) sotalol group 3 deaths/137 (2 sudden) PC group (no significant difference)
Zimetbaum PJ, et al., 1999 (204) 10072241	Prospective	172 Amiodarone 66 (38%) Flecainide 45 (26%) Sotalol 20 (12%) Disopyramide 16 (9%) Propafenone 11 (6%) Quinidine 8 (5%) Procainamide 6 (4%)	SR	Outpatient	Pts with AF in sinus at time of initiation started on oral antiarrhythmic medication Received 1 or 2 doses of AAD in hospital or clinic and monitored for ≤8 h and then 10 d continuous loop event recorder Exlusion: QTc>550 ms, NYHA class III or IV CHF, or pacemaker	6 symptomatic AEs (none before d 4) Class Ic 3 atrial flutter with 1:1 d 6 or 7 1 symptomatic brady d 4 Sotalol 1 symptomatic bradycardia d 7 1 QT prolongation 370-520 ms d 4

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

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) 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) PC (720)	AF and underlying CV disease, diabetes, or left atrial enlargement	Co-primary endpoints: Time to first recurrence of AF, 295 d valsartan, 271 d PC 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) Reduction in AF greatest in pts with HF (RR: 0.44; p=0.007) No significant reduction in pts with HTN (RR: 0.12; p=0.4) although 1 study 29% reduction in pts with LVH (RR: 0.29)	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 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 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 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) AAD (37)	Paroxysmal	Segmental PVI with electrical isolation	Freedom from AF at 12 mo (Any recurrence of symptomatic AF or asymptomatic AF>15 s) 87% RFA 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) AAD – primarily amiodarone (69)	Paroxysmal and persistent	Circumferential PVI with anatomic isolation	Freedom from AF at 12 mo 55.9% RFA 8.7% AAD p<0.001	56%	9%	p<0.001	57%	4.4% major complications RFA	N/A

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

	diabetes				isolation							
Thermocool Wilber DJ, et al., 2010 (217) 20103757	Compare RFA to AAD in paroxysmal AF	RCT (167)	RFA (106) 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 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 Packer DL, et al., 2013 (218) 23500312	Assess efficacy of cryoballoon catheter ablation to AAD Tx in PAF	RCT (245)	Cryoballoon ablation (163) 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 69.9% cryoballoon (57.7% off drug) vs. 7.3% AAD (intention to treat) 60.1% single ablation (n=98)	70%	7.3%	p<0.001	79%	All events: cryoablation 12.3%, AAD 14.6% Procedure event rate 6.3% Phrenic nerve paralysis 11.2% (29) with 86.2% (25) resolved at 12 mo	N/A
RAAFT2 Morillo C, et al., 2014 (219)	Compare RFA to AAD as first-line therapy for pts with AF	RCT (127)	RFA (66) 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 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

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 Per visit burden at 24 mo Freedom from AF at 24 mo	 9% AF burden at 24 mo 85%	 18% AF burden at 24 mo71%	 p=0.007 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
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%) Multiple procedure success rate of AAD was 71% (95% CI: 65% to 77%) Multiple procedure success rate on AAD or with unknown AAD usage was 77% (95% CI: 73% to 81%)	Major complication rate 4.9% Stroke/TIA 0.5% Mortality 0.7% Cardiac tamponade 0.8% PV stenosis 1.6% 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 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 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

	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
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 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 Death from any cause (32% in the rhythm-control group and 33% in the rate-control group) Ischemic or hemorrhagic stroke 3% and 4%, respectively Worsening HF (defined as HF requiring hospitalization, administration of an IV diuretic, or change in Tx strategy) Composite outcome of death from CV causes, stroke, or worsening HF	None of the 2° outcomes differed significantly between the Tx groups 95% CI: 0.86-1.30; p=0.53 95% CI: 0.80-1.17; p=0.73 95% CI: 0.40-1.35; p=0.32 95% CI: 0.72-1.06; p=0.17 95% CI: 0.77-1.06; p=0.20	HR: 1.06 HR: 0.97 HR: 0.74 HR: 0.87 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

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 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 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

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 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 After additional 6 mo, 42 pts in dronedarone group (13.5%) and 39 pts in PC group (12.3%) died 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 p=0.60; 95% CI: 0.73-1.74 p=0.12; 95% CI: 0.92-2.09	HR: 2.13 HR: 1.13 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

RACE II Van Gelder IC, et al., 2010 (167) 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) Exclusion Criteria: Paroxysmal AF; contraindications for either strict or lenient rate control (e.g., previous adverse effects on negative chronotrophic drugs); unstable HF defined as NYHA IV HF or HF necessitating hospital admission <3 mo before inclusion; cardiac surgery <3 mo; any stroke; current or foreseen pacemaker, ICD, and/or cardiac resynchronization Tx; signs of sick sinus syndrome or AV conduction disturbances (i.e., symptomatic bradycardia or asystole >3 s or escape rate <40 bpm in awake Sx-free pts; untreated hyperthyroidism or <3 mo euthyroidism; inability to walk or bike	Composite of death from CV causes, hospitalization for HF, and stroke, SE, bleeding and life-threatening arrhythmic events. FU duration 2 y, with a maximum of 3 y	1° outcome incidence at 3 y was 12.9% in the lenient-control group and 14.9% in the strict-control group. Absolute difference with respect to the lenient-control group of -2.0 percentage points More pts in the lenient-control group met the heart rate target or targets (304 [97.7%] vs. 203 [67.0%] in the strict-control group) Frequencies of Sx and AEs were similar in the 2 groups	Absolute risk difference, -2.0% Absolute risk difference, CI: -7.6-3.5; p<0.001 90% CI: 0.58-1.21; p=0.001 p<0.001	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) 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 Characteristics: age 58±11 y, time from AF onset 7.3±6.2 y, left atrial volume 170±48 mL, 19±10 mo clinical FU	Pulmonary vein isolation at RFCA plus linear lesions	64% overall success rate 10 of these 16 success pts were off AAD Tx at final evaluation 77% success rate in PAF compared with 50% in the subgroup with permanent AF	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

Kilicaslan F, et al., 2006 (227) 16500298	The purpose of this study was to report the results and outcome of PV antrum isolation in pts with AF and HOCM	27	27 pts with AF and HOCM who underwent PV antrum isolation between February 2002 and May 2004 Mean age 55±10 y Mean AF duration was 5.4±3.6 y AF was paroxysmal in 14 (52%), persistent in 9 (33%), and permanent in 4 (15%) Mean FU of 341±237 d	Maintenance of sinus rhythm after PV antrum isolation	13 pts (48%) had AF recurrence 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 Final success rate=70% (19/27) 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 Paroxysmal AF=21 (64%) pts had paroxysmal AF Persistent/permanent AF=12 (36%) had persistent/permanent AF Duration AF=6.2±5.2 y Average EF=0.63±0.12 Average left atrial volume index was 70±24 mL/m^2 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

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; Time from AF onset 5.7±5.5 y Paroxysmal AF=35; (57%) Recent persistent AF=15; (25%) Long-standing persistent AF=11; (18%) Ablation scheme: pulmonary vein isolation plus linear lesions 32 of 61 pts, 32 (52%) required redo procedures. Antiarrhythmic Tx was maintained in 22 (54%) FU: 29±16 mo 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). 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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