

2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Updating the 2006 Guideline): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

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J. Am. Coll. Cardiol. 2011;57:223-242; originally published online Dec 20, 2010; doi:10.1016/j.jacc.2010.10.001

This information is current as of January 4, 2011

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://content.onlinejacc.org/cgi/content/full/57/2/223>

JACC

JOURNAL of the AMERICAN COLLEGE of CARDIOLOGY



PRACTICE GUIDELINE

2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Updating the 2006 Guideline)

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

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This document was approved by the American College of Cardiology Foundation Board of Trustees in July 2010, by the American Heart Association Science Advisory and Coordinating Committee in August 2010, and by the Heart Rhythm Society in August 2010.

The American College of Cardiology requests that this document be cited as follows: Wann LS, Curtis AB, January CT, Ellenbogen KA, Lowe JE, Estes NAM 3rd, Page RL, Ezekowitz MD, Slotwiner DJ, Jackman WM, Stevenson WG, Tracy CM, writing on behalf of the 2006 ACC/AHA/ESC Guidelines for the Management of Patients With Atrial Fibrillation Writing Committee. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2011;57:223–42.

This article has been copublished in *Circulation* and *HeartRhythm*.

Copies: This document is available on the World Wide Web sites of the American College of Cardiology (www.cardiosource.org), and the American Heart Association (my.americanheart.org). For copies of this document, please contact Elsevier Inc. Reprint Department, fax 212-633-3820; e-mail reprints@elsevier.com.

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Preamble

A primary challenge in the development of clinical practice guidelines is keeping pace with the stream of new data on which recommendations are based. In an effort to respond promptly to new evidence, the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Task Force on Practice Guidelines has created a “focused update” process to revise the existing guideline recommendations that are affected by the evolving data or opinion. Before the initiation of this focused approach, periodic updates and revisions of existing guidelines required up to 3 years to complete. Now, however, new evidence will be reviewed in an ongoing fashion to more efficiently respond to important science and treatment trends that could have a major impact on patient outcomes and quality of care. Evidence will be reviewed at least twice a year, and updates will be initiated on an as-needed basis and completed as quickly as possible while maintaining the rigorous methodology that the ACCF and AHA have developed during their partnership of more than 20 years.

These updated guideline recommendations reflect a consensus of expert opinion after a thorough review primarily of late-breaking clinical trials identified through a broad-based vetting process as being important to the relevant patient population, as well as other new data deemed to have an impact on patient care (see Section 1.1, *Methodology and Evidence Review*, for details). This focused update is not intended to represent an update based on a full literature review from the date of the previous guideline publication. Specific criteria/considerations for inclusion of new data include the following:

- publication in a peer-reviewed journal;
- large, randomized, placebo-controlled trial(s);
- nonrandomized data deemed important on the basis of results affecting current safety and efficacy assumptions;
- strength/weakness of research methodology and findings;
- likelihood of additional studies influencing current findings;
- impact on current and/or likelihood of need to develop new performance measure(s);
- request(s) and requirement(s) for review and update from the practice community, key stakeholders, and other sources free of relationships with industry or other potential bias;
- number of previous trials showing consistent results; and
- need for consistency with a new guideline or guideline revisions.

In analyzing the data and developing updated recommendations and supporting text, the focused update writing group used evidence-based methodologies developed by the ACCF/AHA Task Force on Practice Guidelines that are described elsewhere (1). The Task Force on Practice Guidelines makes every effort to avoid actual, potential, or perceived conflicts of interest that may arise as a result of industry relationships or personal interests among the writing group. Specifically, all members of the writing group, as well as peer reviewers of the document, are asked to disclose ALL relevant relationships and those existing 12 months before initiation of the writing effort. In response to implementation of a new relationship with industry and other entities (RWI) policy approved by the ACC and AHA, it is also required that the writing group chair plus a majority of the writing group (50%) have no *relevant* RWI. All guideline recommendations require a confidential vote by the writing group members before and after external review of the document and must be approved by a consensus of the members voting. Members who were recused from voting are noted on the title page of this document and in [Appendix 1](#). Members must recuse themselves from voting on any recommendations to which their RWI apply. Any writing group member who develops a new RWI during his or her tenure is required to notify guideline staff in writing. These statements are reviewed by the Task Force on Practice Guidelines and all members during each conference call and/or meeting of the writing group and are updated as changes occur. For detailed information about guideline policies and procedures, please refer to the ACCF/AHA methodology and policies manual (1). Authors’ and peer reviewers’ RWI pertinent to this guideline are disclosed in [Appendixes 1 and 2](#), respectively. Addition-

ally, to ensure complete transparency, writing group members' *comprehensive disclosure information*—including RWI not pertinent to this document—are available online as a data supplement. Disclosure information for the ACCF/AHA Task Force on Practice Guidelines is available online at www.cardiosource.org/ACC/About-ACC/Leadership/Guidelines-and-Documents-Task-Forces.aspx and at www.americanheart.org/presenter.html?id=3039684. Writing committee members who chose not to participate are not listed as authors of this focused update. The work of the writing group was supported exclusively by the ACCF and AHA without commercial support. Writing group members volunteered their time for this effort.

The committee reviewed and ranked evidence supporting current recommendations, with the weight of evidence ranked as Level A if the data were derived from multiple randomized clinical trials or meta-analyses. The committee ranked available evidence as Level B when data were derived from a single randomized trial or nonrandomized studies. Evidence was ranked as Level C when the primary source of the recommendation was consensus opinion of experts, case studies, or standard of care. In the narrative portions of these guidelines, evidence is generally presented in chronological order of development. Studies are identified as observational, retrospective, prospective, or randomized where appropriate. For certain conditions for which inadequate data are available, recommendations are based on expert consensus and clinical experience and ranked as Level C. An example is the use of penicillin for pneumococcal pneumonia, where there are no randomized trials and treatment is based on clinical experience. When recommendations at Level C are supported by historical clinical data, appropriate references (including clinical reviews) are cited if available. For issues where sparse data are available, a survey of current practice among the clinicians on the writing committee was the basis for Level C recommendations and no references are cited. The schema for Classification of Recommendations (COR) and Level of Evidence (LOE) is summarized in Table 1, which also illustrates how the grading system provides an estimate of the size of the treatment effect and an estimate of the certainty of the treatment effect. A new addition to the ACCF/AHA methodology is a separation of the Class III recommendations to delineate whether the recommendation is determined to be of “no benefit” or 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/strategy with respect to another for COR I and IIa, LOE A or B only have been added.

The ACCF/AHA practice guidelines address patient populations (and healthcare providers) residing in North America. As such, drugs that are not currently available in North America are discussed in the text without a specific COR. For studies performed in large numbers of subjects outside of North America, each writing group reviews the potential impact of different practice patterns and patient populations on the treatment effect and the relevance to the ACCF/AHA target population to determine whether the findings should inform a specific recommendation.

The ACCF/AHA practice guidelines are intended to assist healthcare providers in clinical decision making by describing a range of generally acceptable approaches for 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 regarding care of a particular patient must be made by the healthcare provider and patient in light of all the circumstances presented by that patient. Thus, there are circumstances in which deviations from these guidelines may be appropriate. Clinical decision making should consider the quality and availability of expertise in the area where care is provided.

Prescribed courses of treatment in accordance with these recommendations are effective only if they are followed. Because lack of patient understanding and adherence may adversely affect treatment outcomes, physicians and other healthcare providers should make every effort to engage the patient's active participation in prescribed medical regimens and lifestyles. When these guidelines are used as the basis for regulatory or payer decisions, the goal should be improvement in quality of care aligned with the patient's best interest.

With the exception of the recommendations presented here, the full-text guideline remains current. Only the recommendations from the affected section(s) of the full-text guideline are included in this focused update. For easy reference, all recommendations from any section of a guideline affected by a change are presented with notation as to whether they remain current, are new, or have been modified. When evidence affects recommendations in more than 1 set of guidelines, those guidelines are updated concurrently.

The recommendations in this focused update will be considered current until they are superseded by another focused update or the full-text guidelines are revised. This focused update is published in the *Journal of the American College of Cardiology*, *Circulation*, and *HeartRhythm* as an update to the full-text guideline (2), and it is available on the ACC (www.cardiosource.org), AHA (my.americanheart.org), and Heart Rhythm Society (hrsonline.org) World Wide Web sites.

Alice K. Jacobs, MD, FACC, FAHA
Chair, ACCF/AHA Task Force on Practice Guidelines

1. Introduction

1.1. Methodology and Evidence Review

Late-breaking clinical trials presented at the 2009 annual scientific meetings of the ACC, AHA, and European Society of Cardiology (ESC), as well as selected other data reported through April 2010, were reviewed by the standing guideline writing committee along with the Task Force on Practice Guidelines and other experts to identify those trials and other key data that may impact guideline recommendations. On the basis of the criteria/considerations noted above, recent trial data and other clinical information were considered important enough to prompt a focused update of the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation (2).

Table 1. Applying Classification of Recommendation and Level of Evidence

		SIZE OF TREATMENT EFFECT			
		CLASS I <i>Benefit >>> Risk</i> Procedure/Treatment SHOULD be performed/administered	CLASS IIa <i>Benefit >> Risk</i> <i>Additional studies with focused objectives needed</i> IT IS REASONABLE to perform procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> <i>Additional studies with broad objectives needed; additional registry data would be helpful</i> Procedure/Treatment MAY BE CONSIDERED	CLASS III <i>No Benefit</i> or CLASS III <i>Harm</i>
					Procedure/ Test Treatment
					COR III: No benefit Not Helpful No Proven Benefit
					COR III: Harm Excess Cost w/o Benefit or Harmful Harmful to Patients
ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Sufficient evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Only expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Only diverging expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Only diverging expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> 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 done is not useful/beneficial/effective
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			

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. 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. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

†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.

To provide clinicians with a comprehensive set of data, whenever deemed appropriate or when published in the article, data from the clinical trial will be used to calculate the absolute risk difference (ARD) and number needed to treat (NNT) or harm (NNH); data related to the relative treatment effects will also be provided, such as odds ratio (OR), relative risk (RR), hazard ratio (HR), or incidence rate ratio (IRR) along with confidence interval (CI) when available.

Consult the full-text version or executive summary of the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation (2) for policy on clinical areas not covered by the focused update. The individual recommendations in this focused update will be incorporated into future revisions and/or updates of the full-text guideline.

1.2. Organization of the Writing Committee

For this focused update, all members of the 2006 Atrial Fibrillation Writing Committee were invited to participate; those who agreed (referred to as the 2011 Focused Update Writing Group) were required to disclose all RWI relevant to the data under consideration. The Heart Rhythm Society was invited to be a partner on this update and provided 3 representatives.

1.3. Document Review and Approval

This document was reviewed by 2 official reviewers each nominated by the ACCF, the AHA, the Heart Rhythm Society, and 25 individual content reviewers (including

Table 2. Recommendation for Rate Control During Atrial Fibrillation

2011 Focused Update Recommendation	Comments
Class III—No Benefit	
1. Treatment to achieve strict rate control of heart rate (<80 bpm at rest or <110 bpm during a 6-minute walk) is not beneficial compared to achieving a resting heart rate <110 bpm in patients with persistent AF who have stable ventricular function (left ventricular ejection fraction >0.40) and no or acceptable symptoms related to the arrhythmia, though uncontrolled tachycardia may over time be associated with a reversible decline in ventricular performance (3). (Level of Evidence: B)	New recommendation

members of the ACCF Electrophysiology Committee, the Atrial Fibrillation Performance Measures Committee, and the Atrial Fibrillation Data Standards Committee). All reviewer RWI information was collected and distributed to the writing committee and is published in this report (Appendix 2).

This document was approved for publication by the governing bodies of the ACCF, AHA, and Heart Rhythm Society.

8. Management

This guideline update focuses on several areas in which new data on management of patients with atrial fibrillation (AF) have become available, including a) recommendations for strict versus lenient heart rate control, b) combined use of antiplatelet and anticoagulant therapy, and c) use of dronedarone. Recommendations are not made for use of dabigatran, a new antithrombotic agent which was not approved by the U.S. Food and Drug Administration (FDA) at the time of organizational approval of this document, or for the Watchman device for occlusion of the left atrial appendage which is investigational pending FDA approval.

8.1.3. Rate Control During Atrial Fibrillation

CRITERIA FOR RATE CONTROL. In patients with AF, the ventricular rate may accelerate excessively during exercise even when it is well controlled at rest (Table 2). Rate reduction, allowing adequate time for ventricular filling and avoiding rate-related ischemia, may result in improved hemodynamics. Therefore, evaluating the heart rate response to submaximal or maximal exercise or to monitor the rate over an extended period (e.g., by 24-hour Holter recording) may be an option. In addition, rate variability during AF provides information about the status of the autonomic nervous system that may have independent prognostic implications (4–7). Parameters for optimal rate control in AF remain controversial. The definition of adequate rate control has been based primarily on short-term hemodynamic benefits and has not been well studied with respect to regularity or irregularity of the ventricular response to AF, quality of life, symptoms, or development of cardiomyopathy. No standard method for assessment of heart rate control has been established to guide management of patients with AF. Criteria for rate control vary with patient age but usually involve achieving ventric-

ular rates between 60 and 80 bpm at rest and between 90 and 115 bpm during moderate exercise. For the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) study, adequate control was defined as an average heart rate of up to 80 bpm at rest and either an average rate of up to 100 bpm over at least 18 hours of ambulatory Holter monitoring with no rate greater than 100% of the maximum age-adjusted predicted exercise heart rate or a maximum heart rate of 110 bpm during a 6-minute walk test (8).

The potential benefits of strict (resting heart rate <80 bpm, heart rate <110 bpm during moderate exercise) versus lenient (resting heart rate <110 bpm) rate control were addressed in the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation) trial of 614 patients with permanent AF (3). AF was treated with a variety of atrioventricular (AV) nodal blocking agents to control heart rate (3). Primary endpoints were death from cardiovascular causes, hospitalization for heart failure, stroke, systemic embolism, bleeding, and life-threatening arrhythmias. The 3-year estimated cumulative incidence of the primary outcome was 12.9% in the lenient-control group and 14.9% in the strict-control group (Appendix 3), with an absolute difference between lenient control and strict control of –2.0 percentage points (90% CI: –7.6 to 3.5; $p < 0.001$) and HR of 0.84 (90% CI: 0.58 to 1.21; $p = 0.001$ for the prespecified noninferiority margin). Symptoms were also similar in both groups. All patients included in the study were ambulatory and relatively young (mean age, 68 years), predominantly male, and may have been healthier and less symptomatic than many patients encountered in clinical practice. Long-term effects of a more rapid heart rate response to AF on ventricular function were not studied. If a lenient rate control strategy is chosen for patients with persistent AF who have stable ventricular function (left ventricular [LV] ejection fraction >0.40) and or no acceptable symptoms related to AF, LV function should be monitored.

The RACE II study reported only a total of 81 composite events in 614 patients and was not adequately powered to make conclusive comments on whether there were or were not clinically relevant differences in clinical outcomes between strict- and lenient-rate control (3). Nevertheless, strict targeting of treatment to achieve an arbitrary heart rate seems unnecessary. The RACE II study shows that lenient-rate control <110 bpm is not inferior to strict-rate control <80 bpm. As lenient-rate control is generally more convenient, requiring fewer outpatient visits and examinations, lenient-rate control may be adopted as a reasonable strategy in patients with permanent AF.

The Atrial Fibrillation and Congestive Heart Failure Trial compared the benefits of rhythm control with rate control in a randomized, multicenter trial of 1,376 patients with AF and congestive heart failure (9). AF was defined as 1 episode of AF lasting at least 6 hours or requiring cardioversion within the preceding 6 months or an episode lasting for at least 10 minutes within the previous 6 months and previous cardioversion. Congestive heart failure was defined as an ejection fraction of $\leq 35\%$ and symptomatic New York Heart Association (NYHA) class II or IV heart failure within the previous 6 months, or an ejection fraction of $\leq 25\%$. Rhythm control included cardioversion and antiarrhythmic therapy,

Table 3. Recommendation for Combining Anticoagulant With Antiplatelet Therapy

2011 Focused Update Recommendation	Comments
Class IIb	
1. The addition of clopidogrel to aspirin (ASA) to reduce the risk of major vascular events, including stroke, might be considered in patients with AF in whom oral anticoagulation with warfarin is considered unsuitable due to patient preference or the physician's assessment of the patient's ability to safely sustain anticoagulation (10). (Level of Evidence: B)	New recommendation

primarily using amiodarone, repeat cardioversion if needed, and possible referral for nonpharmacologic therapy. Rate control was achieved primarily using beta blockers with digitalis to achieve a target heart rate of <80 bpm at rest or <110 bpm during a 6-minute walk test. No difference was found in the primary endpoint of death from cardiovascular causes with a mean follow-up of 37 months. One hundred eighty-two (27%) in the rhythm-control group died compared with 175 (25%) in the rate-control group (HR: 1.06; 95% CI: 0.86 to 1.30; p=0.59) by log rank test. Secondary outcomes, including death from any cause, worsening heart failure, stroke, and composite and death from cardiovascular causes, were also similar in both groups. Patients treated with rhythm control were more likely to be hospitalized than those treated with rate control (9). This trial showed no benefit for use of a routine strategy of rhythm control in patients with AF and systolic heart failure compared with a strategy of rate control.

8.1.4.2.4. RECOMMENDATION FOR COMBINING ANTICOAGULANT WITH ANTIPLATELET THERAPY (NEW SECTION). Multiple studies have demonstrated that oral anticoagulation with warfarin is effective for prevention of thromboembolism in AF patients (Table 3) (2,11–16). Aspirin (ASA) offers only modest protection against stroke for AF patients (13,17–23). Adjusted-dose oral anticoagulation is more efficacious than ASA for prevention of stroke in patients with AF (2,24). Recent studies have assessed the thienopyridine antiplatelet agent clopidogrel with ASA for stroke prevention in AF patients (10,25).

The ACTIVE-W (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) trial (25) compared clopidogrel plus ASA with oral anticoagulation therapy with warfarin for prevention of vascular events in AF patients with an average of 2 stroke risk factors. The primary outcome was first occurrence of stroke, noncentral nervous system systemic embolism, myocardial infarction (MI), or vascular death. There were 165 primary events in patients receiving oral anticoagulation therapy (annual risk: 3.93%) and 234 in those receiving clopidogrel plus ASA (annual risk: 5.60%; RR: 1.44 [95% CI: 1.18 to 1.76; p=0.0003; NNT: 47]). Although rates of hemorrhage were similar between the 2 groups, significantly greater minor and total bleeds occurred with clopidogrel and ASA than with oral anticoagulation therapy. Major hemorrhages (severe and fatal) occurred in 2.42% of patients treated with clopidogrel plus ASA and in

2.21% of those treated with oral anticoagulation (RR: 1.10; 95% CI: 0.83 to 1.45; p=0.53). Total hemorrhagic complications occurred in 15.40% of patients treated with clopidogrel plus ASA and in 13.21% of those treated with oral anticoagulation (RR: 1.21; 95% CI: 1.08 to 1.35; p=0.001). The total adverse outcome (primary outcome and major bleeds) was 316 in clopidogrel and ASA and 229 in oral anticoagulation (RR: 1.41; 95% CI: 1.19 to 1.67; p<0.001). Oral anticoagulation therapy with warfarin proved superior to clopidogrel plus ASA for prevention of vascular events in AF patients. Treatment with clopidogrel plus ASA was associated with bleeding risk similar to treatment with warfarin.

The ACTIVE-A (Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation) trial assessed whether the addition of clopidogrel to ASA would reduce the risk of vascular events in AF patients who were considered unsuitable for therapy with oral anticoagulation with warfarin (10) (Appendix 3). Patients were deemed “unsuitable” for oral anticoagulation due to a specific risk of bleeding (22.9%), patient preference (26%), or physician preference (49.7%). The primary outcome was the composite of stroke, MI, noncentral nervous system systemic embolism, or death from vascular causes. At 3.6 years of follow-up, major vascular events had occurred in 832 patients receiving ASA plus clopidogrel (6.8% per year) and in 924 patients receiving ASA plus placebo (7.6% per year) (RR with clopidogrel: 0.89; 95% CI: 0.81 to 0.98; p=0.01). The difference was primarily due to a reduction in the rate of stroke with clopidogrel. Stroke occurred in 296 patients receiving ASA plus clopidogrel (2.4% per year) and in 408 patients receiving placebo (3.3% per year; RR: 0.72; 95% CI: 0.62 to 0.83; p<0.001). MI occurred in 90 patients receiving clopidogrel (0.7% per year) and in 115 patients receiving placebo (0.9% per year) (RR: 0.78; 95% CI: 0.59 to 1.03; p=0.08). Major bleeding occurred in 251 patients receiving ASA plus clopidogrel (2.0% per year) and in 162 patients receiving ASA plus placebo (1.3% per year; RR: 1.57; 95% CI: 1.29 to 1.92; p<0.001). In AF patients for whom oral anticoagulation with warfarin was considered unsuitable, the addition of clopidogrel to ASA reduced the risk of major vascular events, especially stroke, and increased the risk of major hemorrhage.

The combined use of dual-antiplatelet therapy with both clopidogrel and ASA plus anticoagulation with warfarin (triple therapy) has been suggested as a strategy for treatment and prevention of complications of 2 or more coexisting conditions such as AF, mechanical valve prosthesis, or the presence of a drug-eluting coronary stent (26). This strategy is associated with an increase in bleeding complications that might range from mild or moderate to severe or life threatening. No prospective randomized trials have been reported addressing this important clinical issue.

8.1.4.2.5. EMERGING AND INVESTIGATIONAL ANTITHROMBOTIC AGENTS. The RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial of dabigatran (27), a prodrug that is rapidly converted to an active direct thrombin inhibitor independent of the cytochrome P-450, was reviewed by the 2011 Focused Update Writing Group, but recommendations about its use are not included in this focused update because

Table 4. Recommendations for Use of Dronedaron in Atrial Fibrillation

2011 Focused Update Recommendations	Comments
Class IIa	
1. Dronedaron is reasonable to decrease the need for hospitalization for cardiovascular events in patients with paroxysmal AF or after conversion of persistent AF. Dronedaron can be initiated during outpatient therapy (29). (Level of Evidence: B)	New recommendation
Class III–Harm	
1. Dronedaron should not be administered to patients with class IV heart failure or patients who have had an episode of decompensated heart failure in the past 4 weeks, especially if they have depressed left ventricular function (left ventricular ejection fraction ≤35%) (30). (Level of Evidence: B)	New recommendation

dabigatran was not approved for clinical use by the FDA at the time of organizational approval.

8.1.4.3. NONPHARMACOLOGIC APPROACHES TO PREVENTION OF THROMBOEMBOLISM

The 2011 Focused Update Writing Group considered the Watchman device for atrial appendage closure in its deliberations in anticipation of FDA approval of this device (28). Because the FDA has not approved clinical use of the Watchman device pending the results of additional ongoing trials, the writing group’s deliberations and recommendations regarding the Watchman device are not included in the final version of this focused update. A future guideline writing committee will address this and other evolving areas in the management of AF.

8.1.8.3. RECOMMENDATIONS FOR DRONEDARONE FOR THE PREVENTION OF RECURRENT ATRIAL FIBRILLATION (NEW SECTION)

Dronedaron is similar to amiodaron but lacks an iodine moiety. Its multiple electrophysiologic actions include sympatholytic effects as well as inhibition of the L-type calcium current, the inward sodium current, and multiple potassium currents (Table 4) (31). Two randomized trials (EURIDIS [European Trial In Atrial Fibrillation or Flutter Patients Receiving Dronedaron for the Maintenance of Sinus Rhythm] and ADONIS [American-Australian-African Trial With Dronedaron in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm]) found that dronedaron prolongs the time to recurrence of AF (Appendix 3) (32,33). In patients with persistent AF, DAFNE (Dronedaron Atrial Fibrillation study after Electrical Cardioversion) showed that administration of dronedaron converted only 5.8% to sinus rhythm (3.1% converted with placebo) and did not improve the acute success of electrical cardioversion (33). Dronedaron slows the ventricular rate in AF by an average of 11 to 13 bpm (33,34). Incidence of spontaneous conversion to sinus rhythm was dose related (i.e., 800, 1,200, and 1,600 mg). The conversion ratio was 5.8% (800 mg), 8.2% (1,200 mg), and 14.2% (1,600 mg), but the incidence of successful electrical cardioversion was not statistically different between groups

(800 mg=77.3%; 1,200 mg=87.9%; and 1,600 mg=76.6% versus 73.0% in the placebo group) (33).

Dronedaron is generally less efficacious than amiodaron (35). The DIONYSOS (Efficacy & Safety of Dronedaron Versus Amiodaron for the Maintenance of Sinus Rhythm in Patients With Persistent Atrial Fibrillation) study was a short-term, randomized, double-blind, parallel-group study that evaluated the efficacy and safety of dronedaron versus amiodaron (36). In patients with persistent AF, dronedaron was less effective than amiodaron in decreasing AF recurrence in 504 patients with persistent AF randomized to treatment with either dronedaron or amiodaron, but it was better tolerated (Appendix 3). The primary composite endpoint was recurrence of AF (including unsuccessful electrical cardioversion, no spontaneous conversion, and no electrical cardioversion) or premature study discontinuation was achieved in 75.1% of patients taking dronedaron and 58.8% taking amiodaron at 12 months (HR: 1.59; 95% CI: 1.28 to 1.98; p<0.0001). Premature discontinuation of study drug occurred in 10.4% of the dronedaron group and 13.3% of the amiodaron group. Main safety endpoints were observed in 39.3% of dronedaron patients versus 44.5% of amiodaron patients (HR: 0.80; 95% CI: 0.60 to 1.07; p=0.129). Fewer thyroid, neurologic, dermatologic, and ocular events occurred in the dronedaron group.

The ATHENA (A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedaron 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patients with Atrial fibrillation/atrial flutter) trial included patients with paroxysmal or persistent AF or atrial flutter and risk factors for thromboembolism (29) (Appendix 3). Dronedaron reduced the combined endpoint of death and cardiovascular hospitalizations, largely by reducing hospitalizations related to AF (and cardiovascular death); death from any cause was not reduced (29). Maintenance of sinus rhythm was not a discrete endpoint in this trial. Fewer strokes occurred in the dronedaron group, although this effect was not prespecified and requires confirmation by other trials (37). The ATHENA trial excluded patients with decompensated heart failure within the previous 4 weeks, or with NYHA class IV heart failure. There was no evidence of an adverse effect of dronedaron in patient subgroups with a history of congestive heart failure or LV ejection fraction <35% (29). Note that evidence of efficacy is based on reduced hospitalization for AF, acute coronary syndrome and all cause mortality, not maintenance of sinus rhythm.

In a trial of patients with recently decompensated heart failure and depressed LV function, ANDROMEDA (Antiarrhythmic Trial with Dronedaron in Moderate to Severe CHF Evaluating Morbidity Decrease), dronedaron increased mortality after a median follow-up of only 2 months; 8.1% in the dronedaron group died and 3.8% in the placebo group died (HR: 2.13; 95% CI: 1.07 to 4.25; p=0.03) (Appendix 3) (30). The higher mortality was associated with more progression of heart failure. Therefore, dronedaron should not be administered to patients with depressed ventricular function and recent heart failure decompensation or NYHA class IV heart failure.

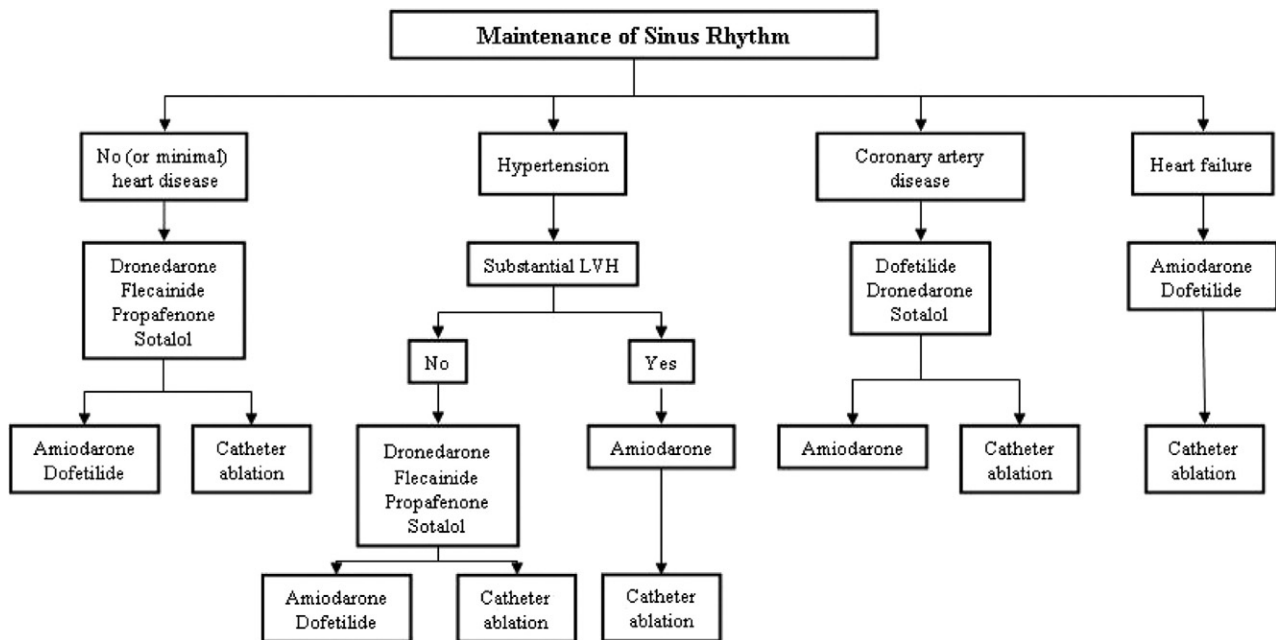


Figure 1. Therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent atrial fibrillation. Drugs are listed alphabetically and not in order of suggested use. The seriousness of heart disease progresses from left to right, and selection of therapy in patients with multiple conditions depends on the most serious condition present. LVH indicates left ventricular hypertrophy. Modified from Fuster et al. (2) (formerly Figure 15 from 2006 Section 8.3.3).

The major adverse cardiac effects of dronedarone are bradycardia and QT prolongation. Torsades de pointes has been reported (29). Like amiodarone, dronedarone inhibits renal tubular secretion of creatinine, which can increase plasma creatinine levels. However, there is no reduction in glomerular filtration rate. Dronedarone increases digoxin levels 1.7- to 2.5-fold (31). Dronedarone is predominantly metabolized by the liver (CYP3A4) with a half-life of approximately 19 hours. It should not be administered with strong inhibitors of CYP3A4 (e.g., ketoconazole and macrolide antibiotics) because these may potentiate the effects of dronedarone. It can be administered with verapamil or diltiazem, which are moderate CYP3A4 inhibitors, but low doses of these agents should be used initially and titrated according to response and tolerance (31). Dronedarone does not alter the international normalization ratio when used with warfarin. The recommended oral dose of dronedarone is 400 mg twice a day with meals. An intravenous form is not available.

8.3. Maintenance of Sinus Rhythm

8.3.1. Recommendations for Therapy

Figure 1 incorporates dronedarone into the algorithm previously recommended for therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent AF (Table 5).

8.3.1.4. FUTURE DIRECTIONS IN CATHETER-BASED ABLATION THERAPY FOR ATRIAL FIBRILLATION (NEW SECTION)

Catheter ablation to maintain sinus rhythm has been reported in trials and meta-analyses including data from more than 6,900 patients (38–51). Patients undergoing ablation are a selected population characterized by a predominance of those with symptomatic paroxysmal AF that has failed treatment with one or more antiarrhythmic drugs, with normal size or

mildly dilated atria, normal or mildly reduced ventricular function, and absence of severe pulmonary disease. Following ablation, most patients are free of recurrent, paroxysmal AF for 1 year or more.

In the ThermoCool trial, a randomized multicenter study of 167 symptomatic patients with paroxysmal AF who had not shown improvement with at least 1 antiarrhythmic drug, radiofrequency catheter ablation with pulmonary vein isolation resulted in significantly fewer episodes of recurrent AF than did treatment with additional antiarrhythmic drugs (51) (Appendix 3). Quality-of-life and symptom severity scores were significantly better after 3 months in the group treated with catheter ablation. Major treatment-related adverse events were similar between catheter-treated and drug-treated groups at 30 days. More than 5,000 patients were screened to recruit these 167 study subjects. Important exclusions included patients with AF >30 days' duration, ejection fraction <40%, left atrial diameter >5 cm, severe pulmonary disease, recent MI, coronary artery bypass graft surgery, thromboemboli, treatment with amiodarone, or previous catheter ablations for AF (51). The average age of patients undergoing catheter ablation was relatively young at 55.7 years (95% CI: 54.1 to 57.4), and they had paroxysmal, symptomatic AF for a relatively long time: 5.7 years (95% CI: 4.8 to 6.6). All ablation procedures were performed by highly experienced operators in high-volume centers. Although the primary endpoint in all centers was electrical isolation of all pulmonary veins in each patient who underwent AF ablation, other aspects of the ablation procedures were not standardized, including the use of linear lesions. Repeat catheter ablation procedures were performed in 12.6% of the ablation group. Ultimately, 34% of ablation patients had recurrence of symptomatic AF during the 9-month follow-up period, com-

Table 5. Recommendations for Maintenance of Sinus Rhythm

2006 Recommendations	2011 Focused Update Recommendations	Comments
Class I		
Before initiating antiarrhythmic drug therapy, treatment of precipitating or reversible causes of AF is recommended. (Level of Evidence: C)	1. Before initiating antiarrhythmic drug therapy, treatment of precipitating or reversible causes of AF is recommended. (Level of Evidence: C)	2006 recommendation remains current.
	2. Catheter ablation performed in experienced centers* is useful in maintaining sinus rhythm in selected patients with significantly symptomatic, paroxysmal AF who have failed treatment with an antiarrhythmic drug and have normal or mildly dilated left atria, normal or mildly reduced LV function, and no severe pulmonary disease (38–51). (Level of Evidence: A)	Modified recommendation (class of recommendation changed from IIa to I, wording revised, and level of evidence changed from C to A).
Class IIa		
Pharmacological therapy can be useful in patients with AF to maintain sinus rhythm and prevent tachycardia-induced cardiomyopathy. (Level of Evidence: C)	1. Pharmacological therapy can be useful in patients with AF to maintain sinus rhythm and prevent tachycardia-induced cardiomyopathy. (Level of Evidence: C)	2006 recommendation remains current.
Infrequent, well-tolerated recurrence of AF is reasonable as a successful outcome of antiarrhythmic drug therapy. (Level of Evidence: C)	2. Infrequent, well-tolerated recurrence of AF is reasonable as a successful outcome of antiarrhythmic drug therapy. (Level of Evidence: C)	2006 recommendation remains current.
Outpatient initiation of antiarrhythmic drug therapy is reasonable in patients with AF who have no associated heart disease when the agent is well tolerated. (Level of Evidence: C)	3. Outpatient initiation of antiarrhythmic drug therapy is reasonable in patients with AF who have no associated heart disease when the agent is well tolerated. (Level of Evidence: C)	2006 recommendation remains current.
In patients with lone AF without structural heart disease, initiation of propafenone or flecainide can be beneficial on an outpatient basis in patients with paroxysmal AF who are in sinus rhythm at the time of drug initiation. (Level of Evidence: B)	4. In patients with AF without structural or coronary heart disease, initiation of propafenone or flecainide can be beneficial on an outpatient basis in patients with paroxysmal AF who are in sinus rhythm at the time of drug initiation (52–54). (Level of Evidence: B)	Modified recommendation (wording clarified).
Sotalol can be beneficial in outpatients in sinus rhythm with little or no heart disease, prone to paroxysmal AF, if the baseline uncorrected QT interval is less than 460 ms, serum electrolytes are normal, and risk factors associated with Class III drug–related proarrhythmia are not present. (Level of Evidence: C)	5. Sotalol can be beneficial in outpatients in sinus rhythm with little or no heart disease, prone to paroxysmal AF, if the baseline uncorrected QT interval is less than 460 ms, serum electrolytes are normal, and risk factors associated with Class III drug–related proarrhythmia are not present. (Level of Evidence: C)	2006 recommendation remains current.
	6. Catheter ablation is reasonable to treat symptomatic persistent AF (38,48,55–64). (Level of Evidence: A)	New recommendation
Catheter ablation is a reasonable alternative to pharmacological therapy to prevent recurrent AF in symptomatic patients with little or no left atrium enlargement. (Level of Evidence: C)		Modified recommendation (class of recommendation changed from IIa to I, wording revised and level of evidence changed from C to A).
Class IIb		
	1. Catheter ablation may be reasonable to treat symptomatic paroxysmal AF in patients with significant left atrial dilatation or with significant LV dysfunction (38,48,55–64). (Level of Evidence: A)	New recommendation
Class III–Harm		
Antiarrhythmic therapy with a particular drug is not recommended for maintenance of sinus rhythm in patients with AF who have well-defined risk factors for proarrhythmia with that agent. (Level of Evidence: A)	1. Antiarrhythmic therapy with a particular drug is not recommended for maintenance of sinus rhythm in patients with AF who have well-defined risk factors for proarrhythmia with that agent (65,66). (Level of Evidence: A)	2006 recommendation remains current.
Pharmacological therapy is not recommended for maintenance of sinus rhythm in patients with advanced sinus node disease or AV node dysfunction unless they have a functioning electronic cardiac pacemaker. (Level of Evidence: C)	2. Pharmacological therapy is not recommended for maintenance of sinus rhythm in patients with advanced sinus node disease or AV node dysfunction unless they have a functioning electronic cardiac pacemaker. (Level of Evidence: C)	2006 recommendation remains current.

*Refers to pulmonary vein isolation with catheter ablation. An experienced center is defined as one performing more than 50 AF catheter ablation cases per year (67). Evidence-based technical guidelines including operator training and experience necessary to maximize rates of successful catheter ablation are not available; each center should maintain a database detailing procedures; success and complications, engage strategies for continuous quality improvement, and participate in registries and other efforts pooling data in order to develop optimal care algorithms (68).

pared with 84% of the drug-treated group (51). In this highly selected patient population, in patients for whom 1 antiarrhythmic drug has failed, subsequent antiarrhythmic drug treatment is likely to fail; such patients may benefit from catheter ablation.

Despite these advances, the long-term efficacy of catheter ablation to prevent recurrent AF requires further study. Available data demonstrate 1 year or more of freedom from recurrent AF in most (albeit carefully selected) patients (69–71). However, AF can recur without symptoms and be unrecognized by the patient or physician. There is uncertainty as to what the risk of recurrence of AF is over the long term, because AF may recur with minimal symptoms. This distinction has important implications for the duration of anticoagulation therapy in patients with risk factors for stroke associated with AF. In addition, little information is yet available about the late success of ablation in patients with heart failure and other advanced structural heart disease, who may be less likely to enjoy freedom from recurrence of AF (72).

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Appendix

Appendix 1. Author Relationships With Industry and Other Entities—2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation

Committee Member	Employment	Consultant	Speaker	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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(Continued)

Appendix 1. Continued

Committee Member	Employment	Consultant	Speaker	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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This table represents the relevant relationships of committee members with industry that were reported orally at the initial writing committee meeting/conference call and updated in conjunction with all meetings and conference calls of the writing committee during the document development process. 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% or more of the voting stock or share of the business entity, or ownership of \$10 000 or more 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 noted in this table are modest unless otherwise noted.

*Significant relationship.

†Recused from voting on Section 8.1.8.3, Recommendations for Dronedaron.

ACCF indicates American College of Cardiology Foundation; AHA, American Heart Association; HRS, Heart Rhythm Society.

Appendix 2. Peer Reviewer Relationships With Industry and Other Entities—2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Hugh Calkins	Official Reviewer—Heart Rhythm Society and ACCF/AHA Task Force on Performance Measures	<ul style="list-style-type: none"> ● Biosense Webster* ● Boston Scientific ● Medtronic ● Sanofi-aventis 	None	None	<ul style="list-style-type: none"> ● Boston Scientific* ● Medtronic* ● St. Jude Medical* 	None	None
A. John Camm	Official Reviewer—ACCF Board of Trustees	<ul style="list-style-type: none"> ● ARYx Pharmaceuticals ● Biotronik ● Boehringer Ingelheim ● Daiichi Sankyo ● Medtronic ● Portola Pharmaceuticals ● Sanofi-aventis ● St. Jude Medical 	None	None	None	None	● 2009, Plaintiff, arbitration procedure
Christopher Granger	Official Reviewer—American Heart Association	<ul style="list-style-type: none"> ● AstraZeneca ● Boehringer Ingelheim ● Bristol-Myers Squibb ● GlaxoSmithKline ● Sanofi-aventis* 	None	None	<ul style="list-style-type: none"> ● AstraZeneca* ● Boehringer Ingelheim ● Bristol-Myers Squibb* ● GlaxoSmithKline* ● Sanofi-aventis* 	None	None
Jonathan L. Halperin	Official Reviewer—American Heart Association and ACCF/AHA Task Force on Practice Guidelines	<ul style="list-style-type: none"> ● Biotronik* ● Boehringer Ingelheim ● Daiichi Sankyo ● Portola Pharmaceuticals ● Sanofi-aventis 	None	None	None	None	None
Bradley P. Knight	Official Reviewer—Heart Rhythm Society	<ul style="list-style-type: none"> ● Boston Scientific* ● Sanofi-aventis* ● St. Jude Medical* 	<ul style="list-style-type: none"> ● Biosense Webster* ● Boston Scientific* ● Medtronic* ● St. Jude Medical 	None	<ul style="list-style-type: none"> ● Boston Scientific* ● Medtronic* 	None	None

(Continued)

Appendix 2. Continued

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational or Other Financial Benefit	Expert Witness
Allen J. Solomon	Official Reviewer—ACCF Board of Governors	None	● Sanofi-aventis	None	None	None	None
Nancy M. Albert	Content Reviewer—ACCF/ AHA Task Force on Practice Guidelines	● Medtronic	None	None	None	None	None
Cesar Alberte-Lista	Content Reviewer—ACCF Electrophysiology Committee	None	None	None	None	None	None
Sana M. Al-Khatib	Content Reviewer—ACCF Electrophysiology Committee	● Medtronic	None	None	● Biotronik ● Bristol-Myers Squibb* ● Medtronic*	None	None
Jeffrey L. Anderson	Content Reviewer—ACCF/ AHA Task Force on Practice Guidelines	● Sanofi/Bristol-Myers Squibb	None	None	● AstraZeneca (DSMB)	None	None
Nancy C. Berg	Content Reviewer—ACCF Electrophysiology Committee	None	None	None	None	None	None
David S. Cannom	Content Reviewer	None	None	None	None	None	None
Jennifer E. Cummings	Content Reviewer—ACCF Electrophysiology Committee	None	● Boston Scientific ● Medtronic ● Sanofi-aventis ● St. Jude Medical	None	None	None	None
John U. Doherty	Content Reviewer	None	None	None	None	None	None
Andrew Epstein	Content Reviewer	● Boehringer Ingelheim ● Medtronic* ● Portola Pharmaceuticals ● Sanofi-aventis ● St. Jude Medical*	● Biotronik ● Boston Scientific ● Medtronic ● St. Jude Medical	None	● Biosense Webster* ● Biotronik* ● Boston Scientific* ● Medtronic* ● St. Jude Medical*	● Boston Scientific*	None
Steven M. Ettinger	Content Reviewer—ACCF/ AHA Task Force on Practice Guidelines	None	None	None	None	None	None
Robert A. Guyton	Content Reviewer—ACCF/ AHA Task Force on Practice Guidelines	None	None	None	None	None	None
Judith S. Hochman	Content Reviewer—ACCF/ AHA Task Force on Practice Guidelines	● Bristol-Myers Squibb	None	None	None	None	None
Jodie L. Hurwitz	Content Reviewer—ACCF Electrophysiology Committee	● Boston Scientific ● St. Jude Medical	● Medtronic ● Sanofi-aventis	None	None	None	None
Michael H. Kim	Content Reviewer	● Medtronic ● Sanofi-aventis*	● Boehringer Ingelheim ● Sanofi-aventis*	None	None	None	None
Frederick G. Kushner	Content Reviewer—ACCF/ AHA Task Force on Practice Guidelines	None	None	● Bristol-Myers Squibb	● Daiichi Sankyo	None	None
Jean-Yves Le Heuzey	Content Reviewer	● Boehringer Ingelheim ● Daiichi Sankyo ● Sanofi-aventis	None	None	None	None	None
Neil Lippman	Content Reviewer	None	● Medtronic	None	None	None	None
Steven M. Markowitz	Content Reviewer—ACCF Electrophysiology Committee	● Boston Scientific ● Medtronic	None	None	None	● Boston Scientific* ● Medtronic*	None
Frederick A. Masoudi	Content Reviewer—ACCF/ AHA Task Force on Performance Measures	None	None	None	None	None	None
Robert L. McNamara	Content Reviewer—ACCF/ AHA Atrial Fibrillation Data Standards Committee	● Boehringer Ingelheim	None	None	None	None	None

(Continued)

Appendix 2. Continued

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational or Other Financial Benefit	Expert Witness
Erik Magnus Ohman	Content Reviewer—ACCF/ AHA Task Force on Practice Guidelines	• CV Therapeutics	None	None	• Bristol-Myers Squibb • Daiichi Sankyo* • Sanofi- aventis*	None	None
Brian Olshansky	Content Reviewer—ACCF Electrophysiology Committee	• Sanofi-aventis • Medtronic	None	None	None	None	None
Eric N. Prystowsky	Content Reviewer	• Boehringer Ingelheim* • Boston Scientific* • Medtronic* • Sanofi-aventis* • St. Jude Medical*	None	None	None	None	None
William G. Stevenson	Content Reviewer—ACCF/ AHA Task Force on Practice Guidelines	None	None	None	None	None	None

This table represents the relevant relationships of reviewers with industry and other entities that were disclosed at the time of peer review. 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% or more of the voting stock or share of the business entity, or ownership of \$10 000 or more 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 in this table are modest unless otherwise noted.

*Indicates significant relationship.

ACCF indicates American College of Cardiology Foundation; AHA, American Heart Association; and DSMB, data safety monitoring board.

Appendix 3. Summary Table

Study	Aim of Study	Study Size	Patient Population/Inclusion and Exclusion Criteria	Endpoint(s)	Statistical Analysis Reported	CI and/or p Values	OR/HR/RR/Other	Study Conclusion
ACTIVE A, Connolly et al. (10)	To investigate whether the addition of clopidogrel to ASA would reduce risk of vascular events in patients with AF considered unsuitable for oral anticoagulation with warfarin.	7,554	<i>Inclusion criteria:</i> AF at enrollment or at least 2 episodes of intermittent AF in previous 6 mo and at least 1 of the following risk factors for stroke: age ≥ 75 y; systemic HTN during treatment; previous stroke, TIA, or non-CNS systemic embolism; LVEF $< 45\%$; PVD; or age 55–74 y and DM or CAD. <i>Exclusion criteria:</i> Requirement of vitamin K antagonist or clopidogrel or the presence of any of the following risk factors for hemorrhage: documented peptic ulcer disease within previous 6 mo, history of intracerebral hemorrhage, significant thrombocytopenia (platelet count $< 50 \times 10^9$ per liter), or ongoing alcohol abuse.	Primary outcome was composite of stroke, MI, non-CNS systemic embolism, or death from vascular causes.	Major vascular events occurred in 832 patients receiving ASA plus clopidogrel (6.8% per year) and in 924 patients receiving ASA plus placebo (7.6% per year). Stroke occurred in 296 patients receiving ASA plus clopidogrel (2.4% per year) and 408 patients receiving ASA plus placebo (3.3% per year). MI occurred in 90 patients receiving ASA plus clopidogrel (0.7% per year) and in 115 receiving ASA plus placebo (0.9% per year). Major bleeding occurred in 251 patients receiving ASA plus clopidogrel (2.0% per year) and in 162 patients receiving ASA plus placebo (1.3% per year).	95% CI: 0.81 to 0.98; $p=0.01$ 95% CI: 0.62 to 0.83; $p<0.001$ 95% CI: 0.59 to 1.03; $p=0.08$ 95% CI: 1.29 to 1.92; $p<0.001$	RR: 0.89 RR: 0.72 RR: 0.78 RR: 1.57	In AF patients considered unsuitable for warfarin, the addition of clopidogrel to ASA reduced risk of major vascular events, especially stroke, and increased risk of major hemorrhage.
ACTIVE W, Connolly et al. (25)	To determine if clopidogrel plus ASA was noninferior to oral anticoagulation therapy for prevention of vascular events in patients with AF.	6,706	<i>Inclusion criteria:</i> ECG evidence of AF; age ≥ 75 y; treatment for systemic HTN, previous stroke, TIA, or non-CNS systemic embolism; LV dysfunction with LVEF $< 45\%$; PAD; if age 55–74 y without 1 of the other inclusion criteria, then DM requiring drug therapy or previous CAD. <i>Exclusion criteria:</i> Contraindication for clopidogrel or oral anticoagulant (ie, prosthetic mechanical heart valve), documented peptic ulcer disease within previous 6 mo, previous intracerebral hemorrhage, significant thrombocytopenia (platelet count $< 50 \times 10^9$ per liter) or mitral stenosis.	Primary outcome was first occurrence of stroke, non-CNS systemic embolism, MI, or vascular death.	Composite of stroke, non-CNS embolism, MI, vascular death: 164 events in patients on oral anticoagulation (annual risk: 3.90%) and 234 events in patients on clopidogrel plus ASA (annual risk: 5.60%). Stroke (100 events for clopidogrel plus ASA; 59 events for oral anticoagulation). Non-CNS embolism (18 events for clopidogrel plus ASA; 4 for oral anticoagulation). Patients on oral anticoagulation who already received this treatment at study entry had a trend toward greater reduction in vascular events. And a lower risk of major bleeding on oral anticoagulation therapy. Than patients not on oral anticoagulation therapy at entry.	95% CI: 1.18 to 1.76; $p=0.0003$ 95% CI: 1.24 to 2.37; $p=0.001$ 95% CI: 1.58 to 13.8; $p=0.005$ 95% CI: 1.19 to 1.80; $p=0.0005$ 95% CI: 0.94 to 1.79; $p=0.11$ 95% CI: 0.85 to 1.89; $p=0.24$	RR: 1.44 RR: 1.72 RR: 4.66 RR: 1.50 RR: 1.30 RR: 1.27	Oral anticoagulation with warfarin is superior to clopidogrel plus ASA in preventing vascular events, including stroke, in patients with AF.
ADONIS, Singh et al. (32)	To investigate effect of dronedarone for maintenance of SR after electrical, pharmacologic, or spontaneous conversion from AF or atrial flutter.	208 in placebo group and 417 in dronedarone group	<i>Inclusion criteria:</i> Either sex, age at least 21 y, and at least 1 episode of AF (as seen on ECG) in preceding 3 mo and in SR for at least 1 h before randomization. <i>Exclusion criteria:</i> Patients with permanent AF (ie, duration of at least 12 mo); women who could become pregnant and who were not using birth control; patients who had torsades de pointes; patients with persistent bradycardia of < 50 bpm, PR interval of ≥ 0.28 s on ECG, second-degree (or higher) AVB, and clinically significant sinus-node disease without an implanted pacemaker; patients taking Class I or III antiarrhythmic agents; patients with NYHA class III or IV CHF; and patients with serum creatinine level ≥ 1.7 mg/dL (150 $\mu\text{mol/L}$), severe electrolyte abnormalities, and clinically significant hepatic, pulmonary, endocrine, or other disorders associated with AF.	Primary endpoint was time from randomization to first documented recurrence of AF. Secondary endpoints were symptoms and mean ventricular rate during first AF recurrence.	Median times from randomization to documented recurrence of AF were 158 d in dronedarone group and 59 d in placebo group. At 12 mo, 61.1% of patients in dronedarone group and 72.8% of patients in placebo group had recurrence of AF.		HR: 0.73	Dronedarone was significantly more effective than placebo in maintaining SR.

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Appendix 3. Continued

Study	Aim of Study	Study Size	Patient Population/Inclusion and Exclusion Criteria	Endpoint(s)	Statistical Analysis Reported	CI and/or p Values	OR/HR/RR/Other	Study Conclusion
Rhythm Control versus Rate Control for Atrial Fibrillation and Heart Failure (AF and CHF Investigators) (9)	To investigate maintenance of SR (rhythm control) with ventricular rate control in patients with LVEF $\leq 35\%$ and symptoms of CHF and history of AF.	1,376 (682 in rhythm-control group and 694 in rate-control group)	<i>Inclusion criteria:</i> LVEF $\leq 35\%$ (measured by nuclear imaging, echocardiography, or cardiac angiography, with testing performed ≤ 6 mo before enrollment); history of CHF (defined as symptomatic NYHA class II or IV) within previous 6 mo, asymptomatic condition that patient had been hospitalized for HF during previous 6 mo, or LVEF $\leq 25\%$; history of AF (with ECG documentation) defined as 1 episode lasting for at least 6 h or requiring cardioversion within previous 6 mo or episode lasting for at least 10 min within previous 6 mo and previous electrical cardioversion for AF; and eligibility for long-term therapy in either of the 2 study groups. <i>Exclusion criteria:</i> Persistent AF for >12 mo, reversible cause of AF or HF, decompensated HF within 48 h before intended randomization, use of antiarrhythmic drugs for other arrhythmias, second- or third-degree AVB (bradycardia of <50 bpm), history of long-QT syndrome, previous ablation of AV node, anticipated cardiac transplantation within 6 mo, renal failure requiring dialysis, lack of birth control in women of childbearing potential, estimated life expectancy <1 y, and age <18 y.	Primary outcome was time to death from CV causes.	The primary outcome, death from CV causes, occurred in 182 patients (27%) in rhythm-control group and 175 patients (25%) in rate-control group. Death from any cause (32% in rhythm-control group and 33% in rate-control group). Ischemic or hemorrhagic stroke, 3% and 4%, respectively. Worsening HF (defined as HF requiring hospitalization, administration of IV diuretic, or change in treatment strategy). Composite outcome of death from CV causes, stroke, or worsening HF.	None of the secondary outcomes differed significantly between treatment groups. 95% CI: 0.86 to 1.30; $p=0.53$ 95% CI: 0.80 to 1.17; $p=0.73$ 95% CI: 0.40 to 1.35; $p=0.32$ 95% CI: 0.72 to 1.06; $p=0.17$ 95% CI: 0.77 to 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 compared with a rate-control strategy in patients with AF and CHF.
AFFIRM, Olshansky et al. (8)	To evaluate and compare several drug classes for long-term ventricular rate control.	2,027	<i>Inclusion criteria:</i> (All criteria must have been met.) Episode of AF documented on ECG or rhythm strip within last 6 wk, age ≥ 65 y or <65 y plus ≥ 1 clinical risk factor for stroke (systemic HTN, DM, CHF, TIA, prior cerebral vascular accident, left atrium ≥ 50 mm on echocardiogram, fractional shortening $<25\%$ on echocardiogram [unless paced or LBBB present], or LVEF $<40\%$ (on radionuclide ventriculogram, contrast angiography, or quantitative echocardiography), duration of AF episodes in last 6 mo must total ≥ 6 h unless electrical and/or pharmacological cardioversion was performed before 6 h, duration of continuous AF must be <6 mo unless normal SR can be restored and maintained for ≥ 24 h in opinion of clinical investigator, patient (based on clinical and laboratory evaluation before randomization) must be eligible for both treatment groups based on history, patient must be eligible for ≥ 2 antiarrhythmic drugs (or 2 dose levels of amiodarone) and ≥ 2 rate-controlling drugs. <i>Exclusion criteria:</i> Not presented based on 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 follow-up 3.5 \pm 1.3 y).	Overall rate control was met in 70% of patients given beta blockers as the first drug (with or without digoxin) versus 54% with calcium channel blockers (with or without digoxin) and 58% with digoxin alone. Multivariate analysis revealed a significant association between first drug class and several clinical variables, including gender, history of CAD, pulmonary disease, CHF, HTN, qualifying episode being first episode of AF, and baseline heart rate.			Rate control is possible in the majority of patients with AF. In the AFFIRM follow-up study, beta blockers were most effective. The authors noted frequent medication changes and drug combinations were needed.

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Appendix 3. Continued

Study	Aim of Study	Study Size	Patient Population/Inclusion and Exclusion Criteria	Endpoint(s)	Statistical Analysis Reported	CI and/or p Values	OR/HR/RR/Other	Study Conclusion
ANDROMEDA, Kober et al. (30)	To evaluate efficacy of dronedarone in reducing hospitalization due to CHF in patients with symptomatic HF.	627	<i>Inclusion criteria:</i> Patients age ≥ 18 y hospitalized with new or worsening HF and who had at least 1 episode of SOB on minimal exertion or at rest (NYHA class III or IV) or paroxysmal nocturnal dyspnea within 1 mo before admission and wall-motion index of no more than 1.2 (approximating EF of no more than 35%). <i>Exclusion criteria:</i> Acute MI within 7 d before screening, heart rate < 50 bpm, PR interval > 0.28 s, sinoatrial block or second- or third-degree AVB not treated with pacemaker, history of torsades de pointes, corrected QT interval > 500 ms, serum potassium level < 3.5 mmol/L, use of Class I or III antiarrhythmic drugs, drugs known to cause torsades de pointes, or potent inhibitors of P450 CYP3A4 cytochrome system, other serious disease, acute myocarditis, constrictive pericarditis, planned or recent (within preceding month) 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 and previous treatment with dronedarone.	The primary endpoint was composite of death from any cause or hospitalization for HF.	After inclusion of 627 patients, the trial was prematurely terminated for safety reasons. At a median follow-up of 2 mo, death had occurred in 8.1% of the dronedarone group and 3.8% of the placebo group.	95% CI: 1.07 to 4.25; p=0.03	HR: 2.13	Dronedrone increased early mortality in patients recently hospitalized with symptomatic HF and depressed LV function. 96% of deaths were attributed to CV causes, predominantly progressive HF and arrhythmias.
					After an additional 6 mo, 42 patients in the dronedarone group (13.5%) and 39 patients in the placebo group (12.3%) died.	95% CI: 0.73 to 1.74; p=0.60	HR: 1.13	
					The primary endpoint did not differ significantly between the 2 groups; there were 53 events in the dronedarone group (17.1%) and 40 events in the placebo group (12.6%).	95% CI: 0.92 to 2.09; p=0.12	HR: 1.38	
ATHENA, Hohnloser et al. (29)	To determine if dronedarone would reduce rate of composite outcome of hospitalization due to CV events or death in patients with AF.	4,628	<i>Inclusion criteria:</i> Patients with paroxysmal or persistent AF or atrial flutter with at least 1 of the following: age at least 70 y, arterial HTN, DM, previous stroke, TIA, systemic embolism, LA diameter ≥ 50 mm, and LVEF $\leq 40\%$. <i>Exclusion criteria:</i> Permanent AF; unstable hemodynamic condition (ie, decompensated HF within previous 4 wk); NYHA class IV CHF; planned major surgery; acute myocarditis; bradycardia with a heart rate of < 50 bpm or PR interval > 0.28 s or previous clinically significant sinus-node disease; severe noncardiac illness limiting life expectancy; pregnancy, breast-feeding, or lack of adequate birth control among women of childbearing potential; calculated glomerular filtration rate at baseline < 10 mL/min, potassium level < 3.5 mmol/L if not currently being corrected, and requirement for concomitant medication that was prohibited.	Primary outcome was death or first hospitalization due to CV events. Secondary outcomes were death from any cause, death from CV causes, and hospitalization due to CV events.	Primary outcome occurred in 734 patients (31.9%) in the dronedarone group and in 917 patients (39.4%) in the placebo group.	95% CI: 0.69 to 0.84; p $<$ 0.001	HR: 0.76	Dronedrone reduced risk of hospitalization or death in patients with paroxysmal or persistent AF or atrial flutter, which was largely due to a reduction in hospitalization for AF. Death from any cause was not reduced. Adverse effects that were more common with dronedarone than placebo were bradycardia, prolonged QT, diarrhea, nausea, rash, and increase in serum creatinine.
					116 deaths (5%) in the dronedarone group and 139 (6%) in the placebo group.	95% CI: 0.66 to 1.08; p=0.18	HR: 0.84	
					63 deaths from CV causes (2.7%) in the dronedarone group and 90 (3.9%) in the placebo group.	95% CI: 0.51 to 0.98; p=0.03	HR: 0.71	
					675 (29.3%) first hospitalizations due to CV events in the dronedarone group and 859 (36.9%) in the placebo group. A first hospitalization for AF occurred in 14.6% of the dronedarone group and 21.9% of the placebo group.	95% CI: 0.67 to 0.82; p $<$ 0.001	HR: 0.74	
					26 (1.1%) deaths from cardiac arrhythmia in the dronedarone group and 48 (2.1%) in the placebo group.	95% CI: 0.34 to 0.88; p=0.01	HR: 0.55	
Analysis of stroke in ATHENA, Connolly et al. (37)	To assess efficacy of dronedarone 400 mg bid for prevention of CV hospitalization or death from any cause in patients with AF/atrial flutter.	4,628	<i>Inclusion criteria:</i> Paroxysmal or persistent AF or atrial flutter and at least 1 additional risk factor for CV events, including age ≥ 75 y or age 70 y with ≥ 1 of the following: HTN, DM, prior stroke or TIA, LA enlargement (≥ 50 mm Hg), or depressed LVEF ($< 40\%$). <i>Exclusion criteria:</i> Permanent AF, unstable hemodynamic situation, and NYHA class IV HF. Patients must have had both SR and AF or atrial flutter documented in 6 mo before enrollment.	Primary endpoint was first occurrence of CV hospitalization or death due to any cause. Analysis of stroke posthoc and not prespecified.	Risk of stroke decreased from 1.8% per year to 1.2% per year.	95% CI: 0.46 to 0.96; p=0.027	HR: 0.66	Fewer strokes occurred in the dronedarone group, but this finding was not anticipated and was not prespecified. Whether it was a chance finding or due to a beneficial effect of the drug is not certain.

(Continued)

Appendix 3. Continued

Study	Aim of Study	Study Size	Patient Population/Inclusion and Exclusion Criteria	Endpoint(s)	Statistical Analysis Reported	CI and/or p Values	OR/HR/RR/Other	Study Conclusion
DAFNE, Touboul et al. (33)	To determine most appropriate dose of dronedarone for prevention of AF after cardioversion.	474	<i>Inclusion criteria:</i> Either sex, age 21–85 y, with persistent AF (72-h and 12-mo duration) in which cardioversion and antiarrhythmic treatment are warranted. AF either lone or associated with ischemic or hypertensive heart disease or DCM. <i>Exclusion criteria:</i> More than 2 cardioversions in last 6 mo, acute reversible cause; atrial flutter as presenting arrhythmia; unstable angina or recent MI; QT interval >500 ms or history of torsades de pointes; severe bradycardia; advanced AVB; treatment with other antiarrhythmic drugs, NYHA class III or IV CHF; LVEF <35%; Wolff-Parkinson-White syndrome; ICD.	Primary endpoint was time to first documented AF recurrence (AF defined as episode lasting for at least 10 min and documented by 2 distinct ECGs separated by same time duration).	Increased time to AF relapse with 800 mg of dronedarone (effect less apparent at higher doses). Median time to first AF recurrence was 5.3 d in placebo group and at 60 d in the 800-mg dronedarone group. At 6 mo 35% of patients treated with 800-mg dronedarone remained in SR versus 10% of placebo group.	95% CI: 28 to 72; p=0.001	RR reduction: 55%	Dronedarone 800 mg qd appeared to be safe and effective for prevention of AF relapses after cardioversion.
DIONYSOS, Le Heuzey et al. (36)	To compare efficacy and safety of amiodarone and dronedarone in patients with persistent AF.	504 (249 dronedarone 400 mg bid; 255 amiodarone 600 mg qd for 28 d, then 200 mg qd).	<i>Inclusion criteria:</i> Age ≥21 y, documented AF for >72 h in patients for whom cardioversion and antiarrhythmic treatment were indicated and who were receiving oral anticoagulants. <i>Exclusion criteria:</i> Previous chronic treatment with amiodarone, hypo- or hyperthyroidism or other contraindications to amiodarone, corrected QT interval ≥500 ms, paroxysmal AF, atrial flutter, severe NYHA class III or IV CHF, severe bradycardia, or high-degree AVB. Patients in whom contraindicated concomitant treatment was mandatory were excluded (including Vaughan Williams Class I and III antiarrhythmic drugs; drugs that cause torsades de pointes; potent inhibitors of cytochrome P(CYP) 3A4; and substrates of CYP3A4 with narrow therapeutic margin).	Primary composite endpoint was recurrence of AF (including unsuccessful electrical cardioversion, no spontaneous conversion, and no electrical cardioversion) or premature discontinuation of study. MSE was occurrence of thyroid, hepatic, pulmonary, neurologic, dermatologic, ocular, or gastrointestinal-specific events or premature discontinuation of study drug after adverse event.	Dronedarone 75.1%; amiodarone 58.8% AF recurrence after successful cardioversion: 36.5% with dronedarone and 24.3% with amiodarone. Premature discontinuation of drug tended to be less frequent with dronedarone (10.4% versus 13.3%). MSE was 39.3% with dronedarone and 44.5% with amiodarone at 12 mo, mainly driven by fewer thyroid, neurologic, dermatologic, and ocular events in dronedarone group.	95% CI: 1.28 to 1.98; p<0.0001 95% CI: 0.60 to 1.07; p=0.129	HR: 1.59 HR: 0.80	Dronedarone was less effective than amiodarone in decreasing AF recurrence; however, it had a better safety profile.
EURIDIS, Singh et al. (32)	To evaluate dronedarone compared with placebo for maintenance of SR after electrical, pharmacologic, or spontaneous conversion from AF or atrial flutter	612	<i>Inclusion criteria:</i> Either sex, age at least 21 y, and at least 1 episode of AF (as seen on ECG) in preceding 3 mo and in SR for at least 1 h before randomization. <i>Exclusion criteria:</i> Patients with permanent AF (ie, duration of at least 12 mo); women who could become pregnant and who were not using birth control; patients who had torsades de pointes; patients with persistent bradycardia of <50 bpm, a PR interval of ≥0.28 on ECG, second-degree (or higher) AVB, and clinically significant sinus-node disease without an implanted pacemaker; patients taking Class I or III antiarrhythmic agents; patients with NYHA class III or IV CHF; and patients with serum creatinine level ≥1.7 mg/dL (150 μmol/L), severe electrolyte abnormalities, and clinically significant hepatic, pulmonary, endocrine, or other disorders associated with AF.	Primary endpoint was time from randomization to first documented recurrence of AF. Secondary endpoints were symptoms and mean ventricular rate during first AF recurrence.	Median times from randomization to documented recurrence of AF were 96 d in dronedarone group and 41 d in placebo group. At 12 mo 67.1% of patients in dronedarone group and 77.5% of placebo group had recurrence of AF.	95% CI: 0.64 to 0.96; p=0.01	HR: 0.78	Dronedarone was significantly more effective than placebo in maintaining SR.

(Continued)

Appendix 3. Continued

Study	Aim of Study	Study Size	Patient Population/Inclusion and Exclusion Criteria	Endpoint(s)	Statistical Analysis Reported	CI and/or p Values	OR/HR/RR/Other	Study Conclusion
RACE II, Van Gelder et al. (3)	To investigate if lenient rate control is not inferior to strict control for preventing CV morbidity and mortality in patients with permanent AF.	614	<i>Inclusion criteria:</i> Permanent AF up to 12 mo, age \geq 80 y, mean resting heart rate $>$ 80 bpm, and current use of oral anticoagulation therapy (or ASA if no risk factors for thromboembolic complications present). <i>Exclusion Criteria:</i> Paroxysmal AF; contraindications for either strict or lenient rate control (eg, previous adverse effects on negative chronotropic drugs); unstable HF defined as NYHA class IV HF or HF necessitating hospital admission $<$ 3 mo before inclusion; cardiac surgery $<$ 3 mo ago; any stroke; current or foreseen pacemaker, ICD, and/or cardiac resynchronization therapy; signs of sick sinus syndrome or AV conduction disturbances (ie, symptomatic bradycardia or asystole $>$ 3 s or escape rate $<$ 40 bpm in awake symptom-free patients; untreated hyperthyroidism or $<$ 3 mo euthyroidism; inability to walk or ride a bike.	Composite of death from CV causes, hospitalization for HF, and stroke, systemic embolism, bleeding, and life-threatening arrhythmic events. Follow-up duration 2 y, with maximum 3 y.	Primary outcome incidence at 3 y was 12.9% in lenient-control group and 14.9% in strict-control group. Absolute difference with respect to lenient-control group of -2.0% . More patients in lenient-control group met heart rate target or targets (304 [97.7%] versus 203 [67.0%] in strict-control group). Frequencies of symptoms and adverse events were similar in the 2 groups.	90% CI: 0.58 to 1.21; $p=0.001$ Absolute difference -2.0% Absolute difference, 90% CI: -7.6 to 3.5 ; $p<0.001$ $p<0.001$	HR: 0.84	Lenient rate control is as effective as strict rate control and easier to achieve in patients with permanent AF.
ThermoCool, Wilber et al. (51)	To investigate catheter ablation with ADT in patients with symptomatic AF.	167	<i>Inclusion criteria:</i> Enrollment required at least 3 episodes of symptomatic AF (\geq 1 episode verified by ECG) within 6 mo before randomization and not responding to at least 1 antiarrhythmic drug (class I, class III, or AV nodal blocker). <i>Exclusion criteria:</i> AF $>$ 30 d, $<$ 18 y, EF $<$ 40%, previous ablation for AF, documented LA thrombus, amiodarone therapy in previous 6 mo, NYHA class III or IV, MI within previous 2 mo, CABG within previous 12 mo, thromboembolic event in previous 12 mo, severe pulmonary disease, prior valvular cardiac surgical procedure, presence of ICD, contraindication to antiarrhythmic or anticoagulation medications, life expectancy $<$ 12 mo, and LA size of at least 50 mm in parasternal long axis.	Primary endpoint was freedom from protocol-defined treatment failure, which included documented symptomatic paroxysmal AF during effectiveness evaluation period.	66% of patients in catheter ablation group remained free from protocol-defined treatment failure versus 16% of patients treated with ADT. 70% of patients treated by catheter ablation remained free of symptomatic recurrent atrial arrhythmia versus 19% of patients treated with ADT. 63% of patients treated by catheter ablation were free of recurrent atrial arrhythmia versus 17% of patients treated with ADT.	95% CI: 0.19 to 0.47; $p<0.001$ 95% CI: 0.15 to 0.39; $p>0.001$ 95% CI: 0.18 to 0.45; $p<0.001$	HR: 0.30 HR: 0.24 HR: 0.29	Catheter ablation is more effective than medical therapy alone in preventing recurrent symptoms of paroxysmal AF in patients who have already failed treatment with 1 antiarrhythmic drug. Ideal candidates for catheter ablation are younger patients with minimal structural abnormalities and multiple symptomatic episodes of paroxysmal AF over time despite appropriate pharmacological therapy.

ADT indicates antiarrhythmic drug therapy; AF, atrial fibrillation; ASA, aspirin; AV, atrioventricular; AVB, atrioventricular block; bid, twice a day; bpm, beats per minute; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CHF, congestive heart failure; CI: confidence interval; CNS, central nervous system; CYP, cytochrome P; CV, cardiovascular; d, day; DCM, dilated cardiomyopathy; DM, diabetes mellitus; ECG, electrocardiogram; EF, ejection fraction; h, hour; HF, heart failure; HR, hazard ratio; HTN, hypertension; ICD, implantable cardioverter-defibrillator; IV, intravenous; LA, left atrial; LBBB, left bundle-branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; mm, millimeter; mo, month; ms, milliseconds; MSE, main safety endpoint; NYHA, New York Heart Association; PAD, peripheral arterial disease; PR interval, interval between onset of P wave and onset of QRS complex on an ECG; PVD, peripheral vascular disease; qd, once per day; RR, relative risk; s, seconds; SD, standard deviation; SOB, short of breath; SR, sinus rhythm; TIA, transient ischemic attack; wk, week; and y, year.

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KEY WORDS: ACCF/AHA Practice Guidelines ■ anticoagulant therapy ■ antiplatelet therapy ■ antithrombotic agents ■ atrial fibrillation ■ catheter ablation ■ rate control ■ rhythm control ■ thromboembolism.

2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Updating the 2006 Guideline): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

L. Samuel Wann, Anne B. Curtis, Craig T. January, Kenneth A. Ellenbogen, James E. Lowe, N.A. Mark Estes, III, Richard L. Page, Michael D. Ezekowitz, David J. Slotwiner, Warren M. Jackman, William G. Stevenson, Cynthia M. Tracy, Valentin Fuster, Lars E. Rydén, David S. Cannom, Jean-Yves Le Heuzey, Harry J. Crijns, James E. Lowe, Anne B. Curtis, S. Bertil Olsson, Kenneth A. Ellenbogen, Eric N. Prystowsky, Jonathan L. Halperin, Juan Luis Tamargo, G. Neal Kay, and L. Samuel Wann

J. Am. Coll. Cardiol. 2011;57;223-242; originally published online Dec 20, 2010; doi:10.1016/j.jacc.2010.10.001

This information is current as of January 4, 2011

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