

## ACC/AHA/HRS GUIDELINE

# 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

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

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■ warfarin

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## PREAMBLE (FULL VERSION)

Since 1980, the American College of Cardiology (ACC) and American Heart Association (AHA) have translated scientific evidence into clinical practice guidelines with recommendations to improve cardiovascular health. These guidelines, which are based on systematic methods to evaluate and classify evidence, provide a foundation for the delivery of quality cardiovascular care. The ACC and AHA sponsor the development and publication of clinical practice guidelines without commercial support, and members volunteer their time to the writ-

ing and review efforts. Guidelines are official policy of the ACC and AHA. For some guidelines, the ACC and AHA partner with other organizations. This guideline is a collaboration of the ACC and AHA with the Heart Rhythm Society (HRS) as a partner and the Society of Thoracic Surgeons as a collaborator.

## Intended Use

Clinical practice guidelines provide recommendations applicable to patients with or at risk of developing cardiovascular disease. The focus is on medical practice in the United States, but these guidelines are relevant to patients throughout the world. Although guidelines may be used to inform regulatory or payer decisions, the intent is to improve quality of care and align with patients' interests. Guidelines are intended to define practices meeting the needs of patients in most, but not all, circumstances, and should not replace clinical judgment.

## Clinical Implementation

Management, in accordance with guideline recommendations, is effective only when followed by both practitioners and patients. Adherence to recommendations can be enhanced by shared decision-making between clinicians and patients, with patient engagement in selecting interventions on the basis of individual values, preferences, and associated conditions and comorbidities.

## Methodology and Modernization

The ACC/AHA Task Force on Clinical Practice Guidelines (Task Force) continuously reviews, updates, and modifies guideline methodology on the basis of published standards from organizations, including the Institute of Medicine,<sup>P-1,P-2</sup> and on the basis of internal reevaluation. Similarly, presentation and delivery of guidelines are reevaluated and modified in response to evolving technologies and other factors to optimally facilitate dissemination of information to healthcare professionals at the point of care.

Beginning in 2017, numerous modifications to the guidelines have been and continue to be implemented to make guidelines shorter and enhance “user friendliness.” Guidelines are written and presented in a modular knowledge chunk format, in which each chunk includes a table of recommendations, a brief synopsis, recommendation-specific supportive text and, when appropriate, flow diagrams or additional tables. Hyperlinked references are provided for each modular knowledge chunk to facilitate quick access and review. More

structured guidelines—including word limits (“targets”) and a web guideline supplement for useful but non-critical tables and figures—are 2 such changes. Also, to promote conciseness, the Preamble is presented in abbreviated form in the executive summary and full-text guideline documents.

In recognition of the importance of cost–value considerations in certain guidelines, when appropriate and feasible, an analysis of value for a drug, device, or intervention may be performed in accordance with the ACC/AHA methodology.<sup>P-3</sup>

To ensure that guideline recommendations remain current, new data are reviewed on an ongoing basis, with full guideline revisions commissioned ideally in approximate 6-year cycles. Publication of potentially practice-changing new study results relevant to an existing or new drug, device, or management strategy prompts evaluation by the Task Force, in consultation with the relevant guideline writing committee, to determine whether a focused update should be commissioned. For additional information and policies on guideline development, we encourage readers to consult the ACC/AHA guideline methodology manual<sup>P-4</sup> and other methodology articles.<sup>P-5–P-8</sup>

### Selection of Writing Committee Members

The Task Force strives to ensure that the guideline writing committee both contains requisite expertise and is representative of the broader medical community by selecting experts from a broad array of backgrounds, representing different geographic regions, sexes, races, ethnicities, intellectual perspectives/biases, and scopes of clinical practice, and by inviting organizations and professional societies with related interests and expertise to participate as partners or collaborators.

### Relationships With Industry and Other Entities

The ACC and AHA have rigorous policies and methods to ensure that documents are developed without bias or improper influence. The complete policy on relationships with industry and other entities (RWI) can be found [online](#). Appendix 1 of the guideline lists writing committee members’ relevant RWI; for the purposes of full transparency, their comprehensive disclosure information is available [online](#). Comprehensive disclosure information for the Task Force is also available [online](#).

### Evidence Review and Evidence Review Committees

In developing recommendations, the writing committee uses evidence-based methodologies that are based on all available data.<sup>P-4–P-6</sup> Literature searches focus on randomized controlled trials (RCTs) but also include registries, nonrandomized comparative and descriptive studies, case series, cohort studies, systematic reviews, and expert opinion. Only key references are cited.

An independent evidence review committee is commissioned when there are one or more questions deemed of utmost clinical importance that merit formal systematic review to determine which patients are most likely to benefit from a drug, device, or treatment strategy, and to what degree. Criteria for commissioning an evidence review committee and formal systematic review include absence of a current authoritative systematic review, feasibility of defining the benefit and risk in a timeframe consistent with the writing of a guideline, relevance to a substantial number of patients, and likelihood that the findings can be translated into actionable recommendations. Evidence review committee members may include methodologists, epidemiologists, clinicians, and biostatisticians. Recommendations developed by the writing committee on the basis of the systematic review are marked “<sup>SR</sup>.”

### Guideline-Directed Management and Therapy

The term *guideline-directed management and therapy* encompasses clinical evaluation, diagnostic testing, and both pharmacological and procedural treatments. For these and all recommended drug treatment regimens, the reader should confirm dosage with product insert material and evaluate for contraindications and interactions. Recommendations are limited to drugs, devices, and treatments approved for clinical use in the United States.

### Class of Recommendation and Level of Evidence

The Class of Recommendation (COR) indicates the strength of recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk. The Level of Evidence (LOE) rates the quality of scientific evidence supporting the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources (Table 1).<sup>P-5</sup>

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Chair, ACC/AHA Task Force on Clinical Practice Guidelines

**Table 1.** Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care\* (Updated August 2015)

CLASS (STRENGTH) OF RECOMMENDATION	LEVEL (QUALITY) OF EVIDENCE‡
<b>CLASS I (STRONG)</b> <span style="float: right;">Benefit &gt;&gt;&gt; Risk</span> Suggested phrases for writing recommendations: <ul style="list-style-type: none"> <li>■ Is recommended</li> <li>■ Is indicated/useful/effective/beneficial</li> <li>■ Should be performed/administered/other</li> <li>■ Comparative-Effectiveness Phrases†:               <ul style="list-style-type: none"> <li>○ Treatment/strategy A is recommended/indicated in preference to treatment B</li> <li>○ Treatment A should be chosen over treatment B</li> </ul> </li> </ul>	<b>LEVEL A</b> <ul style="list-style-type: none"> <li>■ High-quality evidence‡ from more than 1 RCT</li> <li>■ Meta-analyses of high-quality RCTs</li> <li>■ One or more RCTs corroborated by high-quality registry studies</li> </ul>
<b>CLASS IIa (MODERATE)</b> <span style="float: right;">Benefit &gt;&gt; Risk</span> Suggested phrases for writing recommendations: <ul style="list-style-type: none"> <li>■ Is reasonable</li> <li>■ Can be useful/effective/beneficial</li> <li>■ Comparative-Effectiveness Phrases†:               <ul style="list-style-type: none"> <li>○ Treatment/strategy A is probably recommended/indicated in preference to treatment B</li> <li>○ It is reasonable to choose treatment A over treatment B</li> </ul> </li> </ul>	<b>LEVEL B-R (Randomized)</b> <ul style="list-style-type: none"> <li>■ Moderate-quality evidence‡ from 1 or more RCTs</li> <li>■ Meta-analyses of moderate-quality RCTs</li> </ul>
<b>CLASS IIb (WEAK)</b> <span style="float: right;">Benefit ≥ Risk</span> Suggested phrases for writing recommendations: <ul style="list-style-type: none"> <li>■ May/might be reasonable</li> <li>■ May/might be considered</li> <li>■ Usefulness/effectiveness is unknown/unclear/uncertain or not well established</li> </ul>	<b>LEVEL B-NR (Nonrandomized)</b> <ul style="list-style-type: none"> <li>■ Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies</li> <li>■ Meta-analyses of such studies</li> </ul>
<b>CLASS III: No Benefit (MODERATE)</b> <span style="float: right;">Benefit = Risk</span> <i>(Generally, LOE A or B use only)</i> Suggested phrases for writing recommendations: <ul style="list-style-type: none"> <li>■ Is not recommended</li> <li>■ Is not indicated/useful/effective/beneficial</li> <li>■ Should not be performed/administered/other</li> </ul>	<b>LEVEL C-LD (Limited Data)</b> <ul style="list-style-type: none"> <li>■ Randomized or nonrandomized observational or registry studies with limitations of design or execution</li> <li>■ Meta-analyses of such studies</li> <li>■ Physiological or mechanistic studies in human subjects</li> </ul>
<b>CLASS III: Harm (STRONG)</b> <span style="float: right;">Risk &gt; Benefit</span> Suggested phrases for writing recommendations: <ul style="list-style-type: none"> <li>■ Potentially harmful</li> <li>■ Causes harm</li> <li>■ Associated with excess morbidity/mortality</li> <li>■ Should not be performed/administered/other</li> </ul>	<b>LEVEL C-EO (Expert Opinion)</b> Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).  
 A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.  
 \* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).  
 † For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.  
 ‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.  
 COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

## 1. INTRODUCTION

The purpose of this document is to update the “2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation”<sup>51,3-1</sup> (2014 AF Guideline) in areas for which new evidence has emerged since its publication. The scope of this focused update of the 2014 AF Guideline includes revisions to the section on anticoagulation (because of the approval of new medications and thromboembolism protection devices), revisions to the section on catheter ablation of atrial fibrillation (AF), revisions to the section on the man-

agement of AF complicating acute coronary syndrome (ACS), and new sections on device detection of AF and weight loss. The areas of the 2014 AF Guideline that were updated were limited to those for which important new data from clinical trials had emerged and/or new US Food and Drug Administration (FDA) indications for thromboembolism protection devices have appeared in the data available to the writing group up to August 2018.

All recommendations (new, modified, and unchanged) for each updated clinical section are included to provide a comprehensive assessment. The text ex-

plains new and modified recommendations, whereas recommendations from the previous guideline that have been deleted or superseded no longer appear. Please consult the full-text version of the 2014 AF Guideline<sup>S1.3-1</sup> for text and evidence tables supporting the unchanged recommendations and for clinical areas not addressed in this focused update. Individual recommendations in this focused update will be incorporated into the full-text guideline in the future. Recommendations from the prior guideline that remain current have been included for completeness, but the LOE reflects the COR/LOE system used when initially developed. New and modified recommendations in this focused update reflect the latest COR/LOE system, in which LOE B and C are subcategorized for greater specificity.<sup>S1.3-2-S1.3-4</sup> The section numbers correspond to the full-text guideline sections.

### 1.1. Methodology and Evidence Review

Clinical trials presented at the annual scientific meetings of the ACC, AHA, Heart Rhythm Society (HRS), and European Society of Cardiology, as well as other selected data published in a peer-reviewed format through August 2018, were reviewed by the Task Force and members of the 2014 AF Guideline writing group to identify trials and other key data that might affect guideline recommendations. The information considered important enough to prompt updated recommendations is included in evidence tables in the [Online Data Supplement](#). The complete section of recommendations (new, modified, and unchanged) for each clinical section is included to provide a comprehensive overview for the reader. Recommendations that have been deleted or superseded are not incorporated. The text supporting the new and modified recommendations is provided.

After the preliminary recommendation and text were drafted for percutaneous approaches to occlusion of the left atrial appendage (LAA), it was appreciated that the primary author of the section had, by strict criteria, an RWI relevant to the section. Task Force and organizational leadership directed that both the recommendation and text be discarded and the section be constructed de novo by both a new primary author and new primary reviewer, both without RWI. This new section was thoroughly reviewed by the entire writing group, and the de novo formulated recommendation, as with all recommendations in the focused update, was formally voted on by the writing group.

### 1.2. Organization of the Writing Group

For this focused update, representative members of the 2014 AF writing committee were invited to participate, and they were joined by additional invited members to

form a new writing group, referred to as the 2018 AF Guideline Focused Update Writing Group. Members were required to disclose all RWI relevant to the data under consideration. The group was composed of clinicians with broad expertise related to AF and its treatment, including the areas of adult cardiology, electrophysiology, cardiothoracic surgery, and heart failure (HF). The writing group included representatives from the ACC, AHA, HRS, and the Society of Thoracic Surgeons.

### 1.3. Document Review and Approval

The focused update was reviewed by 2 official reviewers each nominated by the ACC, AHA, and HRS; 1 AHA/ACC lay reviewer; 1 organizational reviewer from the Society of Thoracic Surgeons; and 29 individual content reviewers. Reviewers' abbreviated RWI information is published in this document (Appendix 2), and their detailed disclosures are available [online](#).

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

### 1.4. Abbreviations

Abbreviation	Meaning/Phrase
ACS	acute coronary syndrome
AF	atrial fibrillation
AHRE	atrial high-rate episodes
CHADS <sub>2</sub>	congestive heart failure, hypertension, age >75 years, diabetes mellitus, stroke/transient ischemia attack/thromboembolism
CHA <sub>2</sub> DS <sub>2</sub> -VASc	congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 years, sex category
CI	confidence interval
CKD	chronic kidney disease
CMS	US Centers for Medicare & Medicaid Services
CrCl	creatinine clearance
DAPT	dual-antiplatelet therapy
FDA	US Food and Drug Administration
HF	heart failure
HFrEF	heart failure with reduced left ventricular ejection fraction
HR	hazard ratio
INR	international normalized ratio
LAA	left atrial appendage
LV	left ventricular
MI	myocardial infarction
NOAC	non-vitamin K oral anticoagulant
PCI	percutaneous coronary intervention
RCT	randomized controlled trial
TIMI	Thrombolysis in Myocardial Infarction

## 4. PREVENTION OF THROMBOEMBOLISM

### 4.1. Risk-Based Anticoagulant Therapy (Modified From Section 4.1., "Risk-Based Antithrombotic Therapy," in the 2014 AF Guideline)

#### 4.1.1. Selecting an Anticoagulant Regimen—Balancing Risks and Benefits (Modified From Section 4.1.1., "Selecting an Antithrombotic Regimen—Balancing Risks and Benefits," in the 2014 AF Guideline)

##### Introductory Text

The distinction between nonvalvular and valvular AF has confused clinicians, varying among AF clinical trials of non-vitamin K oral anticoagulants (NOACs) (ie, dabigatran [a direct thrombin inhibitor] and rivaroxaban, apixaban, and edoxaban [factor Xa inhibitors]; also referred to as direct-acting oral anticoagulants [DOACs]) and between North American and European AF guidelines. Valvular AF generally refers to AF in the setting of moderate-to-severe mitral stenosis (potentially requiring surgical intervention) or in the presence of an artificial (mechanical) heart valve. Valvular AF is considered an indication for long-term anticoagulation with warfarin. In contrast, nonvalvular AF does not imply the absence of valvular heart disease. Instead, as used in the present focused update, nonvalvular AF is AF in the absence of moderate-to-severe mitral stenosis or a mechanical heart valve. This is because in most AF NOAC clinical trials, up to approximately 20% of patients were enrolled with various valvular defects, including mild mitral stenosis, mitral regurgitation, aortic stenosis, aortic regurgitation, and tricuspid regurgitation;<sup>54.1.1-1,54.1.1-2</sup> some trials enrolled small numbers of patients with valve repair, valvuloplasty, and bioprosthetic valves. Furthermore, meta-analysis-derived data from the original clinical trials suggest that, among patients with AF and these valvular lesions and operations, NOACs reduce stroke and systemic embolism compared with warfarin, but with differences in bleeding risk.<sup>54.1.1-3</sup> For recommendations from the 2014 AF guideline that were modified only to define the exclusion criteria for valvular AF or to change "antithrombotic" to "anticoagulant," LOE and supportive text have not been updated. A fifth NOAC, betrixaban, has not been approved by the FDA for use in patients with AF. Antithrombotic (anticoagulant combined with antiplatelet) therapy is discussed in Sections 4.4.1. and 7.4.<sup>54.1.1-4</sup>

Recommendations for Selecting an Anticoagulant Regimen—Balancing Risks and Benefits		
Referenced studies that support new or modified recommendations are summarized in <a href="#">Online Data Supplements 1 and 2</a> .		
COR	LOE	Recommendations
I	A	1. For patients with AF and an elevated CHA <sub>2</sub> DS <sub>2</sub> -VASC score of 2 or greater in men or 3 or greater in women, oral anticoagulants are recommended. Options include: Warfarin (LOE: A) <sup>54.1.1-5-54.1.1-7</sup> Dabigatran (LOE: B) <sup>54.1.1-8</sup> Rivaroxaban (LOE: B) <sup>54.1.1-9</sup> Apixaban (LOE: B), <sup>54.1.1-10</sup> or Edoxaban (LOE: B-R) <sup>54.1.1-11</sup> <b>MODIFIED:</b> This recommendation has been updated in response to the approval of edoxaban, a new factor Xa inhibitor. More precision in the use of CHA <sub>2</sub> DS <sub>2</sub> -VASC scores is specified in subsequent recommendations. The LOEs for warfarin, dabigatran, rivaroxaban, and apixaban have not been updated for greater granularity as per the new LOE system. (Section 4.1. in the 2014 AF Guideline) The original text can be found in Section 4.1 of the 2014 AF guideline. Additional information about the comparative effectiveness and bleeding risk of NOACs can be found in Section 4.2.2.2.
	B	
	B	
	B-R	
I	A	2. NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve). <sup>54.1.1-8-54.1.1-11</sup> <b>NEW:</b> Exclusion criteria are now defined as moderate-to-severe mitral stenosis or a mechanical heart valve. When the NOAC trials are considered as a group, the direct thrombin inhibitor and factor Xa inhibitors were at least noninferior and, in some trials, superior to warfarin for preventing stroke and systemic embolism and were associated with lower risks of serious bleeding.
I	A	3. Among patients treated with warfarin, the international normalized ratio (INR) should be determined at least weekly during initiation of anticoagulant therapy and at least monthly when anticoagulation (INR in range) is stable. <sup>54.1.1-12-54.1.1-14</sup> <b>MODIFIED:</b> "Antithrombotic" was changed to "anticoagulant."
I	B	4. In patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve), the CHA <sub>2</sub> DS <sub>2</sub> -VASC score is recommended for assessment of stroke risk. <sup>54.1.1-5-54.1.1-7</sup> <b>MODIFIED:</b> Exclusion criteria are now defined as moderate-to-severe mitral stenosis or a mechanical heart valve. Patients with AF with bioprosthetic heart valves are addressed in the supportive text. (Section 4.1. in the 2014 AF guideline)
I	B	5. For patients with AF who have mechanical heart valves, warfarin is recommended. <sup>54.1.1-15-54.1.1-19</sup> <b>MODIFIED:</b> New information is included in the supportive text.

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Recommendations for Selecting an Anticoagulant Regimen—Balancing Risks and Benefits (Continued)		
COR	LOE	Recommendations
I	B	6. Selection of anticoagulant therapy should be based on the risk of thromboembolism, irrespective of whether the AF pattern is paroxysmal, persistent, or permanent. <sup>54.1.1-20-54.1.1-23</sup> <b>MODIFIED:</b> “Antithrombotic” was changed to “anticoagulant.”
I	B-NR	7. Renal function and hepatic function should be evaluated before initiation of a NOAC and should be reevaluated at least annually. <sup>54.1.1-11,54.1.1-24-54.1.1-28</sup> <b>MODIFIED:</b> Evaluation of hepatic function was added. LOE was updated from B to B-NR. New evidence was added. (Section 4.1. in the 2014 AF Guideline)
I	C	8. In patients with AF, anticoagulant therapy should be individualized on the basis of shared decision-making after discussion of the absolute risks and relative risks of stroke and bleeding, as well as the patient’s values and preferences. <b>MODIFIED:</b> “Antithrombotic” was changed to “anticoagulant.”
I	C	9. For patients with atrial flutter, anticoagulant therapy is recommended according to the same risk profile used for AF. <b>MODIFIED:</b> “Antithrombotic” was changed to “anticoagulant.”
I	C	10. Reevaluation of the need for and choice of anticoagulant therapy at periodic intervals is recommended to reassess stroke and bleeding risks. <b>MODIFIED:</b> “Antithrombotic” was changed to “anticoagulant.”
I	C-EO	11. For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) who are unable to maintain a therapeutic INR level with warfarin, use of a NOAC is recommended. <b>MODIFIED:</b> Exclusion criteria are now defined as moderate-to-severe mitral stenosis or a mechanical heart valve, and this recommendation has been changed in response to the approval of edoxaban. (Section 4.1. in the 2014 AF Guideline)
IIa	B	12. For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and a CHA <sub>2</sub> DS <sub>2</sub> -VASc score of 0 in men or 1 in women, it is reasonable to omit anticoagulant therapy. <sup>54.1.1-24,54.1.1-25</sup> <b>MODIFIED:</b> Exclusion criteria are now defined as moderate-to-severe mitral stenosis or a mechanical heart valve. (Section 4.1. in the 2014 AF Guideline)
IIb	B-NR	13. For patients with AF who have a CHA <sub>2</sub> DS <sub>2</sub> -VASc score of 2 or greater in men or 3 or greater in women and who have end-stage chronic kidney disease (CKD; creatinine clearance [CrCl] <15 mL/min) or are on dialysis, it might be reasonable to prescribe warfarin (INR 2.0 to 3.0) or apixaban for oral anticoagulation. <sup>54.1.1-26,54.1.1-29,54.1.1-30</sup> <b>MODIFIED:</b> New evidence has been added. LOE was updated from B to B-NR. (Section 4.1. in the 2014 AF Guideline)

Recommendations for Selecting an Anticoagulant Regimen—Balancing Risks and Benefits (Continued)		
COR	LOE	Recommendations
IIb	B-R	14. For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and moderate-to-severe CKD (serum creatinine ≥1.5 mg/dL [apixaban], CrCl 15 to 30 mL/min [dabigatran], CrCl ≤50 mL/min [rivaroxaban], or CrCl 15 to 50 mL/min [edoxaban]) with an elevated CHA <sub>2</sub> DS <sub>2</sub> -VASc score, treatment with reduced doses of direct thrombin or factor Xa inhibitors may be considered (eg, dabigatran, rivaroxaban, apixaban, or edoxaban). <sup>54.1.1-11</sup> <b>MODIFIED:</b> Exclusion criteria are now defined as moderate-to-severe mitral stenosis or a mechanical heart valve, and this recommendation has been changed in response to the approval of edoxaban. LOE was updated from C to B-R. (Section 4.1. in the 2014 AF Guideline)
IIb	C-LD	15. For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and a CHA <sub>2</sub> DS <sub>2</sub> -VASc score of 1 in men and 2 in women, prescribing an oral anticoagulant to reduce thromboembolic stroke risk may be considered. <sup>54.1.1-31-54.1.1-35</sup> <b>MODIFIED:</b> Exclusion criteria are now defined as moderate-to-severe mitral stenosis or a mechanical heart valve, and evidence was added to support separate risk scores by sex. LOE was updated from C to C-LD. (Section 4.1. in the 2014 AF Guideline)
III: No Benefit	C-EO	16. In patients with AF and end-stage CKD or on dialysis, the direct thrombin inhibitor dabigatran or the factor Xa inhibitors rivaroxaban or edoxaban are not recommended because of the lack of evidence from clinical trials that benefit exceeds risk. <sup>54.1.1-8-54.1.1-11,54.1.1-36-54.1.1-38</sup> <b>MODIFIED:</b> New data have been included. Edoxaban received FDA approval and has been added to the recommendation. LOE was updated from C to C-EO. (Section 4.1. in the 2014 AF Guideline)
III: Harm	B-R	17. The direct thrombin inhibitor dabigatran should not be used in patients with AF and a mechanical heart valve. <sup>54.1.1-39</sup> <b>MODIFIED:</b> Evidence was added. LOE was updated from B to B-R. Other NOACs are addressed in the supportive text. (Section 4.1. in the 2014 AF Guideline)

**Recommendation-Specific Supportive Text (New or Modified)**

1. New data are available for edoxaban. Edoxaban (30 or 60 mg once daily) was studied in a large randomized prospective AF trial; it was found to be noninferior to warfarin with regard to the prevention of stroke or systemic embolization and was associated with significantly lower rates of bleeding and death from cardiovascular causes.<sup>54.1.1-11</sup> Treatment of patients with AF with edoxaban, either 30 mg or 60 mg, should be based on assessment of the risks of stroke and bleeding. In ENGAGE-TIMI 48 (Effective Anticoagulation With

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Factor Xa Next Generation in Atrial Fibrillation—Thrombolysis in Myocardial Infarction 48), the rate of systemic embolism and stroke was 1.5% with warfarin, compared with 1.2% with 60 mg of edoxaban (hazard ratio [HR]: 0.79; 97.5% CI: 0.63–0.99;  $p < 0.001$  for noninferiority) and 1.6% with 30 mg of edoxaban (HR: 1.07; 97.5% CI: 0.87–1.31;  $p = 0.005$  for noninferiority). The rate of major bleeding was 3.4% with warfarin, versus 2.8% with 60 mg of edoxaban (HR: 0.80; 95% CI: 0.71–0.91;  $p < 0.001$ ) and 1.6% with 30 mg of edoxaban (HR: 0.47; 95% CI: 0.41–0.55;  $p < 0.001$ ).<sup>S4.1.1-11</sup> In the 2014 AF Guideline, the presence of a prior stroke, a prior transient ischemic attack, or a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2 or greater was an indication to consider oral anticoagulants. In the present focused update, we are adding precision to the CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring system on the basis of new published information. The COR and LOE of warfarin, dabigatran, rivaroxaban, and apixaban are unchanged from the 2014 AF Guideline.

2. There have been 4 RCTs<sup>S4.1.1-8–S4.1.1-11</sup> comparing NOACs with warfarin. There was consistent evidence of at least noninferiority for the combined endpoint of stroke or systemic embolism. When combined with a superior safety profile, they are recommended as firstline therapy for eligible patients.
4. The recommendation is similar to the 2014 AF Guideline. New evidence has appeared that emphasizes the substantial variation across different cohorts of patients with AF, including various non-European populations, in overall stroke rates for a given CHA<sub>2</sub>DS<sub>2</sub>-VASc point score.<sup>S4.1.1-40</sup> Additional approaches to stroke risk prediction and serious net clinical outcome prediction in selected patients with AF, including for specific anticoagulant management, have been published.<sup>S4.1.1-41–S4.1.1-42</sup> Anticoagulation for AF and hypertrophic cardiomyopathy remain the same as in the 2014 AF Guideline.

Patients with bioprosthetic heart valves were not included in studies validating the CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring system. For bioprosthetic valves, very limited published experience exists for the use of the CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring system for long-term assessment of thromboembolism risk in patients with AF. In 1 brief report in patients with AF, increasing age and the CHA<sub>2</sub>DS<sub>2</sub>-VASc score were independent predictors of thromboembolic events. In these patients with AF, a low CHA<sub>2</sub>DS<sub>2</sub>-VASc score was associated with low thromboembolic risk regardless of whether the patients had bioprosthetic valves.<sup>S4.1.1-43</sup> In addition, in the ARISTOTLE (Apixaban for Reduction

in Stroke and Other Thromboembolic Events in Atrial Fibrillation; apixaban) and ENGAGE AF-TIMI 48 (edoxaban) AF trials, small numbers of these patients (with mitral or aortic bioprosthetic valve implants) were included. In these small subgroups, the findings suggested that apixaban (41 patients) and edoxaban (191 patients) appeared to be equitable alternatives to warfarin in patients with AF and remote bioprosthetic valve implantation.<sup>S4.1.1-44–S4.1.1-45</sup> Although short-term anticoagulation of bioprosthetic valves after implantation is standard practice, further study is needed before the routine long-term use of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score can be recommended in AF patients with bioprosthetic heart valves.<sup>S4.1.1-18, S4.1.1-19</sup>

5. One mechanical aortic valve replacement has FDA-approved recommendations of an INR of 1.5 to 2.0 (3 months after implantation) along with low-dose aspirin, based on a limited clinical trial.<sup>S4.1.1-46</sup> This trial was designed to test whether it is safe and effective to treat patients with less aggressive anticoagulation therapy after implantation of an approved mechanical valve prosthesis (On-X). Although patients with AF were not excluded, very few were enrolled (see also the AHA/ACC valvular heart disease guidelines<sup>S4.1.1-18–S4.1.1-19</sup>).
7. All 4 NOACs with FDA approval for use in patients with AF have dosing defined by renal function (creatinine or CrCl using the Cockcroft-Gault equation). Apixaban adds additional dosing considerations of age  $\geq 80$  years or weight  $\leq 60$  kg.<sup>S4.1.1-47</sup> Edoxaban is not approved for use in patients with poor renal function (CrCl  $< 30$  mL/min) or upper-range renal function (CrCl  $> 95$  mL/min).<sup>S4.1.1-27</sup> Renal function should be regularly monitored and CrCl calculated at an interval that depends on the individual degree of renal dysfunction and likelihood of fluctuation, and dose adjustments should be made according to FDA dosing guidelines.<sup>S4.1.1-48</sup> In addition, for the factor Xa inhibitors, hepatic function should occasionally be monitored. NOACs are not recommended for use in patients with severe hepatic dysfunction.
11. Edoxaban (30 mg or 60 mg once daily) was studied in a large randomized prospective AF trial (ENGAGE AF-TIMI 48); it was noninferior to warfarin with regard to the prevention of stroke or systemic embolization and was associated with significantly lower rates of bleeding and death from cardiovascular causes.<sup>S4.1.1-11</sup>
12. Many risk factors contribute to the increased risk of stroke in patients with AF as expressed in the CHA<sub>2</sub>DS<sub>2</sub>-VASc score. The evidence for female sex as a risk factor has been assessed in many studies. Most studies support the finding that females

with AF are at increased risk of stroke. One meta-analysis found a 1.31-fold (95% CI: 1.18–1.46) elevated risk of stroke in females with AF, with the risk appearing greatest for females  $\geq 75$  years of age.<sup>S4.1.1-35</sup> Recent studies have suggested that female sex, in the absence of other AF risk factors (CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0 in males and 1 in females), carries a low stroke risk that is similar to males. The excess risk for females was especially evident among those with  $\geq 2$  non-sex-related stroke risk factors; thus, female sex is a risk modifier and is age dependent.<sup>S4.1.1-49</sup> Adding female sex to the CHA<sub>2</sub>DS<sub>2</sub>-VASc score matters for age  $> 65$  years or  $\geq 2$  non-sex-related stroke risk factors.<sup>S4.1.1-49</sup>

13. Patients with end-stage CKD who receive dialysis have increased prevalence of AF and other associated risk factors for stroke<sup>S4.1.1-50</sup> and have increased bleeding risk.<sup>S4.1.1-50–S4.1.1-52</sup> Warfarin, when studied in large retrospective studies, has been shown to offer protection from cardiovascular events without increasing bleeding,<sup>S4.1.1-29</sup> however, in a recent meta-analysis, warfarin did not offer reduction in deaths, ischemic events, or strokes but increased the incidence of major bleeding.<sup>S4.1.1-26, S4.1.1-53</sup>

Limited data exist on single- and multiple-dose apixaban (2.5 mg or 5 mg) in patients with AF and CKD on dialysis compared to healthy patients.<sup>S4.1.1-54–S4.1.1-57</sup> Patients with CKD on dialysis accumulate apixaban (increase in apixaban area-under-the-plasma-concentration-versus-time-curve and trough drug levels), and apixaban 2.5 mg twice daily resulted in steady-state drug exposure comparable to 5 mg twice daily in patients with preserved renal function. Dialysis had a limited impact on apixaban clearance. Bleeding complications were decreased. A recent trial compared apixaban (5 mg versus 2.5 mg twice daily) and warfarin in dialysis-dependent patients with AF. Patients receiving standard-dose apixaban (5 mg) had a lower risk of stroke/embolism than those receiving low-dose apixaban (2.5 mg) and warfarin. Standard-dose apixaban was associated with a lower risk of death than that observed with low-dose apixaban and warfarin, and there was a lower risk of major bleeding with apixaban than with warfarin.<sup>S4.1.1-30</sup> Use of warfarin or apixaban might be reasonable in dialysis-dependent patients with AF, but further study is warranted.

14. Edoxaban (30 mg or 60 mg once daily) was studied in ENGAGE AF-TIMI 48; it was found to be noninferior to warfarin with regard to the prevention of stroke or systemic embolization and was associated with significantly lower

rates of bleeding and death from cardiovascular causes.<sup>S4.1.1-11</sup>

15. There has been uncertainty about whether anticoagulation is warranted in men and women who have AF with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 or 2, respectively. Women with AF are likely to be older and have an increased risk of stroke.<sup>S4.1.1-31–S4.1.1-33</sup> Female sex alone, however, does not convey increased risk in the absence of other factors.<sup>S4.1.1-34, S4.1.1-35, S4.1.1-58</sup> Recent studies of a large community-based cohort of patients with AF addressed the benefit of anticoagulation among patients with AF who have 1 non-sex-related AF risk factor (CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 in males and 2 in females).<sup>S4.1.1-58</sup> The authors found that nonanticoagulated patients with AF who had 1 non-sex-related stroke risk factor (CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 versus 0 in males and 2 vs. 1 in females) had an increased risk of serious cardiovascular events during follow-up. Importantly, warfarin anticoagulation use was associated with a small positive net clinical benefit (measured as ischemic stroke reduction balanced against increased intracranial hemorrhage) compared with no anticoagulation or antiplatelet therapy use. Similar studies with NOACs in such patients are needed.
16. Edoxaban is 50% renally excreted and dosed once a day; it is not recommended in patients with end-stage renal disease or on dialysis.<sup>S4.1.1-11</sup> Limited single-dose pharmacokinetic data have been published for rivaroxaban use in patients with end-stage kidney disease on dialysis.<sup>S4.1.1-59, S4.1.1-60</sup> Dabigatran and rivaroxaban have been studied by using prescription patterns in a dialysis population.<sup>S4.1.1-61</sup> Dabigatran and rivaroxaban were associated with a higher risk of hospitalization or death from bleeding than that of warfarin.<sup>S4.1.1-61</sup>
17. The RE-ALIGN trial (Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients After Heart Valve Replacement) was a multicenter, prospective, randomized, phase II dose-validation study of dabigatran versus warfarin that enrolled patients (18–75 years of age) with one of the following: mechanical valve replacement in the aortic or mitral position (or both) within the prior 7 days (population A) or mechanical mitral valve (with or without aortic valve) replacement more than 3 months before randomization (population B). The trial was stopped after it had enrolled 252 patients because of unacceptable thromboembolic and bleeding event rates in the dabigatran group. Similar drug safety and efficacy information is lacking for mechanical

heart valves and rivaroxaban, apixaban, and edoxaban. On the basis of the outcomes of the RE-ALIGN trial, the presence of a mechanical heart valve is considered a contraindication to all NOACs.<sup>S4.1.1-39,S4.1.1-62</sup>

## 4.2. Anticoagulant Options (Modified From Section 4.2., "Antithrombotic Options," in the 2014 AF Guideline)

### 4.2.2. Non-Vitamin K Oral Anticoagulants (Modified From Section 4.2.2., "New Target-Specific Oral Anticoagulants," in the 2014 AF Guideline)

Most NOACs represent an advance in therapeutic safety when compared with warfarin for prevention of thromboembolism in patients with AF. The NOAC AF trials demonstrated that NOACs are noninferior<sup>S4.2.2.2-1,S4.2.2.2-2</sup> or superior<sup>S4.2.2.2-3,S4.2.2.2-4</sup> to warfarin in preventing stroke or thromboembolism. NOACs reduce intracranial bleeding as compared with warfarin.<sup>S4.2.2.2-5</sup> Although no direct RCT data are available, limited data comparing individual NOACs to one another are emerging from meta-analyses of the original NOAC clinical trials<sup>S4.2.2.2-6</sup> and registries and patient databases,<sup>S4.2.2.2-6-S4.2.2.2-14</sup> and more data are expected. Specific NOACs, such as apixaban, may have lower risks of bleeding (including intracranial hemorrhage) and improved efficacy for stroke prevention, whereas the risk of bleeding for rivaroxaban is comparable to that of warfarin. In other studies, uninterrupted dabigatran had a more favorable outcome than warfarin in ablation of AF (RE-CIRCUIT Trial [Uninterrupted Dabigatran Etxilate in Comparison to Uninterrupted Warfarin in Pulmonary Vein Ablation]).<sup>S4.2.2.2-15</sup> Over time, NOACs (particularly dabigatran and rivaroxaban) may be associated with lower risks of adverse renal outcomes than warfarin in patients with AF.<sup>S4.2.2.2-16</sup> Among older adults with AF receiving anticoagulation, dabigatran was associated with a lower risk of osteoporotic fracture than warfarin.<sup>S4.2.2.2-17</sup> Data on drug interactions with NOACs are emerging.<sup>S4.2.2.2-18</sup> Interpretation of these data requires careful consideration of trial design, including factors such as absence of control groups, incomplete laboratory and historical data, missing data for some drugs (particularly edoxaban), and varying NOAC drug doses (some approved doses in the United States differ from those in Europe). Head-to-head prospective RCT data for NOACs are needed for further evaluation of comparative bleeding risk and effectiveness.

Commercial assays to measure NOAC serum levels are now available, but reference ranges derived from

published literature are variable and are not well correlated with safety, efficacy, and clinical outcomes. Indications for measurement of NOAC serum levels might include:

- Measurement of drug levels in patients undergoing urgent surgical procedures.
- Uncovering accumulation of potentially toxic drug levels in patients with CKD or those undergoing dialysis.
- Detection of potential drug–drug interactions to guide dose adjustment.
- Evaluation of drug absorption in severely obese patients (body mass index >35 or weight >120 kg)
- Assessment of patient adherence.

## 4.3. Interruption and Bridging Anticoagulation

**Recommendations for Interruption and Bridging Anticoagulation**  
Referenced studies that support new or modified recommendations are summarized in Online Data Supplement 3.

COR	LOE	Recommendations
I	C	1. Bridging therapy with unfractionated heparin or low-molecular-weight heparin 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.
I	B-R	2. For patients with AF without mechanical heart valves who require interruption of warfarin for procedures, decisions about bridging therapy (unfractionated heparin or low-molecular-weight heparin) should balance the risks of stroke and bleeding and the duration of time a patient will not be anticoagulated. <sup>S4.3-1</sup> <b>MODIFIED:</b> LOE was updated from C to B-R because of new evidence. (Section 4.1. in the 2014 AF Guideline)
I	B-NR	3. Idarucizumab is recommended for the reversal of dabigatran in the event of life-threatening bleeding or an urgent procedure. <sup>S4.3-2</sup> <b>NEW:</b> New evidence has been published about idarucizumab to support LOE B-NR.
Ia	B-NR	4. Andexanet alfa can be useful for the reversal of rivaroxaban and apixaban in the event of life-threatening or uncontrolled bleeding. <sup>S4.3-3,S4.3-4</sup> <b>NEW:</b> New evidence has been published about andexanet alfa to support LOE B-NR.

## Recommendation-Specific Supportive Text (New or Modified)

2. The BRIDGE (Bridging Anticoagulation in Patients who Require Temporary Interruption

of Warfarin Therapy for an Elective Invasive Procedure or Surgery) study was a randomized, double-blind, placebo-controlled trial of bridging versus no bridging in 1 884 patients with AF (except with moderate to severe mitral stenosis or a mechanical heart valve) requiring periprocedural interruption of warfarin therapy.<sup>S4.3-1</sup> Absence of bridging was found to be noninferior to bridging with low-molecular-weight heparin for prevention of arterial thromboembolism and was found to decrease the risk of bleeding. Bridging anticoagulation may be appropriate only in patients (on warfarin) with a very high thromboembolic risk.

3. The analysis of 503 patients from the RE-VERSE AD (Reversal Effects of Idarucizumab on Active Dabigatran) trial found that idarucizumab, a monoclonal antibody fragment that binds dabigatran, rapidly normalized hemostasis and reduced levels of circulating dabigatran in subjects on dabigatran who had serious bleeding or required an urgent procedure.<sup>S4.3-2</sup> Idarucizumab has received full FDA approval.
4. Andexanet alfa (coagulation factor Xa [recombinant], inactivated-zhzo) is a bioengineered, recombinant modified protein designed to serve as an antidote against direct factor Xa inhibitors. It was reported to reverse the effects of rivaroxaban and apixaban<sup>S4.3-3,S4.3-4</sup> and was approved under the FDA's accelerated-approval pathway on the basis of effects in healthy volunteers. Continued approval may be contingent on postmarketing studies to demonstrate an improvement in hemostasis in patients.

## 4.4. Nonpharmacological Stroke Prevention

### 4.4.1. Percutaneous Approaches to Occlude the LAA

Recommendation for Percutaneous Approaches to Occlude the LAA		
Referenced studies that support the new recommendation are summarized in Online Data Supplement 4.		
COR	LOE	Recommendation
IIb	B-NR	1. Percutaneous LAA occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation. <sup>S4.4.1-1-S4.4.1-5</sup> <b>NEW:</b> Clinical trial data and FDA approval of the Watchman device necessitated this recommendation.

### Recommendation-Specific Supportive Text (New)

1. Percutaneous LAA occlusion with the Watchman device has been compared with warfarin in patients with AF (in the absence of moderate to severe mitral stenosis or a mechanical heart valve) at increased risk of stroke in 2 RCTs: the PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation)<sup>S4.4.1-1</sup> and the PREVAIL (Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy)<sup>S4.4.1-2</sup> trials. A meta-analysis combining data from these 2 trials and their registries demonstrated that patients receiving the device had significantly fewer hemorrhagic strokes than did those receiving warfarin, but there was an increase in ischemic strokes in the device group.<sup>S4.4.1-3</sup> However, when periprocedural events were excluded, the difference in ischemic strokes was not significant.

Oral anticoagulation remains the preferred therapy for stroke prevention for most patients with AF and elevated stroke risk. However, for patients who are poor candidates for long-term oral anticoagulation (because of the propensity for bleeding or poor drug tolerance or adherence), the Watchman device provides an alternative. There are important differences in wording between the FDA approval and the Centers for Medicare & Medicaid Services (CMS) approval. In the FDA approval, the device was restricted to patients who were deemed suitable for long-term warfarin (mirroring the inclusion criteria for enrollment in the clinical trials) but had an appropriate rationale to seek a nonpharmacological alternative to warfarin. Conversely, CMS states that the device is an option for patients who are suitable for short-term warfarin but deemed unable to take long-term oral anticoagulation. CMS has specified that patients should have a CHADS<sub>2</sub> score ≥2 or a CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥3 to be considered for the device. A number of unresolved issues remain, including the optimal patient selection and periprocedural antithrombotic regimen. The current FDA labeling specifies that patients should be deemed suitable for anticoagulation and, in particular, a period of periprocedural anticoagulation. Patients unable to take oral anticoagulation were excluded from the Watchman RCTs. However, there is increasing experience outside the United States with LAA closure in oral anticoagulation–ineligible patients using an antiplatelet regimen only,<sup>S4.4.1-6,S4.4.1-7</sup> and this is the focus of an ongoing RCT.<sup>S4.4.1-8</sup>

**4.4.2. Cardiac Surgery—LAA Occlusion/Excision**

Recommendation for Cardiac Surgery—LAA Occlusion/Excision		
Referenced studies that support the modified recommendation are summarized in Online Data Supplement 5.		
COR	LOE	Recommendation
IIb	B-NR	1. Surgical occlusion of the LAA may be considered in patients with AF undergoing cardiac surgery <sup>54,4.2-1</sup> , as a component of an overall heart team approach to the management of AF. <b>MODIFIED:</b> LOE was updated from C to B-NR because of new evidence.

**Recommendation-Specific Supportive Text (Modified)**

1. New evidence exists supporting surgical LAA occlusion in patients with a history of AF. An observational study evaluated the association between surgical LAA occlusion (usually with surgical atrial ablation) performed concurrently with cardiac operations in older patients with a history of AF and the risk of postoperative thromboembolic complications.<sup>54,4.2-1</sup> The authors used patient information from the Society of Thoracic Surgeons Adult Cardiac Surgery Database registry, which contains perioperative information with short-term (mainly 30-day) outcomes. The study linked the Society of Thoracic Surgeons Adult Cardiac Surgery Database patient information to Medicare claims data (age ≥65 years), with the primary outcome of readmission within 3 years of operation for thromboembolism (stroke, transient ischemic attack, or systemic embolism). The study identified 10524 patients who underwent cardiac surgical procedures, including 3892 patients (37%) with surgical LAA occlusion. At a mean follow-up of 2.6 years, surgical LAA occlusion, compared with no LAA occlusion, was associated with lower unadjusted rates of readmission for thromboembolism (4.2% versus 6.2%), all-cause mortality (17.3% versus 23.9%), and the composite endpoint (20.5% versus 28.7%) but no significant difference in rates of hemorrhagic stroke (0.9% each). These findings suggest that surgical LAA occlusion may be associated with reduced postoperative thromboembolic events in older patients with a history of AF.

In subgroup analyses stratified by anticoagulation status at hospital discharge, patients with a history of AF who received LAA occlusion without postoperative anticoagulation had a significantly lower thromboembolism rate than those who received neither LAA occlusion nor anticoagulation. There also was no signifi-

cant difference in the risk of thromboembolism among patients with a history of AF discharged with anticoagulation therapy, whether they received surgical LAA occlusion or not. These data support a role for anticoagulation in patients with a history of AF, particularly in patients not receiving LAA occlusion.

A propensity-matched analysis of prophylactic surgical LAA occlusion in patients undergoing cardiac surgery did not demonstrate an association between LAA occlusion and long-term thromboembolic events.<sup>54,4.2-2</sup> The propensity-matched LAA occlusion and non-LAA occlusion groups were relatively small (461 patients per group), and fewer than half the patients in each group had a history of AF. The study did show that surgical LAA occlusion, which often was incomplete, was associated with increased risk of early postoperative AF, but it did not influence the risk of stroke or death.

There are several important limitations to these studies, and future RCTs may be valuable.

**6. RHYTHM CONTROL**

**6.1. Electrical and Pharmacological Cardioversion of AF and Atrial Flutter**

**6.1.1. Prevention of Thromboembolism**

Recommendations for Prevention of Thromboembolism		
Referenced studies that support modified recommendations are summarized in Online Data Supplement 6.		
COR	LOE	Recommendations
I	B-R	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), a factor Xa inhibitor, or direct thrombin inhibitor is recommended for at least 3 weeks before and at least 4 weeks after cardioversion, regardless of the CHA <sub>2</sub> DS <sub>2</sub> -VASc score or the method (electrical or pharmacological) used to restore sinus rhythm. <sup>56,1.1-1-56.1.1-12</sup> <b>MODIFIED:</b> The 2014 AF Guideline recommendation for use of warfarin around the time of cardioversion was combined with the 2014 AF Guideline recommendation for NOACs to create a single recommendation. This combined recommendation was updated to COR I/LOE B-R from COR IIa/LOE C for NOACs in the 2014 AF Guideline on the basis of additional trials that have evaluated the use of NOACs with cardioversion.
I	C	2. For patients with AF or atrial flutter of more than 48 hours' duration or unknown duration that requires immediate cardioversion for hemodynamic instability, anticoagulation should be initiated as soon as possible and continued for at least 4 weeks after cardioversion unless contraindicated.

Recommendations for Prevention of Thromboembolism (Continued)		
COR	LOE	Recommendations
I	C-EO	<p>3. After cardioversion for AF of any duration, the decision about long-term anticoagulation therapy should be based on the thromboembolic risk profile and bleeding risk profile.</p> <p><b>MODIFIED:</b> The 2014 AF Guideline recommendation was strengthened with the addition of bleeding risk profile to the long-term anticoagulation decision-making process.</p>
IIa	B-NR	<p>4. For patients with AF or atrial flutter of less than 48 hours' duration with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2 or greater in men and 3 or greater in women, administration of heparin, a factor Xa inhibitor, or a direct thrombin inhibitor is reasonable as soon as possible before cardioversion, followed by long-term anticoagulation therapy.<sup>S6.1.1-13,S6.1.1-14</sup></p> <p><b>MODIFIED:</b> Recommendation COR was changed from I in the 2014 AF Guideline to IIa, and LOE was changed from C in the 2014 AF Guideline to B-NR. In addition, a specific CHA<sub>2</sub>DS<sub>2</sub>-VASc score is now specified.</p>
IIa	B	<p>5. 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 LAA, provided that anticoagulation is achieved before transesophageal echocardiography and maintained after cardioversion for at least 4 weeks.<sup>S6.1.1-15</sup></p>
IIb	B-NR	<p>6. For patients with AF or atrial flutter of less than 48 hours' duration with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0 in men or 1 in women, administration of heparin, a factor Xa inhibitor, or a direct thrombin inhibitor, versus no anticoagulant therapy, may be considered before cardioversion, without the need for postcardioversion oral anticoagulation.<sup>S6.1.1-13,S6.1.1-14,S6.1.1-16</sup></p> <p><b>MODIFIED:</b> Recommendation LOE was changed from C in the 2014 AF Guideline to B-NR to reflect evidence from 2 registry studies and to include specific CHA<sub>2</sub>DS<sub>2</sub>-VASc scores derived from study results.</p>

**Recommendation-Specific Supportive Text (New or Modified)**

1. Three prospective RCTs have evaluated the safety and efficacy of newly initiated factor Xa inhibitors (rivaroxaban and apixaban) for cardioversion as an alternative to warfarin.<sup>S6.1.1-7,S6.1.1-8,S6.1.1-17</sup> In addition, retrospective analyses have been performed on the subset of patients undergoing cardioversion within the context of the larger randomized trials that compared each of the FDA-approved NOACs with warfarin for thromboembolism prevention with AF. The results were consistent and support the assertion that NOACs are an effective and safe alternative to warfarin

for patients undergoing cardioversion. An alternative to waiting 3 weeks before cardioversion is to perform transesophageal echocardiography to exclude thrombus (see separate recommendation in this section). The decision about long-term anticoagulant therapy (beyond 4 weeks) is based on the thromboembolic risk profile (Section 4) and bleeding risk profile. The "48-hour rule" has also been questioned, because delay to cardioversion of 12 hours or longer from symptom onset was associated with a greater risk of thromboembolic complications compared to cardioversion of less than 12 hours (1.1% versus 0.3%)<sup>S6.1.1-18</sup> and the risk of thromboembolic complications with cardioversion of 12 hour or longer increases substantially in patients >75 years of age and in women.<sup>S6.1.1-19</sup>

4. The data supporting the safety of current practices of cardioversion of AF without oral anticoagulation in patients with AF duration <48 hours are limited. Two recent retrospective studies demonstrate that the risk of thromboembolic complication after a cardioversion for AF lasting <48 hours is in the range of 0.7% to 1.1%, with higher risk in patients with risk factors that include female sex, HF, and diabetes mellitus, whereas patients <60 years of age without thromboembolic risk factors and those with postoperative AF appear to have a lower risk.<sup>S6.1.1-13,S6.1.1-14</sup> In 1 study (567 cardioversions in 484 patients), the risk of thromboembolism was nearly 5 times higher in patients without therapeutic anticoagulation than in those on therapeutic anticoagulation with either warfarin or heparin. All events in that study occurred in patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of ≥2.<sup>S6.1.1-14</sup> In the absence of randomized trials, the risk of thromboembolic events should be weighed against the risk of anticoagulant-related bleeding for the individual patient.

6. Two recent retrospective studies evaluated the risk of thromboembolism in patients after cardioversion for AF lasting <48 hours. In 1 study (567 cardioversions in 484 patients), the risk of thromboembolism was nearly 5 times higher in patients without therapeutic anticoagulation than in those on therapeutic anticoagulation with either warfarin or heparin, with no events in patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of <2.<sup>S6.1.1-14</sup> In the second study, for patients with AF lasting <48 hours and a CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≤1, the overall event rate was low (0.4%), but this group accounted for 10 of the 38 thromboembolic events (26%) that occurred in the study.<sup>S6.1.1-13</sup> These studies agree with prior studies of cardioversion in short-term AF.<sup>S6.1.1-20</sup> In the absence of randomized trials, the risk of thromboembolic events should be weighed

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against the risk of anticoagulant-related bleeding for the individual patient.

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

#### 6.3.4. Catheter Ablation in HF

**Recommendation for Catheter Ablation in HF**  
 Referenced studies that support the new recommendation are summarized in **Online Data Supplement 7**.

COR	LOE	Recommendation
IIb	B-R	1. AF catheter ablation may be reasonable in selected patients with symptomatic AF and HF with reduced left ventricular (LV) ejection fraction (HFrEF) to potentially lower mortality rate and reduce hospitalization for HF. <sup>S6.3.4-1,S6.3.4-2</sup> <b>NEW:</b> New evidence, including data on improved mortality rate, has been published for AF catheter ablation compared with medical therapy in patients with HF.

#### Recommendation-Specific Supportive Text (New)

1. In an RCT (CASTLE-AF [Catheter Ablation vs. Standard Conventional Treatment in Patients With LV Dysfunction and AF]), selected patients with HFrEF with paroxysmal or persistent AF and an implanted cardioverter-defibrillator or cardiac resynchronization therapy defibrillator device who did not respond to or could not take antiarrhythmic drugs were randomized to receive AF catheter ablation versus medical therapy (rate or rhythm control) in addition to guideline-directed management and therapy for HFrEF.<sup>S6.3.4-1</sup> Patients in the AF catheter ablation group had significantly reduced overall mortality rate, reduced rate of hospitalization for worsening HF, and improved LV ejection fraction as compared with the medical therapy group, and according to device interrogation, more patients in the AF catheter ablation group were in sinus rhythm. An additional RCT in a population of patients with persistent AF, HFrEF, and an implanted cardioverter-defibrillator or cardiac resynchronization therapy defibrillator device demonstrated that AF catheter ablation was superior to amiodarone for maintenance of sinus rhythm, with secondary endpoint analyses suggesting a lower rate of unplanned hospitalization and death.<sup>S6.3.4-2</sup> Both studies have limitations, including relatively small and highly selected patient populations. Further, larger studies are needed to validate these findings.

Other small studies conducted in patients with AF and HFrEF have shown the superiority of AF ablation over antiarrhythmic drugs in the maintenance of sinus rhythm and in outcomes such as improved LV ejection fraction, performance in a 6-minute walk test, and quality of life.<sup>S6.3.4-3,S6.3.4-4</sup>

However, the recent CABANA (Catheter Ablation versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation) trial (n=2204 patients randomized to either catheter ablation or drug therapy) showed that AF ablation was not superior to drug therapy for the primary cardiovascular outcomes of death, disabling stroke, serious bleeding, or cardiac arrest at 5 years among patients with new-onset or untreated AF that required therapy.<sup>S6.3.4-5,S6.3.4-6</sup>

## 7. SPECIFIC PATIENT GROUPS AND AF

### 7.4. AF Complicating ACS

**Recommendations for AF Complicating ACS**  
 Referenced studies that support new or modified recommendations are summarized in **Online Data Supplement 8**.

COR	LOE	Recommendations
I	B-R	1. For patients with ACS and AF at increased risk of systemic thromboembolism (based on CHA <sub>2</sub> DS <sub>2</sub> -VASc risk score of 2 or greater), anticoagulation is recommended unless the bleeding risk exceeds the expected benefit. <sup>S7.4-1-S7.4-3</sup> <b>MODIFIED:</b> New published data are available. LOE was updated from C in the 2014 AF Guideline to B-R. Anticoagulation options are described in supportive text.
I	C	2. Urgent direct-current cardioversion of new-onset AF in the setting of ACS is recommended for patients with hemodynamic compromise, ongoing ischemia, or inadequate rate control.
I	C	3. 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.
IIa	B-NR	4. If triple therapy (oral anticoagulant, aspirin, and P2Y <sub>12</sub> inhibitor) is prescribed for patients with AF at increased risk of stroke (based on CHA <sub>2</sub> DS <sub>2</sub> -VASc risk score of 2 or greater) who have undergone percutaneous coronary intervention (PCI) with stenting for ACS, it is reasonable to choose clopidogrel in preference to prasugrel. <sup>S7.4-4,S7.4-5</sup> <b>NEW:</b> New published data are available.
IIa	B-R	5. In patients with AF at increased risk of stroke (based on CHA <sub>2</sub> DS <sub>2</sub> -VASc risk score of 2 or greater) who have undergone PCI with stenting for ACS, double therapy with a P2Y <sub>12</sub> inhibitor (clopidogrel or ticagrelor) and dose-adjusted vitamin K antagonist is reasonable to reduce the risk of bleeding as compared with triple therapy. <sup>S7.4-3,S7.4-6-S7.4-8</sup> <b>NEW:</b> New RCT data and data from 2 registries and a retrospective cohort study are available.
IIa	B-R	6. In patients with AF at increased risk of stroke (based on CHA <sub>2</sub> DS <sub>2</sub> -VASc risk score of 2 or greater) who have undergone PCI with stenting for ACS, double therapy with P2Y <sub>12</sub> inhibitors (clopidogrel) and low-dose rivaroxaban 15 mg daily is reasonable to reduce the risk of bleeding as compared with triple therapy. <sup>S7.4-2</sup> <b>NEW:</b> New published data are available.

Recommendations for AF Complicating ACS (Continued)		
COR	LOE	Recommendations
IIa	B-R	7. In patients with AF at increased risk of stroke (based on CHA <sub>2</sub> DS <sub>2</sub> -VASc risk score of 2 or greater) who have undergone PCI with stenting for ACS, double therapy with a P2Y <sub>12</sub> inhibitor (clopidogrel) and dabigatran 150 mg twice daily is reasonable to reduce the risk of bleeding as compared with triple therapy. <sup>57,4-1</sup> <b>NEW:</b> New published data are available.
IIb	B-R	8. If triple therapy (oral anticoagulant, aspirin, and P2Y <sub>12</sub> inhibitor) is prescribed for patients with AF who are at increased risk of stroke (based on CHA <sub>2</sub> DS <sub>2</sub> -VASc risk score of 2 or greater) and who have undergone PCI with stenting (drug eluting or bare metal) for ACS, a transition to double therapy (oral anticoagulant and P2Y <sub>12</sub> inhibitor) at 4 to 6 weeks may be considered. <sup>57,4-9,57,4-10</sup> <b>NEW:</b> New published data are available.
IIb	C	9. Administration of amiodarone or digoxin may be considered to slow a rapid ventricular response in patients with ACS and AF associated with severe LV dysfunction and HF or hemodynamic instability.
IIb	C	10. Administration of nondihydropyridine calcium antagonists may be considered to slow a rapid ventricular response in patients with ACS and AF only in the absence of significant HF or hemodynamic instability.

## Synopsis

The incidence of AF in patients with ACS ranges from 10% to 21% and increases with patient age and severity of myocardial infarction (MI).<sup>57,4-11,57,4-12</sup> In the Medicare population, AF is associated with increased in-hospital mortality rate (25.3% with AF versus 16.0% without AF), 30-day mortality rate (29.3% versus 19.1%), and 1-year mortality rate (48.3% versus 32.7%).<sup>57,4-12</sup> With multivariate adjustment, AF remains an independent predictor of death: in hospital (odds ratio: 1.21), at 30 days (odds ratio: 1.20), and at 1 year (odds ratio: 1.34).<sup>57,4-12</sup> Patients who develop AF during hospitalization have a worse prognosis than those with AF on admission.<sup>57,4-12</sup> Stroke rates are higher in patients with MI and AF than in those without AF (3.1% for those with AF versus 1.3% for those in sinus rhythm).<sup>57,4-11</sup> Thus, AF is an independent predictor of poor long-term outcome in patients with ACS.<sup>57,4-13,57,4-14</sup>

Patients treated for ACS normally require dual-antiplatelet therapy (DAPT) with aspirin plus a platelet P2Y<sub>12</sub> receptor inhibitor and may require the addition of warfarin or a NOAC (“triple therapy”) for primary prevention for patients with AF at increased risk of stroke<sup>57,4-3</sup> (Section 4.3.). An option is to consider double therapy—the use of an oral anticoagulant plus a P2Y<sub>12</sub> inhibitor without aspirin.<sup>57,4-3</sup> If triple therapy is used, efforts may be directed to

minimize duration of triple therapy to a period of 4 to 6 weeks, as this is the period of greatest risk of stent thrombosis, especially in patients with ACS, such as ST-segment–elevation MI. Use of DAPT alone may be considered for patients with ACS who have AF and a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0 to 1, with reconsideration of the indications for anticoagulation over time.<sup>57,4-15,57,4-16</sup> Whereas Section 4.1.1. provides specific guidance on the presence/absence of stroke risk associated with female sex in the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, the randomized data set referenced in this section on double versus triple therapy in patients undergoing PCI (subset with ACS) does not present the data analysis stratified by sex; therefore, the recommendation is provided in the context of overall CHA<sub>2</sub>DS<sub>2</sub>-VASc score. The HAS-BLED score can be used to assess bleeding risk in patients for whom anticoagulation is being considered.<sup>57,4-17</sup>

Urgent direct-current cardioversion is appropriate in patients with ACS presenting with new-onset AF and intractable ischemia, hemodynamic instability, or inadequate rate control. Intravenous administration of a beta blocker is indicated for rate control in patients with ACS to reduce myocardial oxygen demands. Intravenous amiodarone is an appropriate alternative for rate control and may facilitate conversion to sinus rhythm. Digoxin may be considered in those with severe LV dysfunction and HF or hemodynamic instability. However, recent data from the ARISTOTLE AF NOAC trial study population show that digoxin was independently associated with higher mortality rate in patients with AF regardless of HF, and in patients with AF taking digoxin, the risk of death increased with higher serum digoxin concentrations.<sup>57,4-18</sup> Other meta-analysis studies support these conclusions.<sup>57,4-19</sup> Treatment with angiotensin-converting enzyme inhibitors appears to reduce the incidence of AF in patients with LV dysfunction after ACS.<sup>57,4-20,57,4-21</sup>

## Recommendation-Specific Supportive Text (New or Modified)

1. This recommendation is modified to incorporate the data from WOEST (What is the Optimal Antiplatelet & Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting)<sup>57,4-3</sup> and the recent evidence from PIONEER AF-PCI (Open-Label, Randomized, Controlled, Multicenter Study Exploring two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation who Undergo Percutaneous Coronary Intervention)<sup>57,4-2</sup> and RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran Versus Triple Therapy With

Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention)<sup>57.4-1</sup> (see supportive text for recommendations 6 and 8 below). These 3 clinical trials enrolled both patients with stable ischemic disease and patients with ACS treated with PCI. These trials did not include patients with ACS managed medically. On the basis of these clinical trials, options for anticoagulants in this patient population include warfarin, rivaroxaban, and dabigatran. Although the use of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score has been validated only in several small studies of patients with AF and ACS, we believe it is reasonable to use this methodology to estimate the risk of systemic thromboembolism.<sup>57.4-22,57.4-23</sup>

4. A single-center prospective cohort study found that, as compared with triple therapy with clopidogrel, triple therapy with prasugrel was associated with a higher incidence of Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding events.<sup>57.4-4</sup> This finding was corroborated by the TRANSLATE-ACS (Treatment with Adenosine Diphosphate Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome) study,<sup>57.4-5</sup> a multicenter prospective cohort study of patients who underwent PCI for an acute MI. That study found that, as compared with triple therapy with clopidogrel, triple therapy with prasugrel was associated with a higher incidence of BARC (Bleeding Academic Research Consortium)-defined bleeding events. These events, however, were patient-reported bleeding events that did not require hospitalization.
5. WOEST was an RCT that showed that, as compared with triple therapy (aspirin, clopidogrel, and warfarin), double therapy with warfarin and clopidogrel was associated with fewer bleeding complications. WOEST, however, was not powered to assess stent thrombosis.<sup>57.4-3</sup> Two other registry-based studies similarly showed that double therapy with warfarin and clopidogrel was not associated with higher risk of coronary ischemia than triple therapy.<sup>57.4-6,57.4-7</sup> Furthermore, a hospital-based retrospective cohort study found that double therapy with warfarin and ticagrelor had thrombotic and bleeding rates that were similar to those observed with triple therapy.<sup>57.4-8</sup> The aforementioned studies were not based exclusively on patients with AF and ACS; patients with AF undergoing elective PCI for stable coronary artery disease were also included.
6. PIONEER AF-PCI was an international, multicenter, randomized, open-label trial of 2 124 patients with AF (without moderate to severe mitral stenosis or a mechanical heart valve) who had undergone PCI with stenting. Patients were randomized in a 1:1:1 ratio to low-dose rivaroxaban (15 mg once daily) plus a P2Y<sub>12</sub> inhibitor for 12 months (Group 1); very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months (Group 2); or standard therapy with a dose-adjusted vitamin K antagonist (once daily) plus DAPT for 1, 6, or 12 months (Group 3). Clopidogrel was the most common P2Y<sub>12</sub> inhibitor used (>90%). The rates of clinically significant bleeding were lower in Groups 1 and 2 than in Group 3.<sup>57.4-2</sup> The rates of death from cardiovascular causes, MI, or stroke were similar in the 3 groups.<sup>57.4-2</sup> It is important to note that the dose of rivaroxaban used in that study was lower than the dose recommended for stroke prophylaxis in AF. The study was not powered to evaluate risk of stent thrombosis or systemic thromboembolism.<sup>57.4-2</sup>
7. RE-DUAL PCI was an international, multicenter, randomized open-label trial of 2 725 patients with nonvalvular AF who had undergone PCI with stenting. Patients were randomized to receive 1 of 3 treatments: double therapy with dabigatran (110 mg twice daily) plus either clopidogrel or ticagrelor (110-mg dual-therapy group), double therapy with dabigatran (150 mg twice daily) plus either clopidogrel or ticagrelor (150-mg dual-therapy group), or triple therapy with warfarin plus aspirin (≤100 mg daily) and either clopidogrel or ticagrelor (triple-therapy group). The incidence of major or clinically relevant nonmajor bleeding was higher in the triple-therapy group than in the 110-mg dual-therapy group and the 150-mg dual-therapy group. In addition, the 2 dual-therapy groups combined were noninferior to the triple-therapy group with regard to the composite efficacy endpoint of thromboembolic events (MI, stroke, or systemic embolism), death, or unplanned revascularization. Clopidogrel was the most common P2Y<sub>12</sub> inhibitor used (88%). Notably, the study was not powered to evaluate risk of stent thrombosis or systemic thromboembolism.<sup>57.4-1</sup>

In aggregate, the data to date on comparisons of double versus triple therapy demonstrate that double therapy significantly reduces the risk of bleeding without a signal of harm with regard to stent thrombosis in clinical trials that enrolled both patients with stable ischemic disease and patients with ACS. With regard to the antithrombotic dosages studied, only the RE-DUAL PCI trial and WOEST trials studied antithrombotic dosages known to reduce the risk of systemic

thromboembolism.<sup>57.4-1,57.4-3</sup> The ongoing AUGUSTUS (A Study of Apixaban in Patients With Atrial Fibrillation, not Caused by a Heart Valve Problem, who are at Risk for Thrombosis due to Having had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart) trial is an open-label 2x2 factorial RCT to evaluate the safety of apixaban versus vitamin K antagonist and aspirin versus aspirin placebo in patients with AF and ACS or PCI.<sup>57.4-24</sup> The ENTRUST-AF-PCI (Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) is an ongoing trial evaluating edoxaban treatment versus vitamin K antagonist treatment in patients with AF undergoing PCI.<sup>57.4-25</sup> These trials will provide further evidence on treatment approaches designed to mitigate bleeding while reducing the risks of stent thrombosis and systemic thromboembolism.

8. The ISAR-TRIPLE (Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation) trial<sup>57.4-9</sup> was a randomized, open-label trial of patients receiving anticoagulation who underwent PCI with drug-eluting stents. Patients received concomitant anticoagulant and aspirin and were randomized to 6 weeks versus 6 months of clopidogrel. There was no difference between the 2 groups in terms of the primary composite endpoint of death, MI, definite stent thrombosis, stroke, or TIMI major bleeding or in terms of the secondary bleeding endpoint of TIMI major bleeding at 9 months.<sup>57.4-9</sup> The Bern PCI Registry<sup>57.4-10</sup> is a prospective registry of consecutive patients who have undergone PCI for stable coronary artery disease or ACS at Bern University Hospital since 2009. Among patients who were discharged on triple therapy, there was no difference between ≤1 month versus >1 month of triple therapy in the primary composite endpoint of cardiac death, MI, stroke, definite stent thrombosis, or TIMI major bleeding at 1 year.<sup>57.4-10</sup> Although both the ISAR-TRIPLE trial and the Bern PCI Registry have limitations, the consistent finding in both patients with ACS and patients with stable ischemic heart disease suggests that with current drug-eluting stents, selecting bare metal stents to shorten the duration of DAPT is no longer indicated. Of the patients treated with triple therapy for 1 month in the Bern PCI Registry, 60% were treated with a current-generation drug-eluting stent.

## 7.12. Device Detection of AF and Atrial Flutter (New)

### Recommendations for Device Detection of AF and Atrial Flutter

Referenced studies that support new recommendations are summarized in [Online Data Supplement 9](#).

COR	LOE	Recommendations
I	B-NR	1. In patients with cardiac implantable electronic devices (pacemakers or implanted cardioverter-defibrillators), the presence of recorded atrial high-rate episodes (AHREs) should prompt further evaluation to document clinically relevant AF to guide treatment decisions. <sup>57.12-1–57.12-5</sup>
Ila	B-R	2. In patients with cryptogenic stroke (ie, stroke of unknown cause) in whom external ambulatory monitoring is inconclusive, implantation of a cardiac monitor (loop recorder) is reasonable to optimize detection of silent AF. <sup>57.12-6</sup>

### Recommendation-Specific Supportive Text (New)

1. Patients with AHREs detected by implanted devices are at increased risk of stroke and abundant data now link device-detected atrial tachycardia or AF (or AHREs) with the development of thromboembolic events.<sup>57.12-1–57.12-5</sup> Remote monitoring with AHRE alerts increases the likelihood of detecting silent AF. However, it is unclear whether patients with AHREs benefit from oral anticoagulation. Careful review of stored electrograms may confirm the presence of AF and rule out false positive events. Occasionally, the addition of extended external electrocardiographic monitoring may be needed if data from the implanted device are uncertain. Prospective clinical trials of prophylactic anticoagulation based on device-detected AF are under way but have not been completed. Although increased duration of AHREs is associated with increased stroke risk, the threshold duration of AHREs that warrants anticoagulation is unclear. Current approaches factor in the duration of device-detected AF and the patient's stroke risk profile, bleeding risk, and preferences to determine whether to initiate long-term anticoagulation.
2. The cause of ischemic stroke remains unknown in 20% to 40% of patients, leading to a diagnosis of cryptogenic stroke. Prolonged electrocardiogram monitoring with an implantable cardiac monitor in these patients (age >40 years) has the advantage of increasing the likelihood of detecting silent AF that would escape detection with short-term monitoring. A recent RCT established

the superiority of an implantable cardiac monitor over conventional monitoring for detecting silent AF, a finding with major clinical ramifications for these patients.<sup>57,12-6</sup> A role in screening for silent AF may also exist for remote electrocardiographic acquisition and transmission with a “smart” worn or handheld WiFi-enabled device with remote interpretation.<sup>57,12-7,57,12-8</sup>

### 7.13. Weight Loss (New)

Recommendation for Weight Loss in Patients with AF		
Referenced studies that support the new recommendation are summarized in Online Data Supplement 10.		
COR	LOE	Recommendation
I	B-R	<p>1. For overweight and obese patients with AF, weight loss, combined with risk factor modification, is recommended.<sup>57,13-1-57,13-3</sup></p> <p><b>NEW:</b> New data demonstrate the beneficial effects of weight loss and risk factor modification on controlling AF.</p>

#### Recommendation-Specific Supportive Text (New)

1. Obesity is associated with atrial electrostructural remodeling<sup>57,13-4</sup> and AF.<sup>57,13-5-57,13-7</sup> One RCT demonstrated that a structured weight management program for obese patients (body mass index >27) with symptomatic AF reduced symptom burden and severity and reduced the number of AF episodes and their cumulative duration when compared with attempts to optimally manage risk factors alone.<sup>57,13-1</sup> Risk factor modification included assessment and treatment of underlying sleep apnea, hypertension, hyperlipidemia, glucose intolerance, and alcohol and tobacco use. A second nonrandomized observational study reported improved outcomes of AF catheter ablation among obese patients who enrolled in a weight loss program.<sup>57,13-2</sup> Observational studies have revealed that the degree of improvement in the AF type and symptoms were related to the degree of weight loss.<sup>57,13-3,57,13-8</sup> Taken together, these studies support a treatment approach that addresses the risk factors for AF.

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## REFERENCES

### PREAMBLE

- P-1. Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, Institute of Medicine (US). *Clinical Practice Guidelines We Can Trust*. Washington, DC: National Academies Press; 2011.
- P-2. Committee on Standards for Systematic Reviews of Comparative Effectiveness Research, Institute of Medicine (US). *Finding What Works in Health Care: Standards for Systematic Reviews*. Washington, DC: National Academies Press; 2011.
- P-3. Anderson JL, Heidenreich PA, Barnett PG, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. *Circulation*. 2014;129:2329–45.
- P-4. ACCF/AHA Task Force on Practice Guidelines. Methodology Manual and Policies From the ACCF/AHA Task Force on Practice Guidelines. American College of Cardiology and American Heart Association. 2010. Available at: [http://assets.cardiosource.com/Methodology\\_Manual\\_for\\_ACC\\_AHA\\_Writing\\_Committees.pdf](http://assets.cardiosource.com/Methodology_Manual_for_ACC_AHA_Writing_Committees.pdf) and [http://professional.heart.org/idc/groups/ahamah-public/@wcm/@sop/documents/downloadable/ucm\\_319826.pdf](http://professional.heart.org/idc/groups/ahamah-public/@wcm/@sop/documents/downloadable/ucm_319826.pdf). Accessed October 31, 2018.
- P-5. Halperin JL, Levine GN, Al-Khatib SM, et al. Further evolution of the ACC/AHA clinical practice guideline recommendation classification system: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2015;133:1426–28.
- P-6. Jacobs AK, Anderson JL, Halperin JL. The evolution and future of ACC/AHA clinical practice guidelines: a 30-year journey: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:1208–17.
- P-7. Jacobs AK, Kushner FG, Ettinger SM, et al. ACCF/AHA clinical practice guideline methodology summit report: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:268–310.
- P-8. Arnett DK, Goodman RA, Halperin JL, et al. AHA/ACC/HHS strategies to enhance application of clinical practice guidelines in patients with cardiovascular disease and comorbid conditions: from the American Heart Association, American College of Cardiology, and US Department of Health and Human Services. *Circulation*. 2014;130:1662–67.

### 1.3. Document Review and Approval

- S1.3-1. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2014;130:e199–267.

- S1.3-2. ACCF/AHA Task Force on Practice Guidelines. Methodology Manual and Policies From the ACCF/AHA Task Force on Practice Guidelines. American College of Cardiology and American Heart Association. 2010. Available at: [http://assets.cardiosource.com/Methodology\\_Manual\\_for\\_ACC\\_AHA\\_Writing\\_Committees.pdf](http://assets.cardiosource.com/Methodology_Manual_for_ACC_AHA_Writing_Committees.pdf) and [http://professional.heart.org/idc/groups/ahamah-public/@wcm/@sop/documents/downloadable/ucm\\_319826.pdf](http://professional.heart.org/idc/groups/ahamah-public/@wcm/@sop/documents/downloadable/ucm_319826.pdf). Accessed October 31, 2018.
- S1.3-3. Halperin JL, Levine GN, Al-Khatib SM, et al. Further evolution of the ACC/AHA clinical practice guideline recommendation classification system: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2015;133:1426–28.
- S1.3-4. Jacobs AK, Kushner FG, Ettinger SM, et al. ACCF/AHA clinical practice guideline methodology summit report: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:268–310.

### 4.1.1. Selecting an Anticoagulant Regimen—Balancing Risks and Benefits (Modified From Section 4.1.1. Selecting an Antithrombotic Regimen—Balancing Risks and Benefits in the 2014 AF Guideline)

- S4.1.1-1. Di Biase L. Use of direct oral anticoagulants in patients with atrial fibrillation and valvular heart lesions. *J Am Heart Assoc*. 2016;5:e002776.
- S4.1.1-2. Ezekowitz MD, Nagarakanti R, Noack H, et al. Comparison of dabigatran and warfarin in patients with atrial fibrillation and valvular heart disease: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulant Therapy). *Circulation*. 2016;134:589–98.
- S4.1.1-3. Pan K-L, Singer DE, Ovbiagele B, et al. Effects of non-vitamin K antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and valvular heart disease: a systematic review and meta-analysis. *J Am Heart Assoc*. 2017;6:e005835.
- S4.1.1-4. Floyd CN, Ferro A. Indications for anticoagulant and antiplatelet combined therapy. *BMJ*. 2017;359:j3782.
- S4.1.1-5. Lip GYH, Nieuwlaar R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. *Chest*. 2010;137:263–72.
- S4.1.1-6. Olesen JB, Torp-Pedersen C, Hansen ML, et al. The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0–1: a nationwide cohort study. *Thromb Haemost*. 2012;107:1172–9.
- S4.1.1-7. Mason PK, Lake DE, DiMarco JP, et al. Impact of the CHA2DS2-VASc score on anticoagulation recommendations for atrial fibrillation. *Am J Med*. 2012;125:e1–6.
- S4.1.1-8. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–51.
- S4.1.1-9. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–91.
- S4.1.1-10. Granger CB, Alexander JH, McMurray JVV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–92.
- S4.1.1-11. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093–104.
- S4.1.1-12. Matchar DB, Jacobson A, Dolor R, et al. Effect of home testing of international normalized ratio on clinical events. *N Engl J Med*. 2010;363:1608–20.
- S4.1.1-13. Ezekowitz MD, James KE, Radford MJ, et al. Initiating and maintaining patients on warfarin anticoagulation: the importance of monitoring. *J Cardiovasc Pharmacol Ther*. 1999;4:3–8.
- S4.1.1-14. Hirsh J, Fuster V. Guide to anticoagulant therapy. Part 2: oral anticoagulants. American Heart Association. *Circulation*. 1994;89:1469–80.
- S4.1.1-15. Cannegieter SC, Rosendaal FR, Wintzen AR, et al. Optimal oral anticoagulant therapy in patients with mechanical heart valves. *N Engl J Med*. 1995;333:11–7.
- S4.1.1-16. Acar J, lung B, Boissel JP, et al. AREVA: multicenter randomized comparison of low-dose versus standard-dose anticoagulation in patients with mechanical prosthetic heart valves. *Circulation*. 1996;94:2107–12.

- S4.1.1-17. Hering D, Piper C, Bergemann R, et al. Thromboembolic and bleeding complications following St. Jude Medical valve replacement: results of the German Experience With Low-Intensity Anticoagulation Study. *Chest*. 2005;127:53–9.
- S4.1.1-18. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:e521–643.
- S4.1.1-19. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135:e1159–95.
- S4.1.1-20. Ahmad Y, Lip GYH, Apostolakis S. New oral anticoagulants for stroke prevention in atrial fibrillation: impact of gender, heart failure, diabetes mellitus and paroxysmal atrial fibrillation. *Expert Rev Cardiovasc Ther*. 2012;10:1471–80.
- S4.1.1-21. Chiang C-E, Naditch-Brülé L, Murin J, et al. Distribution and risk profile of paroxysmal, persistent, and permanent atrial fibrillation in routine clinical practice: insight from the real-life global survey evaluating patients with atrial fibrillation international registry. *Circ Arrhythm Electrophysiol*. 2012;5:632–9.
- S4.1.1-22. Flaker G, Ezekowitz M, Yusuf S, et al. Efficacy and safety of dabigatran compared to warfarin in patients with paroxysmal, persistent, and permanent atrial fibrillation: results from the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study. *J Am Coll Cardiol*. 2012;59:854–5.
- S4.1.1-23. Hohnloser SH, Duray GZ, Baber U, et al. Prevention of stroke in patients with atrial fibrillation: current strategies and future directions. *Eur Heart J*. 2007;10:H4–10.
- S4.1.1-24. Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane Database Syst Rev*. 2005.:CD001927.
- S4.1.1-25. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146:857–67.
- S4.1.1-26. Winkelmayer WC, Liu J, Setoguchi S, et al. Effectiveness and safety of warfarin initiation in older hemodialysis patients with incident atrial fibrillation. *Clin J Am Soc Nephrol*. 2011;6:2662–8.
- S4.1.1-27. Bohula EA, Giugliano RP, Ruff CT, et al. Impact of renal function on outcomes with edoxaban in the ENGAGE AF-TIMI 48 Trial. *Circulation*. 2016;134:24–36.
- S4.1.1-28. Khoury T, Ayman AR, Cohen J, et al. The complex role of anticoagulation in cirrhosis: an updated review of where we are and where we are going. *Digestion*. 2016;93:149–59.
- S4.1.1-29. Bonde AN, Lip GYH, Kamper A-L, et al. Net clinical benefit of antithrombotic therapy in patients with atrial fibrillation and chronic kidney disease: a nationwide observational cohort study. *J Am Coll Cardiol*. 2014;64:2471–82.
- S4.1.1-30. Siontis KC, Zhang X, Eckard A, et al. Outcomes associated with apixaban use in end-stage kidney disease patients with atrial fibrillation in the United States. *Circulation*. 2018;138:1519–29.
- S4.1.1-31. Andersson T, Magnuson A, Bryngelsson I-L, et al. Gender-related differences in risk of cardiovascular morbidity and all-cause mortality in patients hospitalized with incident atrial fibrillation without concomitant diseases: a nationwide cohort study of 9519 patients. *Int J Cardiol*. 2014;177:91–9.
- S4.1.1-32. Fang MC, Singer DE, Chang Y, et al. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study. *Circulation*. 2005;112:1687–91.
- S4.1.1-33. Panchoy SB, Sharma PS, Panchoy DS, et al. Meta-analysis of gender differences in residual stroke risk and major bleeding in patients with nonvalvular atrial fibrillation treated with oral anticoagulants. *Am J Cardiol*. 2014;113:485–90.
- S4.1.1-34. Mikkelsen AP, Lindhardsen J, Lip GYH, et al. Female sex as a risk factor for stroke in atrial fibrillation: a nationwide cohort study. *J Thromb Haemost*. 2012;10:1745–51.
- S4.1.1-35. Wagstaff AJ, Overvad TF, Lip GYH, et al. Is female sex a risk factor for stroke and thromboembolism in patients with atrial fibrillation? A systematic review and meta-analysis. *QJM*. 2014;107:955–67.
- S4.1.1-36. Hariharan S, Madabushi R. Clinical pharmacology basis of deriving dosing recommendations for dabigatran in patients with severe renal impairment. *J Clin Pharmacol*. 2012;52:1195–255.
- S4.1.1-37. Lehr T, Haertter S, Liesenfeld K-H, et al. Dabigatran etexilate in atrial fibrillation patients with severe renal impairment: dose identification using pharmacokinetic modeling and simulation. *J Clin Pharmacol*. 2012;52:1373–8.
- S4.1.1-38. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011;364:806–17.
- S4.1.1-39. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med*. 2013;369:1206–14.
- S4.1.1-40. Quinn GR, Severdija ON, Chang Y, et al. Wide variation in reported rates of stroke across cohorts of patients with atrial fibrillation. *Circulation*. 2017;135:208–19.
- S4.1.1-41. Rivera-Caravaca JM, Roldán V, Esteve-Pastor MA, et al. Prediction of long-term net clinical outcomes using the TIMI-AF score: comparison with CHA2DS2-VASc and HAS-BLED. *Am Heart J*. 2018;197:27–34.
- S4.1.1-42. Fanola CL, Giugliano RP, Ruff CT, et al. A novel risk prediction score in atrial fibrillation for a net clinical outcome from the ENGAGE AF-TIMI 48 randomized clinical trial. *Eur Heart J*. 2017;38:888–96.
- S4.1.1-43. Philippart R, Brunet-Bernard A, Clementy N, et al. CHA2DS2-VASc score for predicting stroke and thromboembolism in patients with AF and biological valve prosthesis. *J Am Coll Cardiol*. 2016;67:343–4.
- S4.1.1-44. Carnicelli AP, De Caterina R, Halperin JL, et al. Edoxaban for the prevention of thromboembolism in patients with atrial fibrillation and bioprosthetic valves. *Circulation*. 2017;135:1273–5.
- S4.1.1-45. Pokorney SD, Rao MP, Wojdyla DM, et al. Apixaban use in patients with atrial fibrillation with bioprosthetic valves: insights from ARISTOTLE. [abstract 17277]. *Circulation* 2015;132 suppl 3:A17277.
- S4.1.1-46. Puskas J, Gerdisch M, Nichols D, et al. Reduced anticoagulation after mechanical aortic valve replacement: interim results from the prospective randomized on-X valve anticoagulation clinical trial randomized Food and Drug Administration investigational device exemption trial. *J Thorac Cardiovasc Surg*. 2014;147:1202–10; discussion 1210–1.
- S4.1.1-47. ELIQUIS (apixaban) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2012.
- S4.1.1-48. Savaysa [package insert] 2015. Daiichi Sankyo, Inc; Parsippany, NJ.
- S4.1.1-49. Nielsen PB, Skjøth F, Overvad TF, et al. Female sex is a risk modifier rather than a risk factor for stroke in atrial fibrillation: should we use a CHA2DS2-VASc score rather than CHA2DS2-VASc? *Circulation*. 2018;137:832–40.
- S4.1.1-50. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141:e531S–75.
- S4.1.1-51. US Renal Data System. 2016 USRDS annual data report: epidemiology of kidney disease in the United States. Bethesda, MD. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2016.
- S4.1.1-52. Sood MM, Komenda P, Sood AR, et al. The intersection of risk and benefit: is warfarin anticoagulation suitable for atrial fibrillation in patients on hemodialysis? *Chest*. 2009;136:1128–33.
- S4.1.1-53. Nochaiwong S, Ruengorn C, Awiphan R, et al. Efficacy and safety of warfarin in dialysis patients with atrial fibrillation: a systematic review and meta-analysis. *Open Heart*. 2016;3:e000441.
- S4.1.1-54. Deal EN, Pope H, Ross W. Apixaban use among patients with severe renal impairment. *Ann Pharmacother*. 2014;48:1667.
- S4.1.1-55. Stanton BE, Barasch NS, Tellor KB. Comparison of the safety and effectiveness of apixaban versus warfarin in patients with severe renal impairment. *Pharmacotherapy*. 2017;37:412–9.
- S4.1.1-56. Mavrakanas TA, Samer CF, Nessim SJ, et al. Apixaban pharmacokinetics at steady state in hemodialysis patients. *J Am Soc Nephrol*. 2017;28:2241–8.
- S4.1.1-57. Reed D, Palkimas S, Hockman R, et al. Safety and effectiveness of apixaban compared to warfarin in dialysis patients. *Res Pract Thromb Haemost*. 2018;2:291–8.
- S4.1.1-58. Fauchier L, Clementy N, Bisson A, et al. Should atrial fibrillation patients with only 1 nongender-related CHA2DS2-VASc risk factor be anticoagulated? *Stroke*. 2016;47:1831–6.
- S4.1.1-59. Dias C, Moore KT, Murphy J, et al. Pharmacokinetics, pharmacodynamics, and safety of single-dose rivaroxaban in chronic hemodialysis. *Am J Nephrol*. 2016;43:229–36.

- S4.1.1-60. De Vriese AS, Caluwé R, Bailleul E, et al. Dose-finding study of rivaroxaban in hemodialysis patients. *Am J Kidney Dis*. 2015;66:91–8.
- S4.1.1-61. Chan KE, Edelman ER, Wenger JB, et al. Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis. *Circulation*. 2015;131:972–9.
- S4.1.1-62. Van de Werf F, Brueckmann M, Connolly SJ, et al. A comparison of dabigatran etexilate with warfarin in patients with mechanical heart valves: the randomized, phase II study to evaluate the safety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement (RE-ALIGN). *Am Heart J*. 2012;163:931–7.e1.

#### 4.2.2.2. Non-Vitamin K Oral Anticoagulants (Modified From Section 4.2.2.2. New Target-Specific Oral Anticoagulants in the 2014 AF Guideline)

- S4.2.2.2-1. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–91.
- S4.2.2.2-2. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093–104.
- S4.2.2.2-3. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–51.
- S4.2.2.2-4. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–92.
- S4.2.2.2-5. Pan K-L, Singer DE, Oviagele B, et al. Effects of non-vitamin K antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and valvular heart disease: a systematic review and meta-analysis. *J Am Heart Assoc*. 2017;6:e005835.
- S4.2.2.2-6. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383:955–62.
- S4.2.2.2-7. Abraham NS, Noseworthy PA, Yao X, et al. Gastrointestinal safety of direct oral anticoagulants: a large population-based study. *Gastroenterology*. 2017;152:1014–22.e1.
- S4.2.2.2-8. Graham DJ, Reichman ME, Wernecke M, et al. Stroke, bleeding, and mortality risks in elderly Medicare beneficiaries treated with dabigatran or rivaroxaban for nonvalvular atrial fibrillation. *JAMA Intern Med*. 2016;176:1662–71.
- S4.2.2.2-9. Larsen TB, Skjøth F, Nielsen PB, et al. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ*. 2016;353:i3189.
- S4.2.2.2-10. Lip GYH, Keshishian A, Kamble S, et al. Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin. A propensity score matched analysis. *Thromb Haemost*. 2016;116:975–86.
- S4.2.2.2-11. Noseworthy PA, Yao X, Abraham NS, et al. Direct comparison of dabigatran, rivaroxaban, and apixaban for effectiveness and safety in nonvalvular atrial fibrillation. *Chest*. 2016;150:1302–12.
- S4.2.2.2-12. Yao X, Abraham NS, Sangaralingham LR, et al. Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. *J Am Heart Assoc*. 2016;5:e003725.
- S4.2.2.2-13. Ntaios G, Papavasileiou V, Makaritsis K, et al. Real-world setting comparison of nonvitamin-K antagonist oral anticoagulants versus vitamin-K antagonists for stroke prevention in atrial fibrillation: a systematic review and meta-analysis. *Stroke*. 2017;48:2494–503.
- S4.2.2.2-14. Bai Y, Shi X-B, Ma C-S, et al. Meta-analysis of effectiveness and safety of oral anticoagulants in atrial fibrillation with focus on apixaban. *Am J Cardiol*. 2017;120:1689–95.
- S4.2.2.2-15. Calkins H, Willems S, Gerstenfeld EP, et al. Uninterrupted dabigatran versus warfarin for ablation in atrial fibrillation. *N Engl J Med*. 2017;376:1627–36.
- S4.2.2.2-16. Yao X, Tangri N, Gersh BJ, et al. Renal outcomes in anticoagulated patients with atrial fibrillation. *J Am Coll Cardiol*. 2017;70:2621–32.
- S4.2.2.2-17. Lau WCY, Chan EW, Cheung C-L, et al. Association between dabigatran vs warfarin and risk of osteoporotic fractures among patients with nonvalvular atrial fibrillation. *JAMA*. 2017;317:1151–8.
- S4.2.2.2-18. Kent AP, Brueckmann M, Fraessdorf M, et al. Concomitant oral anticoagulant and nonsteroidal anti-inflammatory drug therapy in patients with atrial fibrillation. *J Am Coll Cardiol*. 2018;72:255–67.

### 4.3. Interruption and Bridging Anticoagulation

- S4.3-1. Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. *N Engl J Med*. 2015;373:823–33.
- S4.3-2. Pollack CV Jr, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal - full cohort analysis. *N Engl J Med*. 2017;377:431–41.
- S4.3-3. Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. *N Engl J Med*. 2015;373:2413–24.
- S4.3-4. Connolly SJ, Milling TJ Jr, Eikelboom JW, et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2016;375:1131–41.

### 4.4.1. Percutaneous Approaches to Occlude the Left Atrial Appendage

- S4.4.1-1. Reddy VY, Sievert H, Halperin J, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. *JAMA*. 2014;312:1988–98.
- S4.4.1-2. Holmes DR Jr, Kar S, Price MJ, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol*. 2014;64:1–12.
- S4.4.1-3. Holmes DR Jr, Doshi SK, Kar S, et al. Left atrial appendage closure as an alternative to warfarin for stroke prevention in atrial fibrillation: a patient-level meta-analysis. *J Am Coll Cardiol*. 2015;65:2614–23.
- S4.4.1-4. Reddy VY, Gibson DN, Kar S, et al. Post-approval US experience with left atrial appendage closure for stroke prevention in atrial fibrillation. *J Am Coll Cardiol*. 2017;69:253–61.
- S4.4.1-5. Boersma LVA, Schmidt B, Betts TR, et al. Implant success and safety of left atrial appendage closure with the WATCHMAN device: periprocedural outcomes from the EWOLUTION registry. *Eur Heart J*. 2016;37:2465–74.
- S4.4.1-6. Reddy VY, Möbius-Winkler S, Miller MA, et al. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). *J Am Coll Cardiol*. 2013;61:2551–6.
- S4.4.1-7. Boersma LV, Ince H, Kische S, et al. Efficacy and safety of left atrial appendage closure with WATCHMAN in patients with or without contraindication to oral anticoagulation: 1-year follow-up outcome data of the EWOLUTION trial. *Heart Rhythm*. 2017;14:1302–8.
- S4.4.1-8. Holmes DR, Reddy VY, Buchbinder M, et al. The assessment of the Watchman device in patients unsuitable for oral anticoagulation (ASAP-TOO) trial. *Am Heart J*. 2017;189:68–74.

### 4.4.2. Cardiac Surgery—LAA Occlusion/Excision

- S4.4.2-1. Friedman DJ, Piccini JP, Wang T, et al. Association between left atrial appendage occlusion and readmission for thromboembolism among patients with atrial fibrillation undergoing concomitant cardiac surgery. *JAMA*. 2018;319:365–74.
- S4.4.2-2. Melduni RM, Schaff HV, Lee H-C, et al. Impact of left atrial appendage closure during cardiac surgery on the occurrence of early postoperative atrial fibrillation, stroke, and mortality: a propensity score-matched analysis of 10 633 patients. *Circulation*. 2017;135:366–78.

### 6.1.1. Prevention of Thromboembolism

- S6.1.1-1. Gallagher MM, Hennessy BJ, Edvardsson N, et al. Embolic complications of direct current cardioversion of atrial arrhythmias: association with low intensity of anticoagulation at the time of cardioversion. *J Am Coll Cardiol*. 2002;40:926–33.
- S6.1.1-2. Jaber WA, Prior DL, Thamilarasan M, et al. Efficacy of anticoagulation in resolving left atrial and left atrial appendage thrombi: a transesophageal echocardiographic study. *Am Heart J*. 2000;140:150–6.
- S6.1.1-3. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141:e531S–575S.

- S6.1.1-4. Nagarakanti R, Ezekowitz MD, Oldgren J, et al. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. *Circulation*. 2011;123:131–6.
- S6.1.1-5. Piccini JP, Stevens SR, Lokhnygina Y, et al. Outcomes after cardioversion and atrial fibrillation ablation in patients treated with rivaroxaban and warfarin in the ROCKET AF trial. *J Am Coll Cardiol*. 2013;61:1998–2006.
- S6.1.1-6. Flaker G, Lopes RD, Al-Khatib SM, et al. Efficacy and safety of apixaban in patients after cardioversion for atrial fibrillation: insights from the ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation). *J Am Coll Cardiol*. 2014;63:1082–7.
- S6.1.1-7. Cappato R, Ezekowitz MD, Klein AL, et al. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. *Eur Heart J*. 2014;35:3346–55.
- S6.1.1-8. Goette A, Merino JL, Ezekowitz MD, et al. Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. *Lancet*. 2016;388:1995–2003.
- S6.1.1-9. Pallisgaard JL, Lindhardt TB, Hansen ML, et al. Cardioversion and risk of adverse events with dabigatran versus warfarin—a nationwide cohort study. *PLoS ONE*. 2015;10:e0141377.
- S6.1.1-10. Plitt A, Ezekowitz MD, De Caterina R, et al. Cardioversion of atrial fibrillation in ENGAGE AF-TIMI 48. *Clin Cardiol*. 2016;39:345–6.
- S6.1.1-11. Dentali F, Botto GL, Gianni M, et al. Efficacy and safety of direct oral anticoagulants in patients undergoing cardioversion for atrial fibrillation: a systematic review and meta-analysis of the literature. *Int J Cardiol*. 2015;185:72–7.
- S6.1.1-12. Ezekowitz MD, Pollack CV Jr, Halperin JL, et al. Apixaban compared to heparin/vitamin K antagonist in patients with atrial fibrillation scheduled for cardioversion: the EMANATE trial. *Eur Heart J*. 2018;39:2959–71.
- S6.1.1-13. Airaksinen KEJ, Grönberg T, Nuotio I, et al. Thromboembolic complications after cardioversion of acute atrial fibrillation: the FinCV (Finnish CardioVersion) study. *J Am Coll Cardiol*. 2013;62:1187–92.
- S6.1.1-14. Garg A, Khunger M, Seicean S, et al. Incidence of thromboembolic complications within 30 days of electrical cardioversion performed within 48 hours of atrial fibrillation onset. *J Am Coll Cardiol EP*. 2016;2:487–94.
- S6.1.1-15. Klein AL, Grimm RA, Murray RD, et al. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med*. 2001;344:1411–20.
- S6.1.1-16. von Besser K, Mills AM. Is discharge to home after emergency department cardioversion safe for the treatment of recent-onset atrial fibrillation? *Ann Emerg Med*. 2011;58:517–20.
- S6.1.1-17. Pfizer. Study of the blood thinner, apixaban, for patients who have an abnormal heart rhythm (atrial fibrillation) and expected to have treatment to put them back into a normal heart rhythm (cardioversion) (EMANATE). Available at: <https://www.clinicaltrials.gov>. Identifier: NCT02100228. Accessed November 22, 2017.
- S6.1.1-18. Nuotio I, Hartikainen JEK, Grönberg T, et al. Time to cardioversion for acute atrial fibrillation and thromboembolic complications. *JAMA*. 2014;312:647–9.
- S6.1.1-19. Bah A, Nuotio I, Gronberg T, et al. Sex, age, and time to cardioversion. Risk factors for cardioversion of acute atrial fibrillation from the FinCV study. *Ann Med*. 2017;49:254–9.
- S6.1.1-20. Kleemann T, Becker T, Strauss M, et al. Prevalence of left atrial thrombus and dense spontaneous echo contrast in patients with short-term atrial fibrillation < 48 hours undergoing cardioversion: value of transesophageal echocardiography to guide cardioversion. *J Am Soc Echocardiogr*. 2009;22:1403–8.

### 6.3.4. Catheter Ablation in HF

- S6.3.4-1. Marrouche NF, Brachmann J, Andresen D, et al. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med*. 2018;378:417–27.
- S6.3.4-2. Di Biase L, Mohanty P, Mohanty S, et al. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC multicenter randomized trial. *Circulation*. 2016;133:1637–44.
- S6.3.4-3. Prabhu S, Taylor AJ, Costello BT, et al. Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction: the CAMERA-MRI Study. *J Am Coll Cardiol*. 2017;70:1949–61.

- S6.3.4-4. Al Halabi S, Qintar M, Hussein A, et al. Catheter ablation for atrial fibrillation in heart failure patients: a meta-analysis of randomized controlled trials. *J Am Coll Cardiol EP*. 2015;1:200–9.
- S6.3.4-5. Packer DL, Mark DB, Robb RA, et al. Catheter ablation versus antiarrhythmic drug therapy for atrial fibrillation (CABANA) trial: study rationale and design. *Am Heart J*. 2018;199:192–9.
- S6.3.4-6. Packer DL, Mark DB, Robb RA, et al. Catheter ablation vs. antiarrhythmic drug therapy for atrial fibrillation: the results of the Cabana Multicenter International Randomized Clinical Trial. [abstract B-LBCT01-05]. *Heart Rhythm*. 2018;15:940-141.

## 7.4. AF Complicating ACS

- S7.4-1. Cannon CP, Bhatt DL, Oldgren J, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med*. 2017;377:1513–24.
- S7.4-2. Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med*. 2016;375:2423–34.
- S7.4-3. Devilde WJM, Oirbans T, Verheugt FWA, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet*. 2013;381:1107–15.
- S7.4-4. Sarafoff N, Martischign A, Wealer J, et al. Triple therapy with aspirin, prasugrel, and vitamin K antagonists in patients with drug-eluting stent implantation and an indication for oral anticoagulation. *J Am Coll Cardiol*. 2013;61:2060–6.
- S7.4-5. Jackson LR, Ju C, Zettler M, et al. Outcomes of patients with acute myocardial infarction undergoing percutaneous coronary intervention receiving an oral anticoagulant and dual antiplatelet therapy: a comparison of clopidogrel versus prasugrel from the TRANSLATE-ACS Study. *J Am Coll Cardiol Interv*. 2015;8:1880–9.
- S7.4-6. Lamberts M, Gislason GH, Olesen JB, et al. Oral anticoagulation and antiplatelets in atrial fibrillation patients after myocardial infarction and coronary intervention. *J Am Coll Cardiol*. 2013;62:981–9.
- S7.4-7. Rubboli A, Schlitt A, Kiviniemi T, et al. One-year outcome of patients with atrial fibrillation undergoing coronary artery stenting: an analysis of the AFCAS registry. *Clin Cardiol*. 2014;37:357–64.
- S7.4-8. Braun OÖ, Bico B, Chaudhry U, et al. Concomitant use of warfarin and ticagrelor as an alternative to triple antithrombotic therapy after an acute coronary syndrome. *Thromb Res*. 2015;135:26–30.
- S7.4-9. Fiedler KA, Maeng M, Mehilli J, et al. Duration of triple therapy in patients requiring oral anticoagulation after drug-eluting stent implantation: the ISAR-TRIPLE Trial. *J Am Coll Cardiol*. 2015;65:1619–29.
- S7.4-10. Koskinas KC, Räber L, Zanchin T, et al. Duration of triple antithrombotic therapy and outcomes among patients undergoing percutaneous coronary intervention. *J Am Coll Cardiol Interv*. 2016;9:1473–83.
- S7.4-11. Crenshaw BS, Ward SR, Granger CB, et al. Atrial fibrillation in the setting of acute myocardial infarction: the GUSTO-I experience. Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries. *J Am Coll Cardiol*. 1997;30:406–13.
- S7.4-12. Rathore SS, Berger AK, Weinfurt KP, et al. Acute myocardial infarction complicated by atrial fibrillation in the elderly: prevalence and outcomes. *Circulation*. 2000;101:969–74.
- S7.4-13. Goldberg RJ, Seeley D, Becker RC, et al. Impact of atrial fibrillation on the in-hospital and long-term survival of patients with acute myocardial infarction: a community-wide perspective. *Am Heart J*. 1990;119:996–1001.
- S7.4-14. Behar S, Zahavi Z, Goldbourt U, et al. Long-term prognosis of patients with paroxysmal atrial fibrillation complicating acute myocardial infarction. SPRINT Study Group. *Eur Heart J*. 1992;13:45–50.
- S7.4-15. ACTIVE Investigators, Connolly SJ, Pogue J, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med*. 2009;360:2066–78.
- S7.4-16. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141:e531S–75S.
- S7.4-17. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138:1093–100.
- S7.4-18. Lopes RD, Rordorf R, De Ferrari GM, et al. Digoxin and mortality in patients with atrial fibrillation. *J Am Coll Cardiol*. 2018;71:1063–74.

- S7.4-19. Vamos M, Erath JW, Hohnloser SH. Digoxin-associated mortality: a systematic review and meta-analysis of the literature. *Eur Heart J*. 2015;36:1831–8.
- S7.4-20. Pedersen OD, Bagger H, Køber L, et al. The occurrence and prognostic significance of atrial fibrillation/flutter following acute myocardial infarction. TRACE Study group. TRAndolapril Cardiac Evaluation. *Eur Heart J*. 1999;20:748–54.
- S7.4-21. McMurray J, Køber L, Robertson M, et al. Antiarrhythmic effect of carvedilol after acute myocardial infarction: results of the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial. *J Am Coll Cardiol*. 2005;45:525–30.
- S7.4-22. Fauchier L, Lecoq C, Ancey Y, et al. Evaluation of 5 prognostic scores for prediction of stroke, thromboembolic and coronary events, all-cause mortality, and major adverse cardiac events in patients with atrial fibrillation and coronary stenting. *Am J Cardiol*. 2016;118:700–7.
- S7.4-23. Álvarez-Álvarez B, Raposeiras-Roubín S, Abu-Assi E, et al. Is 6-month GRACE risk score a useful tool to predict stroke after an acute coronary syndrome? *Open Heart*. 2014;1:e000123.
- S7.4-24. Bristol-Myers Squibb. A study of apixaban in patients with atrial fibrillation, not caused by a heart valve problem, who are at risk for thrombosis (blood clots) due to having had a recent coronary event, such as a heart attack or a procedure to open the vessels of the heart. Available at: <https://www.clinicaltrials.gov>. Identifier: NCT02415400. Accessed November 1, 2017.
- S7.4-25. Daiichi Sankyo, Inc. Edoxaban treatment versus vitamin K antagonist in patients with atrial fibrillation undergoing percutaneous coronary intervention (ENTRUST-AF-PCI). Available at: <https://www.clinicaltrials.gov>. Identifier: NCT02866175. Accessed November 1, 2017.

## 7.12. Device Detection of AF and Atrial Flutter (New Section)

- S7.12-1. Boriani G, Glotzer TV, Santini M, et al. Device-detected atrial fibrillation and risk for stroke: an analysis of >10 000 patients from the SOS AF project (Stroke prevention Strategies based on Atrial Fibrillation information from implanted devices). *Eur Heart J*. 2014;35:508–16.
- S7.12-2. Glotzer TV, Daoud EG, Wyse DG, et al. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. *Circ Arrhythm Electrophysiol*. 2009;2:474–80.
- S7.12-3. Glotzer TV, Hellkamp AS, Zimmerman J, et al. Atrial high rate episodes detected by pacemaker diagnostics predict death and

stroke: report of the Atrial Diagnostics Ancillary Study of the MODE Selection Trial (MOST). *Circulation*. 2003;107:1614–9.

- S7.12-4. Healey JS, Connolly SJ, Gold MR, et al. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med*. 2012;366:120–9.
- S7.12-5. Martin DT, Bersohn MM, Waldo AL, et al. Randomized trial of atrial arrhythmia monitoring to guide anticoagulation in patients with implanted defibrillator and cardiac resynchronization devices. *Eur Heart J*. 2015;36:1660–8.
- S7.12-6. Sanna T, Diener H-C, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med*. 2014;370:2478–86.
- S7.12-7. Halcox JPJ, Wareham K, Cardew A, et al. Assessment of remote heart rhythm sampling using the AliveCor heart monitor to screen for atrial fibrillation: the REHEARSE-AF Study. *Circulation*. 2017;136:1784–94.
- S7.12-8. Bumgarner JM, Lambert CT, Hussein AA, et al. Smartwatch algorithm for automated detection of atrial fibrillation. *J Am Coll Cardiol*. 2018;71:2381–8.

## 7.13. Weight Loss (New Section)

- S7.13-1. Abed HS, Wittert GA, Leong DP, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. *JAMA*. 2013;310:2050–60.
- S7.13-2. Pathak RK, Middeldorp ME, Lau DH, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol*. 2014;64:2222–31.
- S7.13-3. Pathak RK, Middeldorp ME, Meredith M, et al. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: a long-term follow-up study (LEGACY). *J Am Coll Cardiol*. 2015;65:2159–69.
- S7.13-4. Abed HS, Samuel CS, Lau DH, et al. Obesity results in progressive atrial structural and electrical remodeling: implications for atrial fibrillation. *Heart Rhythm*. 2013;10:90–100.
- S7.13-5. Wang TJ, Parise H, Levy D, et al. Obesity and the risk of new-onset atrial fibrillation. *JAMA*. 2004;292:2471–7.
- S7.13-6. Wong CX, Ganesan AN, Selvanayagam JB. Epicardial fat and atrial fibrillation: current evidence, potential mechanisms, clinical implications, and future directions. *Eur Heart J*. 2017;38:1294–302.
- S7.13-7. Wong CX, Abed HS, Molaei P, et al. Pericardial fat is associated with atrial fibrillation severity and ablation outcome. *J Am Coll Cardiol*. 2011;57:1745–51.
- S7.13-8. Middeldorp ME, Pathak RK, Meredith M, et al. PREvention and regressive Effect of weight-loss and risk factor modification on Atrial Fibrillation: the REVERSE-AF study. *Europace*. 2018;20:1929–35.

**Appendix 1. Author Relationships With Industry and Other Entities (Relevant)—2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation (July 2018)**

Committee Member	Employment	Consultant	Speakers 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	• Astellas	None	None	None	None	None	None
Hugh Calkins	Johns Hopkins Hospital—Professor of Medicine, Director of Electrophysiology	• Abbott • AltaThera • AtriCure • Boehringer Ingelheim† • King Pharmaceuticals, Inc. (Pfizer) • Medtronic • St. Jude Medical‡	None	None	• Boehringer Ingelheim† • Boston Scientific† • St. Jude Medical†	None	None	4.1.1, 4.2.2.2, 4.3, 4.4.1, 4.4.2, 6.1.1, 6.3.4, 7.4, 7.12
Lin Y. Chen§	University of Minnesota Medical School, Cardiovascular Division—Associate Professor of Medicine	None	None	None	None	None	None	None
Joaquin E. Cigarroa	Oregon Health & Science University—Professor of Medicine; Clinical Chief of Knight Cardiovascular Institute Division Head of Cardiology	None	None	None	None	None	None	None
Joseph C. Cleveland, Jr	University of Colorado—Professor of Surgery; Denver Veteran's Administration Hospital—Chief, Cardiac Surgery	None	None	None	• St. Jude Medical	None	None	4.4.1, 4.4.2, 6.3.4, 7.4, 7.12
Patrick T. Ellinor	Massachusetts General Hospital Heart Center, Cardiac Arrhythmia Service—Director	• Bayer	None	None	• Bayer†	None	None	4.1.1, 4.2.2.2, 4.3, 6.1.1, 7.4
Michael D. Ezekowitz	Sidney Kimmel Medical College at Thomas Jefferson University—Professor of Medicine; Lankenau Medical Center, Bryn Mawr Hospital—Attending Cardiologist	• Armetheon† • Bayer† • Boehringer Ingelheim† • Bristol-Myers Squibb† • Cohere† • Daiichi-Sankyo† • Janssen Pharmaceuticals† • Johnson & Johnson† • Medtronic† • Merck† • Pfizer† • Portola Pharmaceuticals† • Sanofi-aventis†	None	None	• Boehringer Ingelheim (PI)† • Pfizer (PI)† • Portola Pharmaceuticals†	None	None	4.1.1, 4.2.2.2, 4.3, 4.4.1, 4.4.2, 6.1.1, 6.3.4, 7.4, 7.12
Michael E. Field	Medical University of South Carolina and Ralph H. Johnson VA Medical Center—Associate Professor of Medicine	None	None	None	None	None	None	None
Karen L. Furie	Rhode Island Hospital, the Miriam Hospital and Bradley Hospital—Neurologist-in-Chief; The Warren Alpert Medical School of Brown University—Chair of Neurology	None	None	None	None	None	None	None
Paul A. Heidenreich	Stanford VA Palo Alto Health Care System—Professor of Medicine	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	• Metabolic Technologies, Inc.	None	None	None	None
Julie B. Shea	Brigham and Women's Hospital	• Medtronic • St. Jude Medical	None	None	None	None	None	4.4.1, 4.4.2, 7.4, 6.3.4, 7.12

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**Appendix 1. Continued**

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
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 ≥\$5 000 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*.

The Atrial Fibrillation Guideline was initiated in September 2016. Over the initial years of the CMS Open Payment System, understandably, there have been many issues related to the accurate reporting of food and beverage payments. For this reason, the ACC and AHA have not considered these minor charges relevant relationships with industry.

\*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply.

†Significant relationship.

‡No financial benefit.

§CMS reported payments related to medical education from Medtronic Vascular to a third party, University of Minnesota Foundation, under Dr. Chen's name in 2016. Medtronic has confirmed that there was no payment made to Dr. Chen, and the entry was made in error. The sections authored by Dr. Chen have been reviewed, and it was affirmed that there was no implication of any influence of industry.

ACC indicates American College of Cardiology; AHA, American Heart Association; CMS, Centers for Medicare & Medicaid Services; HRS, Heart Rhythm Society; PI, principal investigator; and VA, Veterans Affairs.

**Appendix 2. Abbreviated Reviewer Relationships With Industry and Other Entities—2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation (August 2018)\***

Reviewer	Representation	Employment	Comprehensive RWI?
Samuel C. Dudley, Jr	Official Reviewer—AHA	University of Minnesota—Director, Cardiology Division	Yes
Federico Gentile	Official Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Centro Cardiologico Gentile	No
Augustus O. Grant	Official Reviewer—AHA	Duke University School of Medicine—Professor of Medicine; Vice Dean, Faculty Enrichment	No
Eric Stecker	Official Reviewer—ACC Science and Quality Committee	OHSU—Associate Professor of Medicine, Division of Cardiovascular Medicine, School of Medicine	Yes
Eugene Yang	Official Reviewer—ACC Board of Governors	University of Washington School of Medicine	Yes
James R. Edgerton	Organizational Reviewer—STS	The Heart Hospital Baylor—Director of Education	Yes
Fred Morady	Organizational Reviewer—HRS	University of Michigan—McKay Professor of Cardiovascular Disease and Professor of Medicine	Yes
Hakan Oral	Organizational Reviewer—HRS	University of Michigan Hospital—Frederick G. L. Huetwell Professor of Cardiovascular Medicine; Director, Cardiac Arrhythmia Service	Yes
Sana M. Al-Khatib	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Duke Clinical Research Institute—Professor of Medicine	Yes
Joseph S. Alpert	Content Reviewer	University of Arizona Health Sciences Center—Professor of Medicine; Head, Department of Medicine	Yes
Anastasia L. Armbruster	Content Reviewer—ACC Surgeons' Council	St. Louis College of Pharmacy—Associate Professor, Department of Pharmacy Practice	No
Nisha Bansal	Content Reviewer	University of Washington—Associate Professor, Division of Nephrology; Associate Program Director, Nephrology Fellowship	Yes
Coletta Barrett	Content Reviewer—AHA/ACC Lay Reviewer	Our Lady of the Lake Regional Medical Center—Vice President, Mission	No
Kim K. Birtcher	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	University of Houston College of Pharmacy—Clinical Professor	Yes
John A. Bittl	Content Reviewer	Ocala Heart Institute; Munroe Regional Medical Center	No
Yong-Mei Cha	Content Reviewer	Mayo Clinic, Division of Cardiovascular Diseases	No
Jamie B. Conti	Content Reviewer	University of Florida—Professor of Medicine (Cardiology); Chief, Division of Cardiovascular Diseases, Department of Medicine	Yes
Anita Deswal	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Baylor College of Medicine—Professor of Medicine; Michael E. DeBakey VA Medical Center—Chief of Cardiology	Yes
Michael S. Firstenberg	Content Reviewer—ACC Surgeons' Council	The Summa Health System	Yes
Zachary D. Goldberger	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	University of Wisconsin School of Medicine and Public Health—Associate Professor of Medicine, Division of Cardiovascular Medicine/Electrophysiology	No
Maya E. Guglin	Content Reviewer—ACC HF and Transplant Section Leadership Council	University of Kentucky—Professor of Medicine; Director, Mechanical Assisted Circulation, Gill Heart Institute	Yes
Jonathan L. Halperin	Content Reviewer	Mount Sinai Medical Center—Professor of Medicine	Yes
José A. Joglar	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	UT Southwestern Medical Center University—Associate Professor of Internal Medicine	No
Gautam Kumar	Content Reviewer—ACC Interventional Section Leadership Council	Emory University; Atlanta VA Medical Center	Yes
Valentina Kutylfa	Content Reviewer—ACC EP Section Leadership Council	University of Rochester Medical Center—Associate Professor of Medicine	Yes
Glenn N. Levine	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Baylor College of Medicine—Professor of Medicine; Michael E. DeBakey Medical Center—Director, Cardiac Care Unit	Yes
Grace Lin	Content Reviewer—ACC HF and Transplant Section Leadership Council	Mayo Clinic; Mayo Foundation	Yes
Gregory Y. H. Lip	Content Reviewer	University of Birmingham Centre For Cardiovascular Sciences	Yes

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## Appendix 2. Continued

Reviewer	Representation	Employment	Comprehensive RWI?
Patrick T. O'Gara	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Harvard Medical School—Prof of Medicine; Brigham and Women's Hospital—Director, Strategic Planning	Yes
Ratika Parkash	Content Reviewer	Dalhousie University and Nova Scotia Health Authority—Professor of Medicine, Division of Cardiology (Arrhythmia); Director of Research, Division of Cardiology	Yes
Mariann Piano	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Vanderbilt University School of Nursing—Nancy and Hilliard Travis Professor of Nursing; Senior Associate Dean for Research	Yes
Win-Kuang Shen	Content Reviewer	Mayo Clinic Arizona, Phoenix Campus—Professor of Medicine; Consultant	No
Giuseppe Stabile	Content Reviewer	Clinica Mediterranea, Naples, Italy	Yes
William G. Stevenson	Content Reviewer	Vanderbilt Medical Center—Director, Director of Arrhythmia Research	Yes
James Tisdale	Content Reviewer—AHA	Purdue University—Professor, College of Pharmacy; Indiana University School of Medicine—Adjunct Professor	Yes
Shane Tsai	Content Reviewer—ACC Adult Congenital and Pediatric Cardiology Section Leadership Council	University of Nebraska Medical Center—Assistant Professor, Internal Medicine and Pediatrics, Division of Cardiovascular Medicine; Section Chief, Electrophysiology	Yes
Kathryn Wood	Content Reviewer—AHA	Emory University—Associate Professor, Nell Hodgson Woodruff School of Nursing	No

This table represents all relationships of reviewers with industry and other entities that were reported at the time of peer review, including those not deemed to be relevant to this document, at the time this document was under review. 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  $\geq 5\%$  of the voting stock or share of the business entity, or ownership of  $\geq \$5000$  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. Names are listed in alphabetical order within each category of review. Please refer to <http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy> for definitions of disclosure categories or additional information about the ACC/AHA Disclosure Policy for Writing Committees.

\*Detailed reviewer disclosures can be found at this link: <https://www.ahajournals.org/doi/suppl/10.1161/CIR.0000000000000665>.

ACC indicates American College of Cardiology; AHA, American Heart Association; EP, electrophysiology; HF, heart failure; HRS, Heart Rhythm Society; OHSU, Oregon Health & Science University; RWI, relationships with industry and other entities; STS, Society of Thoracic Surgeons; UT, University of Texas; and VA, Veterans Affairs.